

MEDICAL MILESTONES

CELEBRATING KEY ADVANCES SINCE 1840

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Milestones on the long road to knowledge

Fiona Godlee

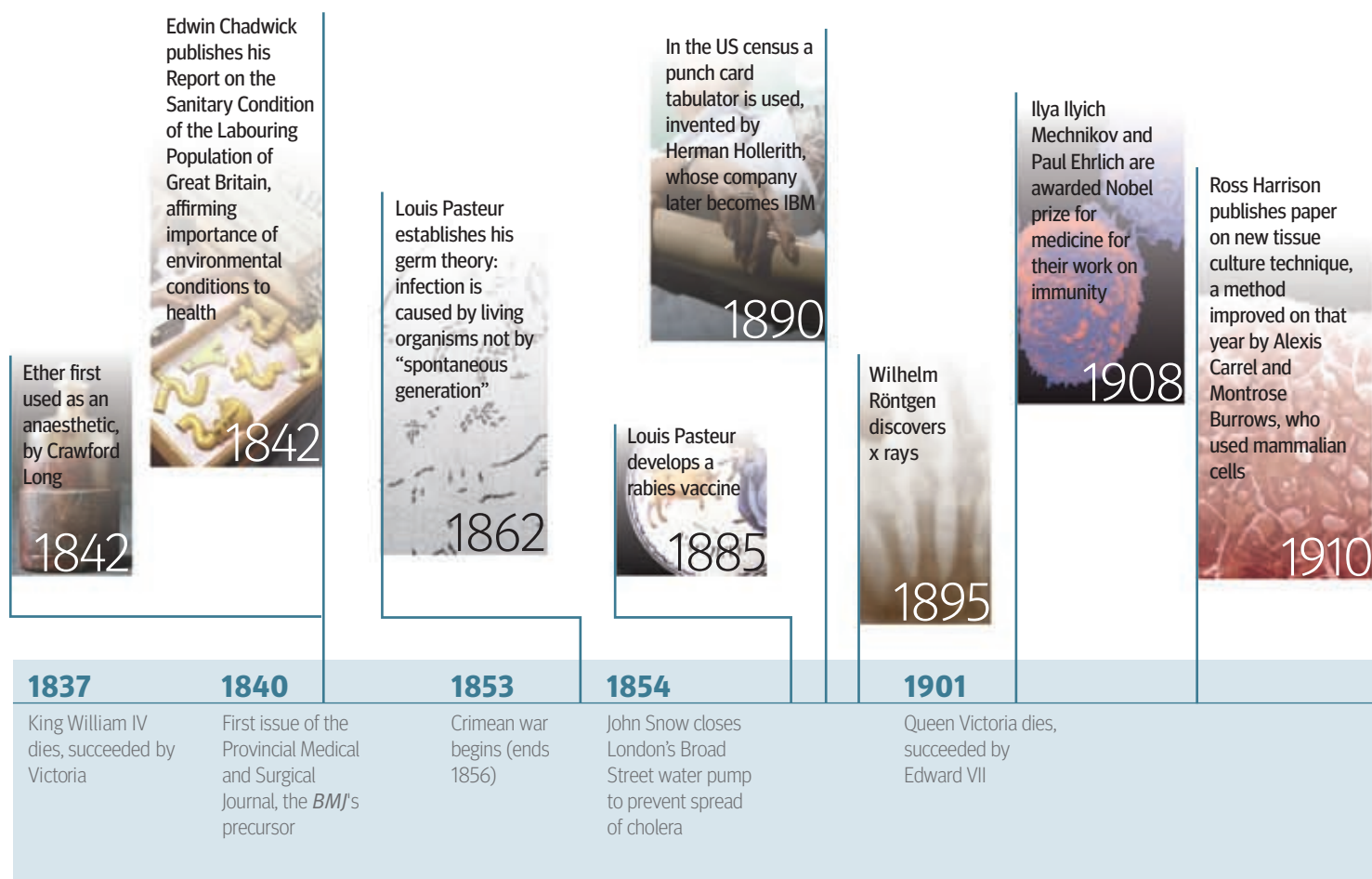
Seeking a way to mark the launch of the new *BMJ*, we hit on the idea of looking back at the most important medical milestones since the forerunner of the *BMJ* was first published in 1840. We asked readers to nominate milestones, which you did in good numbers. A panel of editors and advisers narrowed the field down from more than 70 to 15. We invited champions to write on each one; their contributions make up this commemorative supplement.

Medicine is about stories—the patient's account, the doctor's interpretation, the detective work of diagnosis, the research

journey—and these 15 accounts are all good stories. They combine all the elements of good fiction: serendipity in the discovery of penicillin (p s6) and x rays (p s12); sheer determination in the development of tissue culture (p s18); raw personal ambition—the emergence of ether as an anaesthetic owed much to one dentist's desire to advance his position (p s5); competition in the publication race over chlorpromazine (p s7); drama in turning off the Broad Street pump (p s17); and tragedy in the death of a friend, which led Semmelweis to his discovery (p s11).

Some of the 15 may surprise you. Does it make sense to give milestone status to evidence based medicine? Perhaps it says something about the culture of medicine that an effort to systematise our relation with science should have proved so controversial. As Kay Dickersin and colleagues say (p s10), how can something so intuitively obvious to lay people—the need to make decisions on the best available evidence—not be similarly viewed by clinicians? You'll also no doubt find omissions. Jeffrey Koplan finds several when he compared our list with one he initiated for the US Centers for Disease Control and Prevention eight years ago (p s20). I've found some too. Where are aspirin, *Helicobacter pylori*, and Medline?

But which of these 15—all extraordinary medical advances—will come out top? By the time this supplement is printed, a winner will have been chosen by *BMJ* readers in an online poll (see bmj.com). In terms of number of lives saved, vaccines (p s19) seem hard to beat; if it's societal consequences, then the pill might be the winner. (As Carl Djerassi points out



We can't rely on the chance arrival of genius in our midst to take us forward to the next era of discovery

(p s15), there's no need to ask which pill, so enough said, perhaps.) Alex Jadad and Murray Enkin sweep up the whole history of human intelligence in their enthusiasm for the role of computers in medical advance (p s8). How can humble oral rehydration therapy (p s14), the simple addition of salt and sugar to clean water, compete with that? At least on the grounds of cost effectiveness it can.

What can these 15 milestones tell us of medicine's future prospects? Will genetics deliver on its promise of real clinical benefit? John Burn says that the best is yet to come (p s9). The same might be said of monoclonal antibody technology: will it deliver vaccines and safer treatments for chronic illness (p s13)? Our understanding of the risks of smoking may be,

as Simon Chapman confidently asserts, "all done and dusted" (p s16), but can we share his confidence that the end game for smoking may be just 20 years away? And will we have the wisdom that Jadad and Enkin believe is necessary to ensure that computers help us to transcend all our boundaries rather than contributing to our extinction?

Finally, what do these stories tell us about how medicine advances? The image of researcher as hero is compelling and central to many of these stories. But as Geoff Watts says (p s4), a fixation with breakthroughs skews the picture of how science really progresses: "Knowledge doesn't suddenly appear in neat and tidy quanta. Like patches of lichen spreading over a rock face, it accretes over decades." It follows that we can't rely on the chance arrival of genius in our midst to take us forward to the next era of discovery. Knowledge and its implementation need an infrastructure that supports applied as well as basic research, encourages the systematic implementation of what we already know, nurtures young talent by creating

career structures in research, and encourages commercial investment while protecting against the erosive influence of vested interest.

Knowledge and its implementation also need effective channels for communication. The *BMJ* has played a direct part in at least one of these advances and born witness to all of them. Now the new *BMJ* provides an even better (and better looking) communication channel—a space in print and online where researchers and clinicians can meet, where they can share what they have experienced, thought, or found and where others can confirm, refute, build on, reject, or implement their findings. The new *BMJ* will save you time and effort by covering the important developments in medicine. It will present the evidence based certainties where they exist and the controversies and debate where these are needed. Our aim is to create a journal that helps doctors make better decisions—whether in clinical practice, public health, policy making, or research—to improve the future care of patients.

Fiona Godlee, editor, *BMJ*

Alexander Fleming discovers penicillin in a mould

1929

Daniel Darrow advocates oral and intravenous rehydration solutions to treat infantile diarrhoea

1949

4560 RP, later called chlorpromazine, is synthesised by the chemist Paul Charpentier of the Rhône-Poulenc company

1950

Richard Doll and Austin Bradford Hill and Ernst Wynder and Evarts Graham publish first reports linking tobacco and lung cancer

1950

Carl Djerassi and colleagues (from the Mexican drug company Syntex) synthesise the first oral progestogen, norethindrone

1951

Francis Crick and James Watson publish their paper proposing the double helix structure of DNA

1953

Archie Cochrane publishes *Effectiveness and Efficiency: Random Reflections on Health Services, on the importance of using evidence to provide equitable health care*

1972

1914

First world war begins (ends 1918)

1939

Second world war begins (ends 1945)

1952

George VI dies, succeeded by Elizabeth II

1999

World population reaches six billion

A BRIEF TIMELINE

Let's pension off the major breakthrough

Geoff Watts

Look, I know we all love lists, competitions, prizes, and so on and that choosing the top 15 milestones in medicine is just a bit of fun. But, like the artistic and literary types who get snuffy about the Turner prize for art and the Orange prize for fiction, I'm going to be po-faced and argue that in one respect this enterprise is not only daft but damaging.

It plays to the "breakthrough" view of science: a wholly misguided notion that seeks to portray science as a kind of intellectual trawler. Under the guidance of its steersmen—the elite scientists high up on the bridge—the vessel charts a steady and calculated course across our sea of ignorance. Triumphant figures call down periodically to report that they have fished out another drifting barrel of knowledge and have drunk of the wisdom discovered therein. When what's found in the barrel is deemed exceptionally valuable—a "major breakthrough"—the crew members win medals.

In reality there is not one vessel but many; not one course but a thousand. And the information in the barrels often bears less resemblance to an illuminating draught of fine wine than to a small and bewildering cloud of fog. Which should be no surprise because, in truth, knowledge doesn't suddenly appear in neat and tidy quanta. Like patches of lichen spreading across a rock face, it accretes over decades.

Even medical research's brightest aren't always fully aware of the significance or meaning of what they're engaged in. A sometime colleague at the BBC World Service, a reporter, used to say that César Milstein didn't twig the likely practical impact of monoclonal antibodies until questioned about it by that reporter. As both men are now dead the claim is difficult to verify.

But we do know for a fact what the Nobel prize winning immunologist Frank Macfarlane Burnet wrote 35 years ago about research in cell and molecular biology: "I do not expect conventional benefits to medicine or technology from biological

Knowledge doesn't suddenly appear in neat and tidy quanta. Like patches of lichen spreading across a rock face, it accretes over decades

research to be common in the future. If they should arise they can be accepted as bonuses, but need not be expected." Isn't this a bit wide of the mark?

One man who did understand the fitful and faltering progress of science was Arthur Koestler. By charting the history of astronomy, with all its errors, misapprehensions, blind alleys, and perpetual shuffling between faith and reason, he exposed its true nature. He titled his magisterial account of our changing view of the universe *The Sleepwalkers*. The evidence is clear: there never has been a road map.

One of the most striking illustrations of the piecemeal accumulation of knowledge in science is the byproduct of a painstaking but largely forgotten 1976 study by Julius Comroe and Robert Dripps of the Universities of California and Pennsylvania. Using as an example the medical conditions most familiar to them—cardiovascular and pulmonary disease—they set out to show how clinical advances are often built on work that, at the time it was done, had no clinical application in mind.

Their intention was to make a case for more spending on basic research. To demonstrate the value of research they systematically traced the sources of the knowledge underpinning 10 key advances made over the previous 30 years: the drug treatment of hypertension, for example, and the development of cardiac surgery.



Convex and Concave (1955) by M C Escher

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Comroe and Dripps then showed that these 10 advances were, between them, founded on what they described as 137 "bodies of knowledge." Over several years they tracked down 2500 scientific reports that had played a major part in the development of these bodies of knowledge.

One of the 137 is the development of electrocardiography. As Comroe and Dripps say, "Some might consider that [Willem] Einthoven in 1903 invented the ECG [electrocardiograph] in its 1976 form without help from those who preceded or followed him." Their survey paints a different picture. They discovered that well over 40 published reports had played an essential part in permitting the creation and refinement of electrocardiography. The first of these reports dated from 1660; the last appeared in 1967.

Their comment is as germane now as it was 30 years ago: "We believe that a major defect in education in science in high school and colleges is the perpetuation of the one person=one discovery myth . . . Marconi=wireless; Edison=electric light."

While we're waiting for action on that front, how about a simple experiment? Try entering the phrase "major breakthrough" into the Google search engine along with the word "medicine." On the day I tried it I got 309000 hits. With so many major breakthroughs it's really rather difficult to understand why there are any medical problems left to solve.

So here's a modest but constructive proposal for starting to bring a little more realism to the discussion of new developments in medicine and medical research. Whether we're doctors or scientists, editors or reporters, let's all take a vow: to be parsimonious in our use of the term "medical milestone"—and to abandon entirely the words "major breakthrough." Let this clichéd old soldier be pensioned off for good.

Right, got that off my chest. Now, back to that top 15.

Geoff Watts, freelance medical journalist, London



James Young Simpson's chloroform bottle

Symbol of humanitarianism

Stephanie J Snow

In the 19th century anaesthesia was heralded as a civilising factor of the Western world. In the 21st century, anaesthetics continue to evolve and are the most vivid exemplar of medicine's capacity to lessen suffering

In the anaesthesia room I stroke my 6 year old daughter's hair and watch the liquid enter her veins through the cannula. A large yawn, closed eyelids, and a lolling head signal the shutdown of her conscious self. After her fractured elbow has been repaired, she wakes, remembering nothing except the prick of the needle. To contemplate this happening without anaesthesia is almost impossible. Today's medical interventions may produce discomfort, but rarely do they cause the intense pain that was once endured in operations before anaesthesia. The discovery of a method to alleviate pain during operations is rightly regarded as a landmark in the history of medicine.

By the early 1840s successive cultural and medical changes had resulted in a view of physical pain as purposeless. Doctors had become the masters of pain relief, and the rapid growth in consumption of opiates in Britain from the 1780s indicates that patients welcomed use of the drugs to palliate the pain of chronic disease, death, and childbirth. But the pain of operations remained, despite attempts to circumvent it. Alcohol and opiates were used during operations, but too much of these depressed the body's systems and exacerbated the dangers of surgery. At the same time surgeons began to approach surgery differently. Rather than amputations, they excised diseased or injured tissue and bone; new operations for cataract, stammering, squinting, and club foot were recorded in the *Lancet*. But more complex operations increased the duration of surgery and thus the duration of suffering. Few patients consented to operations unless absolutely necessary.

The Yankee dodge

Some pioneers carried out experiments with nitrous oxide and ether to suspend consciousness—for example, the physician Crawford Long and the dentist Horace Wells in the United States. But these experiments gained little recognition, because breathing gas carried the danger of asphyxia and, ultimately, death. That William Morton succeeded in establishing the use of ether by

demonstrating its effects at the Massachusetts General Hospital in October 1846 is due partly to serendipity (the ether worked and did not cause asphyxia) and partly to Morton's great ambition to expand his dental business with a method of numbing the pain of teeth extraction. Within six months news of ether had spread worldwide.

Anaesthesia became integrated into the structures of 19th century science only when news of ether—the “Yankee dodge”—reached doctors in London. Here John Snow, a young general practitioner (who later achieved fame with his theory of cholera transmission), was among the first to witness the use of ether for a tooth extraction and was captivated by the gas's power to produce “quietude” in patients. But, unlike others, Snow did not rush to treat patients. Instead he began chemical and physiological experiments to establish the parameters of the new technique and developed an inhaler that took into account the relation between temperature and “strength” of ether vapour. In just six months Snow had described the different degrees of anaesthesia that marked ether's sequential suspension of consciousness and volition. Snow's continuing standing among 21st century anaesthetists shows how impressively he secured ether within scientific bodies of knowledge.

Snow mastered the intricacies of ether, but other doctors struggled. Ether's irritant qualities made it difficult to breathe, and ill designed inhalers that gave too little of the vapour stimulated rather than subdued patients. Victorian society prided itself on self control and fortitude, so the spectacle of wriggling and riotous bodies clashed with social mores. Anaesthesia might have remained on the margins of medicine had it not been for the introduction of chloroform by the Scottish obstetrician James Young Simpson in 1847. Simpson discovered chloroform by chance when testing a number of volatile fluids in the hope of finding one that was easier to breathe than ether. Chloroform was less irritating to the lungs and produced unconsciousness swiftly. It immediately replaced ether.

It is hard to overstate the extent to which anaesthesia revolutionised the experience of surgery for patients and surgeons, although it remained a selective practice until the 1860s. It also reconfigured surgical practice: patients were far more willing to be operated on for small injuries, and thus operations became more common.

The risk of haemorrhage and infection continued to deter surgeons from operating in the cavities of the body; nevertheless, it is likely that anaesthesia was a strong stimulus for developing methods to diminish infection. Pain in childbirth too was alleviated by anaesthesia, and Snow's administration of chloroform to Queen Victoria for the births of Prince Leopold in 1853 and Princess Beatrice in 1857 effectively silenced the debate on its risks in labour.

A civilising factor

By the end of the 19th century anaesthesia had become a symbol for the wider humanitarian movement. It was proclaimed as one of the civilising factors of the Western world and remains the most vivid example of medicine's capacity to diminish human suffering. In different circumstances anaesthesia may well have emerged in a different form. Mesmeric anaesthesia, although rejected by the London medical elite as quackery in the early 1840s, was successful in India. But a world entirely without anaesthesia is unimaginable.

Anaesthesia continued to develop in the 20th century: muscle relaxants and techniques such as spinal anaesthesia brought new benefits; anaesthetists extended their practice to intensive care and the management of chronic pain; and new inhaled and intravenous anaesthetic agents facilitated the development of day case surgery. The detail of anaesthesia will surely continue to evolve. But nothing is likely to be as significant as the early demonstrations of ether's potential to alleviate the pain of surgery.

Stephanie J Snow, research associate
Centre for the History of Science, Technology and
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The epitome of a wonder drug

Robert Bud

The discovery of antibiotics not only heralded a dramatically new approach to infection control and health care but also enabled nations to prosper and overturned the concept of health as a moral duty

Antibiotics can truly be considered the epitome of the 20th century's "wonder drugs." This term was widely used in the 1950s, expressing the enthusiasm of patients, doctors, and policy makers for drugs that transformed once mortally feared bacterial infections into curable conditions.

Penicillin is the iconic antibiotic. Its introduction into clinical practice was widely celebrated and was the culmination of individual achievements, long running trends in science, and a supportive environment. In 1929 Alexander Fleming, at St Mary's Hospital Medical School in London, reported his observation that the culture medium on which a penicillium mould had grown attacked certain bacteria. However, chemists and bacteriologists, then working largely separately, failed to isolate the active substance in the mould juice. Only in 1940 was the isolation achieved, at Oxford, where Howard Florey had created a multidisciplinary team. The team's efforts were sustained by the interest and talent of, among others, Ernst Chain, a German refugee, and Norman Heatley, who developed key techniques for growing the mould and isolating the drug. But the financial support of the Rockefeller Foundation in the United States and the Medical Research Council in the United Kingdom was also crucial, as were the need created by the outbreak of war and the remarkable properties of penicillin itself. This confluence of factors led rapidly to laboratory scale production and the demonstration of penicillin's clinical potential.

Cheap production, mass protection

When British industry, under the pressure of German bombing and with little experience in sterile fermentation, failed to take up penicillin with enthusiasm, Florey and Heatley flew to the US to seek help. There they found expertise in chemical production by fermentation and in growing organisms in deep tanks, even aerobic ones. This expertise made cheap mass production possible.

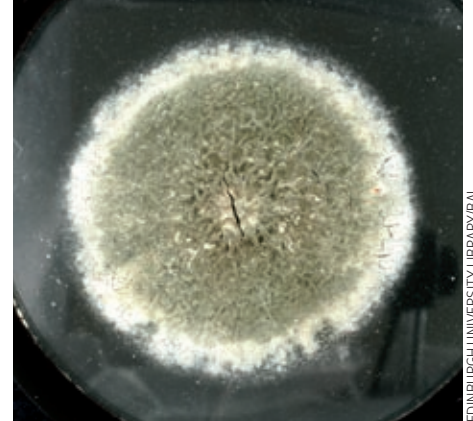
From the time of the Allies' invasion of Italy, soldiers were protected by penicillin not

just from infected wounds but also from the effects of sexually transmitted diseases. Compared with the previous long and risky treatment for syphilis, penicillin provided a swift and effective cure. This would prove a critical benefit in Europe during the early postwar years, when a syphilis epidemic threatened the occupying armies and the impoverished former Axis countries alike. Syphilis might then have proved the threat to Europe that AIDS would later pose in Africa, but penicillin stopped the epidemic decisively.

However, antibiotics had wider consequences than strictly medical ones. The new drugs underpinned a surge in the use of health services in the postwar years. Fast throughput in general practice was possible because antibiotics could be swiftly administered or prescribed after a short consultation. Surgeons undertook more complex operations on patients now protected from infection.

Even more profound were the moral consequences of the use of the drugs. Until the mid-1930s prevention rather than cure had been the general means of control of most infections. Injunctions to the healthy were complemented by a moral disdain for those who lapsed and then succumbed to disease. The introduction of antibiotics in the 1940s converted illness into a strictly technical problem. In richer countries the avoidance of "germs" gradually ceased to be a duty. The immunologist Frank Macfarlane Burnet expressed a then widespread (if eventually misplaced) hope in his *Natural History of Infectious Disease* (1953) that the mid-20th century represented a revolution in human history—the "virtual elimination of infectious disease as a significant factor in social life."

Undoubtedly, other factors also drove the transition in the health of richer nations. Better nutrition and housing were among the most important, but there were also technological innovations. The synthetic sulphonamides, developed in the 1930s, predated the antibiotics derived from natural organisms, but bacteria quickly developed resistance to them. Also, many people suffered severe side effects, and the spectrum of action of



A penicillin mould presented by Alexander Fleming

the drugs was not great by later standards.

The broader category of antibiotics soon developed. Their name had been claimed as early as 1942, when—following quickly on the isolation of penicillin—other new antibacterial drugs were derived from fungi and streptomyces. Selman Waksman, a soil microbiologist at Rutgers University, chose the word to describe those substances "inhibiting the growth or the metabolic activities of bacteria and other micro-organisms by a chemical substance of microbial origin."

Genomic advances

Antibiotics developed rapidly after the second world war, but since the early 1960s few fundamentally new families of antibiotics have been introduced, and at the beginning of the 21st century 14 million people a year die of infectious disease. From the mid-1990s multiply resistant staphylococci and resistant pneumococci have caused widespread anxiety across a world that seemed at imminent risk of the emergence of bacteria that were resistant to all known antibiotics. Resistance has become a public health issue worldwide.

The contemporaneous emergence of genomics gave rise, initially, to the prospect of the selection of many completely new antibiotics through a series of new technologies. The sequencing of bacterial genomes, understanding of the molecular basis of pathogenicity and protein expression, and combinatorial chemistry would, it was hoped, generate huge libraries of potential agents for screening. Such advances have not yet yielded large numbers of new drugs, and the popularity of antibacterial vaccines to combat such diseases as pneumonia has once again emphasised prevention rather than cure. Two generations after the introduction of antibiotics can we see—in the renewed concern for cleanliness in hospitals and greater reluctance to use antibiotics in the community—the revival of the hygienic and perhaps even the moral disciplines that predated the antibiotic revolution?

Robert Bud, principal curator of medicine
Science Museum, London



The Madhouse (1865) by Telemaco Signorini

Unlocking psychosis

Trevor Turner

The discovery of chlorpromazine ushered in a radically changed biological and psychosocial psychiatry that saw an end to the neglect and desperate remedies of the asylums

The sights, sounds, and smells of untreated psychosis linger down the ages, from Shakespeare's Mad Tom in *King Lear* to the screaming inmates of the forbidding New York mental hospital in Anatole Litvak's *The Snake Pit*, 1948's most shocking cinema event. In his *Experiences of an Asylum Doctor* of 1921, the retired general practitioner Montague Lomax described the "lunatics in the refractory ward of our public asylums. Bestialised, apathetic, mutinous, greedy, malevolent ... their habits quarrelsome and filthy, their persons dirty and malodorous." The carefully controlled therapeutic aridity of the ever enlarging lunatic asylum system was the institutional response: museums of madness with their collections of certified inmates.

Yet by the 1940s university research departments and entrepreneurial drug companies were busily synthesising new compounds. By 1926 acetylcholine was known to be a neurotransmitter; in 1937 the anti-histamines were discovered and in 1943 LSD. Psychiatry and its patients—stigmatised, dangerous, some psychoanalysed, but mostly hopeless—were receiving new physical treatments, such as insulin coma therapy, electroconvulsive therapy (ECT), and leucotomy. Sedatives such as bromides, barbiturates, and paraldehyde were available, the last overused for "the noisy and troublesome patient." From the phenothiazine group of the antihistamines, the drug 4560 RP, later called chlorpromazine, was synthesised in 1950 by Paul Charpentier, a chemist with Laboratoires Rhône-Poulenc.

The rise of psychopharmacology

A French surgeon, Henri Laborit, had begun experimenting with antihistamines in 1949, to aid anaesthesia when operating on soldiers in shock, and he noted how some patients became obviously calmer. On moving to Paris he asked for the new 4560 RP, hoping it would enhance autonomic blockade, and on 19 January 1952 a 24 year old man who had mania was injected with chlorpromazine. The report of the experiment described how he lay calm for several hours with his eyes shut.

Within three weeks he had largely settled. But he had also been given ECT, an analgesic, and a barbiturate, so was this a specific effect of chlorpromazine?

Several trials began, but it was Pierre Deniker and his assistant Jean Delay, at St Anne Hospital in Paris, who won the publication race. They treated 38 psychotic patients with injections of between 75 mg and 150 mg a day of chlorpromazine, publishing their findings in the *Annales Médico-Psychologiques* in 1952. Describing the events in 1970, Deniker commented on the limited information about the drug and the "sudden, great interest of the nursing personnel," who were usually "reserved about innovation." The wards were transformed, "aggressiveness and delusive conditions of schizophrenia improved," and contact with the patients re-established.

By 1954 chlorpromazine had been actively used and researched in double blind trials in Canada, the United Kingdom, and the United States, although diehard US psychoanalysts continued to consider it no substitute for "analytically orientated psychotherapy." Because of the drug's combination of effects (and side effects), by 1955 its French researchers decided to call it a neuroleptic ("taking hold of the neuron"). From 1956 the numbers of inmates in UK asylums began to fall dramatically, and over the next few years antidepressants and antipsychotics arrived en masse. A new world of a truly biological as well as psychosocial psychiatry had begun.

Without the discovery of drugs such as chlorpromazine we might still have the miserable confinements witnessed by Montague Lomax—a world of desperate remedies. Then the attendant's role was akin to a zoo-keeper's: feeding, scrubbing, and forcibly treating hundreds of "demented" patients. The psychiatric workforce was largely cut off from surgical and physician colleagues, was of poor quality, and was readily mocked. Ernest Jones, Freud's biographer, remembered jokes about psychiatrists discussing "varieties of Chubb lock" at their meetings. Our modern, multiskilled mental health workforce might never have emerged from

the demeaning nature of the tasks required. The modern emphasis on users and their carers would have been impossible, given the inarticulacy of the patients, locked in their mutism and word salads, and the revulsion and despair of the carers.

A psychic penicillin

The lifetime prevalence of psychoses (schizophrenias and severe bipolar disorders) is about 2% to 3% worldwide. Their effects are prolonged, incapacitating (in terms of self neglect and social unacceptability), and even fatal, with 10% or more of patients committing suicide. It is hard not to see chlorpromazine as a kind of psychic penicillin, enabling patient and carer to communicate and transforming our understanding of human function—neuropsychologically, interpersonally, and in evolutionary terms (as the gene mutation for big forebrains probably carries the risk of psychosis). Importantly, modern psychopharmacology dynamically reflects brain function, enabling non-moralistic assessment of emotions and judgments.

Every clinician longs for more effective, ever safer treatment, whether it be anti-psychotic, antidepressant, anxiolytic, or antibiotic. But the holy grail of psychiatric research probably remains the definitive test or scan that will crack the diagnosis and link psychiatry to scientific medicine. However, genetic markers such as those postulated for schizophrenia tend to attract life insurance salesmen and notions of eugenics; patients prefer being talked to rather than scanned; and clinical skills can become lost in technology.

Yet if the progress initiated by the discovery of chlorpromazine means that we can replace baggy words like depression with psychobiological descriptions like monoamine deficiency syndrome, or paranoid schizophrenia with temporal lobe hyperdopaminergia, we may yet eradicate the monsters of stigma and neglect that still beset mentally ill people.

Trevor Turner, consultant psychiatrist
Homerton Hospital, London

Transcending our limits

Alejandro R Jadad, Murray W Enkin

By transcending physical, geographical, and cultural barriers computer technology can help achieve optimal health for all

The capacity to compute is at least as old as life itself. It has been driven for billions of years by organic software encoded in elaborate sequences of base pairings embedded in DNA. Thanks to this biological computing system, nature was able to explode into a diverse community of living things as simple as prions and as complex as humans—creatures armed with deliberative computers, their brains.

The hominid brain continued to evolve over hundreds of thousands of years, gaining increasing layers of interconnecting neurones. This complex interconnectivity gave us the ability to recognise our limitations and our mortality and set us on an inexorable quest to overcome them.

A perpetual overcoming

Since the Stone Age we have evaluated, interpreted, calculated, and computed. As we observed the effects of our primitive interventions we tried, tried again, and modified our technology. Our legs could take us only so far, until we extended their reach through increasingly sophisticated means of transportation—technology that took us across land and sea and through the air. We overcame the limits of our visual acuity with lenses, opening new vistas of the heavens and the microcosm. Our clinical gaze was augmented by new understandings of anatomy, physiology, and pathology. New tools, such as the stethoscope, radiography, and anaesthesia, let us listen to and see into the human body and tinker with it.

Inevitably, we moved beyond augmenting our limbs and our sense organs. Our powerful brain began to realise its own limitations. With its insatiable urge for self

improvement and its unparalleled parallel processing capacity it began building tools to enhance itself. We created external devices that exponentially increased our ability to calculate, analyse, and learn.

It took us two millennia to jump from the Babylonian abacus to the mechanical eight digit calculator that Pascal built in the Enlightenment. After only two centuries Charles Babbage envisaged a massive, steam powered mechanical calculator designed to print astronomical tables. Less than a century later Alan Turing created Colossus, an electronic computer that helped end a war plagued by our self destructive drive and power.

Over only decades in the second half of the 20th century we developed powerful resources to communicate and exchange unlimited amounts of knowledge, almost anywhere and at any time. We created a global network of computers able to decode the genome; machines capable of seeing our body and its functions in three dimensions; tools to track and control diseases remotely. Computers started to change the way we learn, live, communicate, and heal.

Nevertheless, the effect of computers on the delivery of health services, even in rich countries, was not obvious. By the end of the century most people still lacked electronic health records, and few health professionals used email or even the phone as part of their clinical communication. Most budgets targeted the control or treatment of diseases, rather than prevention or health promotion. Collaboration across institutional or geographical boundaries was almost nonexistent. In deprived areas of the world computers had little effect on perinatal mortality, major infectious diseases, or access to clean water.

Twenty first century visions

Extrapolations of 20th century trends into 21st century visions are not optimistic. Transhumanists believe that our role will be over when our brains create intelligent machines that will continue the exponential pace of evolution for ever. Their views have been



Claudia Mitchell, recipient of a “bionic arm”

reinforced by the defeat of the best human at chess by a computer, the advent of pilotless aircraft and spaceships, the emergence of robots able to perform surgery without human intervention, and the creation of prosthetic limbs that can be operated mentally.

Apocalypics believe that what we call civilisation is nothing more than a dead end trap, leading to human extinction. Current trends in climate change and environmental degradation, the raised threat of nuclear conflict, the prospect of devastating pandemics, and the unmanageable burden of poverty, chronic diseases, and ageing are strong signals that the arrival of the four horsemen of the Apocalypse may not be far off.

Humanodes in the global superorganism

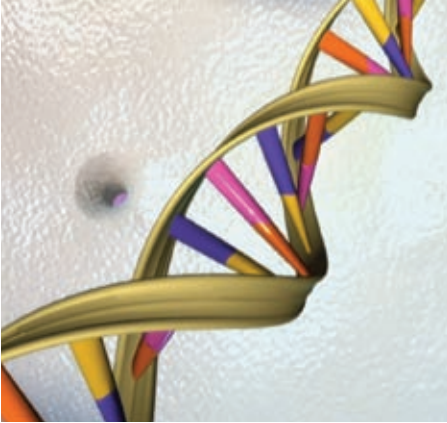
But extrapolation does not acknowledge the complexity of evolution. A more exciting scenario may be unfolding, in which the future is not predetermined by immutable forces but shaped by our values, our interactions, and our will to survive as autonomously as possible against all odds.

The 21st century computer age gives us the opportunity to create a “noosphere,” a true planetary thinking network with individual but interdependent humans as its nodes. The exponential development of wireless networks, mobile computing tools, and the internet may already be giving us a glimpse of a future in which we could work as “humanodes” in a true global superorganism.

Computer technology can help us achieve optimal levels of health and wellbeing regardless of who or where we are. It can help us transcend our cognitive, physical, institutional, geographical, cultural, linguistic, and historical boundaries. Or it can contribute to our extinction. We believe that the choice is ours. We hope that we choose, not just with information, not just with knowledge, but with wisdom.

Alejandro R Jadad, chair, professor, and founder
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Computer technology can help us achieve optimal levels of health and wellbeing regardless of who or where we are



DNA analysis is now important in many specialties

The best is yet to come

John Burn

Watson and Crick's discovery of the structure of DNA has opened up a world of possibilities in new treatments

If the competition to determine the 15 greatest medical milestones was judged on the basis of international recognition, then DNA, the ultimate in three letter acronyms, would easily win the prize. Indeed, as the greatest scientific discovery of the past millennium, the elucidation of the structure of DNA would rank very highly, if not first. Surely, then, a competition that focuses on 166 years of medicine would be a pushover—or perhaps not. For the effects of the discovery of the structure of DNA have yet to reach their peak. Once they have, the case for DNA will be unanswerably strong.

It is appropriate that I declare an interest. My interest in becoming a clinical geneticist was sparked by the excitement of having the code of DNA explained to my sixth form biology class by a visiting scientist. A similarly revelatory moment occurred much later when I took my daughter, who was killing time between her university interviews at Cambridge in 1994, to see the tiny brass plaque “celebrating” the 1953 discovery of the double helix in what is now a bike shed

As we marvelled at this manifestation of typical British understatement, our conversation turned to the imminent impact of the human genome project and, the next day, to a proposal that led to the successful effort to create the millennium landmark Centre for Life in Newcastle, which brings the wonders of DNA to visitors as well as being a centre for teaching, research, and genetic medicine.

Our biggest research project

It is easy, in retrospect, to regard that 1953 discovery by our centre's patrons, Jim Watson and the late Francis Crick, as but a minor step along the road from Gregor Mendel's discovery of the principles of single gene

inheritance in 1866 and Archibald Garrod's recognition in 1923 that alkaptonuria followed the same principles of genetic transmission. Geneticists were able to make great advances before the discovery of the double helix, not least Karl Landsteiner's recognition of blood groups in 1909; but as late as 1952 leaders in research had no idea how genes worked. It was Watson and Crick's recognition, at a stroke, of the digital basis of genetic information and the mechanism of inheritance that opened the floodgates to further discoveries. The most dramatic evidence of that flood of research is the human genome project, humanity's biggest research endeavour, which has permitted ever more rapid progress in linking variants in the sequences of genes to thousands of genetic disorders.

Gene testing for everyone

Genetic disorders are collectively a major health problem in the developed world, but even in these countries many doctors are liable to think DNA means “Did Not Attend.” Technology has not yet caught up with our aspirations, and sequencing is slow and expensive. However, this is changing as “array” technology and “lab on a chip” devices begin to allow low cost, high throughput genetic testing. Meanwhile, large scale projects such as UK Biobank will permit prospective studies that will link genetic predisposition to outcome in common diseases.

Already we are seeing breakthroughs in common diseases such as eczema and inflammatory bowel disease. Mutations in the gene coding for filaggrin, a protein that binds to keratin in skin cells, and in the CARD15 gene sequence are responsible, respectively, for a significant proportion of predisposition to these diseases and affect up to one in 10 people in each case. More importantly, such discoveries expose the relevant pathogenic pathways. New interventions that focus on epidermal permeability in eczema and on recognition in the gut of bacterial cell walls in inflammatory bowel disease are likely to be more important than direct testing of patients for DNA variation in the underlying genes.

Practising clinicians will probably remain

unconvinced: all these promising developments sound like “jam tomorrow.” Yet it is too easy to miss the significance of such developments in many fields. After severe acute respiratory syndrome hit the headlines around the world, no one expressed surprise when the nature of the infectious agent was published in a matter of weeks, a critical step that depended completely on the ability to analyse DNA. Virology and bacteriology have now embraced analytical techniques that are based on DNA testing with an enthusiasm equivalent to that seen in forensic science. In most developed countries every newborn baby is screened for the genetic condition phenylketonuria, and all surgical patients have their blood group analysed—more examples of how genetic science can reach the whole population without being recognised as “genetics.”

Leaping into the future

But the best is yet to come. Human factor VIII, used in the treatment of haemophilia, and human insulin will be followed by any number of human gene products whose manufacture will have its origins in that first report of the double helix. From hepatitis B vaccine to trastuzumab (Herceptin), an understanding of DNA permeates all sorts of developments in treatment. When the first patients are treated with a new stem cell treatment, few will note that treatment's critical dependence on our ability to unravel the genetics of early human development and to manipulate the genetic control of tissue differentiation.

Zhou Enlai, first premier of the People's Republic of China, is reported to have said, when asked to give his opinion of the French revolution, that “it is too soon to say.” Some might make a similar argument in the case of DNA. Such scepticism will risk ridicule in years to come. The evidence already before us is dramatic, but it is nothing compared with the tsunami to come.

John Burn, medical director and head of institute
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The most dramatic evidence of that flood of research is the human genome project, humanity's biggest research endeavour

Increasing, not dictating, choice

Kay Dickersin, Sharon E Straus, Lisa A Bero

The systematic synthesis of evidence is the foundation of all medical discoveries and of good clinical practice

Evidence based medicine is healthcare practice that is based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients' values and circumstances. It is curious, even shocking, that the adjective "evidence based" is needed. The public must wonder on what basis medical decisions are made otherwise. Is it intuition? Magic? The public must also wonder what happens to the research evidence in which they have invested—either directly through taxes or indirectly through buying drugs and other medical products—if it is not guiding clinical practice.

How could something so intuitively obvious to lay people not be similarly viewed by clinicians? And how could this medical milestone be so misunderstood by some? Critics of evidence based medicine worry that it dictates a single "right" way to practise, despite differences among patients; that some self appointed group of "experts" will declare only one type of study to be useful; or that healthcare decisions will be made solely on the basis of costs and cost savings.

Giving a name to evidence based medicine and, now, awarding it milestone status could help everyone to realise that it is about making decisions that are based on the best available evidence, not dictating what clinicians do.

Establishing a modern milestone

The term "evidence based medicine" was coined in 1991 by a group at McMaster University, Ontario. It arose from a confluence of events and changes in our culture. These included a growing recognition that:

- The systematic synthesis of all reliable information on a topic has greater value than traditional reviews
- Bias can explain results in many individual studies, and randomised clinical trials are now recognised as the study design that is best suited to avoiding bias in questions of intervention effectiveness, although other types of study may be better for other types of questions
- Tragedy can result from paying attention

It is curious, even shocking, that the adjective "evidence based" is needed

to poor quality evidence instead of good quality evidence

- Clinicians need information, and they don't get enough from the sources they typically use
- The medical literature is growing exponentially, and there is not enough time in the day to read even the good stuff, and
- Undesirable gaps and variation in practice exist.

Imagine a world without evidence based medicine. Most women with early breast cancer would still be undergoing mastectomy instead of lumpectomy and radiation. Now they can choose.

Many babies born prematurely would still be dying from respiratory distress syndrome, not having the advantage of a mother who took corticosteroids or of being given surfactant themselves.

Pregnant women in Boston might still be taking diethylstilbestrol to prevent miscarriage, on the enthusiastic recommendation of well respected local experts, with the result that many of their children would be developing reproductive abnormalities and cancer.

A boy with asthma might have his treatment changed every six weeks as new drug samples are dropped off at his doctor's surgery. The choice of drug to help prevent a second fracture in an elderly woman might be made on the basis of television advertisements.

Finally, without evidence based medicine, precious health resources might have been spent unnecessarily. In the United States, research into preventing and treating AIDS has cost \$30bn (£16bn; 23bn) since 1981. Had the research results not been applied to practice, more than 50% of hospital beds in the US would be filled with AIDS patients, at a cost of \$1.4 trillion. Similarly, without the application of cardiovascular research



Logo of the journal *Evidence-Based Medicine*

from 1982 to the present, the cost of treating these patients would be 35% higher.

Making the evidence accessible

What is the future for evidence based medicine? The biggest challenge will be getting all clinicians, consumers, policy makers, and other stakeholders on board. We need to help the naysayers to understand what evidence based medicine is and what it isn't. It seems obvious to say that we also need to seek evidence that it is useful. The results of evidence based medicine often clash with the agenda of special interest groups. The challenges created by rich and powerful manufacturers of drugs and devices cannot be overemphasised. Not to be left behind, the industry is developing its own systematic reviews and making them public.

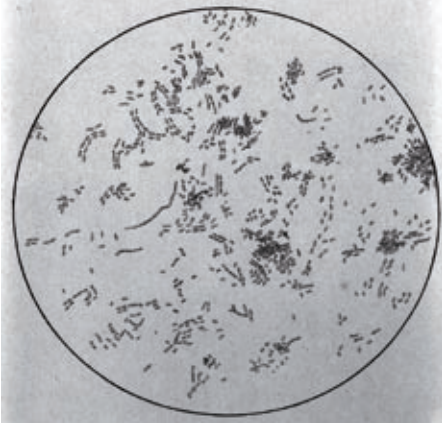
We need to alert clinicians and patients to studies showing that reviews sponsored by the industry almost always favour the sponsor's product, whereas those that aren't sponsored by such companies do not. We also need to provide patients and the general public with the tools to enable them to understand and evaluate systematic reviews. Finally, it is not enough to create high quality, evidence based resources: we need to ensure global access to them.

The question has moved beyond "Why is evidence based medicine important?" to "Why is it not already a reality?" and "How can we all work together to make it a reality, quickly?" Evidence based medicine is one of our most important medical milestones because, without it, the other 14 of the *BMJ*'s milestones would not have been implemented.

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Pasteur's drawing of *Mycoderma aceti* in vinegar

Invisible killers revealed

Harry Burns

Pioneers in several countries shed light on germs, enabling important insights in the prevention and treatment of infectious disease

In May 1847 Jakob Kolletschka, a Viennese doctor, cut his finger while doing an autopsy on a woman who had died of puerperal fever in the city's lying-in hospital. A few days later Kolletschka was dead. His autopsy showed features identical to those found in puerperal sepsis. His friend Ignaz Semmelweis concluded that the disease was being carried on the hands of medical students to the women in labour and insisted that medical students should wash their hands before attending deliveries. Mortality from puerperal sepsis among patients who came into contact with the students fell from 12% to 2%. By general consent Semmelweis had, through his action, turned the germ theory of disease into clinical reality.

Overcoming initial scepticism

Although Semmelweis is credited with being the first to recognise the clinical implications of the germ theory, the existence of particles as the cause of disease had been suspected since Roman times, and germs had actually been seen by Antonie van Leeuwenhoek in the 17th century. Indeed, when the lying-in hospital was opened in 1784 no autopsies were carried out because the director, Lucas Boer, apparently foresaw the danger of infection. In 1823 Boer's successor introduced autopsies for the purpose of teaching. The hospital had two clinics: medical students worked in the first clinic, and the second clinic was used for training midwives. Midwives did not participate in autopsies, and mortality from infection was much lower in their clinic. Recognising the importance of this disease pattern, Semmelweis took action that seems obvious to modern eyes but was far from accepted in Vienna at the time.

Semmelweis's work influenced Joseph Lister, working in Glasgow, who introduced antiseptics to his surgical practice. Lister was aware that carbolic acid was used to treat sewage, and he concluded that the same microbes that caused wound putrefaction might be killed through use of carbolic acid solutions to dress wounds. He also insisted that instruments and surgeons' hands should be washed with the solution. Mortality from

compound fractures fell in his wards as a result of these measures.

Neither in Vienna nor in Glasgow did these innovations meet with approval. Semmelweis left Vienna in 1850 to return to his native Hungary, after the Viennese establishment refused to accept his approach as scientifically valid. Similarly Lister failed to gain the support of the managers of the Glasgow Royal Infirmary for his antiseptics techniques. They argued, with some evidence to support their case, that surgical patients' nutritional state was more important to the outcome of surgery than antiseptics and refused to implement his recommendations. Lister left Glasgow for the chair of surgery in Edinburgh.

The scientific basis for the germ theory was eventually universally accepted after Koch's demonstration that infectious agents transmitted disease, Pasteur's studies of the metabolism of micro-organisms, and ultimately Fleming and others' work leading to the production of antibiotics and new ways to treat infection.

These insights into the prevention and treatment of infectious disease produced an epidemiological transition. They moved us from a society at the end of the 19th century in which infection typically caused 30% of all deaths to one at the end of the 20th in which less than 4% of deaths were due to infection. In 1900 one death in every 120 in the United States was due to infection—40% of them in children aged under 5 years.

By 1980 mortality from infectious disease had declined in the US to 36 deaths in every 100 000, and life expectancy had increased by around 30 years. The fall in childhood mortality had a profound effect on family size and fertility.

Advances in our understanding of hygiene, sanitation, and pathology that followed the development of germ theory have done more to extend life expectancy and change the nature of society than any other medical innovation.

In 2000 *Life* magazine published its list of the 100 most important advances of the previous millennium. It concluded that Gutenberg's invention of the printing press was the

The germ theory was the only medical advance to make it into *Life* magazine's top 10

most important, followed by the discovery of the New World. The germ theory, at number six, was the only medical advance to make it into the top 10.

Had the germ theory not emerged as an explanation for the common causes of death in the 19th century, it is hard to imagine that these major killers would have been overcome in any other way. Admittedly, Jenner had described variolation independently of the work of Semmelweis and Lister. Had anti-biotics not emerged as a treatment for bacterial disease, we might have been forced to explore enhancements of the immune system as a way to defeat infection. However, it is unlikely that such profound societal benefit brought about by our grasp of microbiological science would have been achieved in any other way.

Relearning old lessons

So what remains to be done? The systematic application of existing knowledge will yield many more advances. The developing world needs access to the sanitation and public health advances that have been so successful elsewhere. Research into infections such as HIV and malaria has to continue and expand. We need to improve our systems of surveillance and our understanding and detection of microbiological genetic mutation. We also need to continue research and to develop new ways to control infection. Perhaps the most depressing task that remains before us is to continually restate the lesson Semmelweis taught his medical students 160 years ago. Doctors and other healthcare workers are failing to wash their hands before contact with patients, and such failure is still costing lives. Resistance to the simple but lifesaving 19th century innovations remains alive and well in the 21st century.

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Revealing the world within

Adrian M K Thomas, John Pickstone

A chance discovery in a physics laboratory opened the body to sight—from bones to molecules—and where the eye has penetrated, the hand is now reaching

On 8 November 1895 a German physicist, Wilhelm Conrad Röntgen of Würzburg, was investigating the effects of passing electricity through rarefied gases. He was surprised to find that a distant fluorescent screen glowed in the dark. He was amazed when his wife placed her hand in front of the screen and a shadow image of the bones appeared. Röntgen communicated his discovery in a short manuscript entitled “Über eine neue Art von Strahlen” (“On a new kind of rays”), which he submitted to the Würzburg Physical Medical Society on 28 December 1895. He called the rays “X,” because their nature was unknown. In 1901 he was awarded the first Nobel prize for physics.

In the 19th century many researchers, stimulated in part by the work of Michael Faraday, had studied the passage of electricity through rarefied gases. In England in about 1880 William Crookes had developed an evacuated glass bulb with which he observed “rays” at the negative electrode or cathode. Röntgen was working with a Crookes tube when he discovered his x rays.

Opening new fields of discovery

Röntgen’s news spread rapidly around the world. The phenomena were readily demonstrable in scientific laboratories and also in public fairs. But classical physics could not explain the rays, and the era of modern physics began—a physics that was based on new understandings of atomic structure.

In medicine, too, x rays broke old assumptions. The new technology came into its own as an aid to surgery; it was particularly useful for locating needles and bullets and for visualising difficult fractures. X rays were used in the Italo-Abyssinian war of 1896, and in the first world war all the major armies had well organised radiological services. After that war x ray examinations became routine in civilian hospitals, and radiologists became established as medical specialists, now assisted by radiographers.

By this time, too, more robust tubes were available, and practitioners took precautions against the radiation burns that had cost the

hands or lives of many radiological pioneers. But despite awareness of the dangers of radiation, dedicated x ray machines were used in the mid-20th century as an aid in shoe fitting in many high street shops.

From shadows to slices

Modern digital radiology was introduced with computed tomography, which has transformed investigative medicine. The British designer of computed tomography, Godfrey Hounsfield, and the South African Allan Cormack were jointly awarded the Nobel prize for physiology or medicine in 1979. In this type of scanning Röntgen’s shadows are replaced by detailed, three dimensional images, usually viewed as “slices” through the body. Magnetic resonance imaging and positron emission tomography followed, firstly rendering the body effectively transparent and then revealing the sites of biochemical activity. For example, functional magnetic resonance images can now locate the areas of the brain associated with particular activities, such as listening to music.

X rays also found many other uses in science and industry, one of which was to prove hugely important for biology and medicine. X ray crystallography was pioneered by William and Lawrence Bragg in Britain; and in Cambridge after the second world war it proved the key to unpacking the structures of nucleic acids and proteins. That was the basis of molecular biology, which by the end of the century had redefined many areas of biomedical research and practice.

From investigation to intervention

Shortly after the discovery of x rays their therapeutic potential was realised, and alongside radium treatment they became a mainstay of cancer treatment and palliation. Therapeutic applications continue to develop today, most recently with intensity modulated radiotherapy, which uses a computer to match the beam of x rays to the three dimensional shape of tumours, minimising exposure of the surrounding normal tissue.

Cardiac catheters, initially used to visualise the coronary arteries in coronary artery



Radiograph of a hand (and ring) by W K Röntgen (1895)

WELLCOME LIBRARY, LONDON

The discovery of x rays led to an array of visualisation and interventional techniques that permeate modern practice and continue to astonish

disease, are now used to guide interventions such as angioplasty and insertion of stents. Thus radiology has advanced from diagnosis into treatment; it has become a tool used directly by physicians and surgeons. In rich countries, all cancers are imaged before they are treated. Modern medicine can hardly be imagined without imaging. But is this due only to the success of x rays?

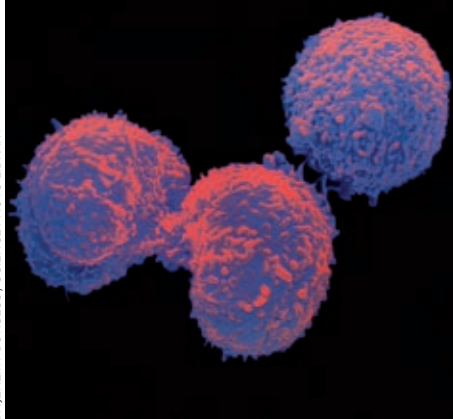
Some recent imaging techniques, notably ultrasonography, arose from technologies outside medicine and might have developed independently of x ray techniques. Computed tomography drew on mathematical principles of interest to several academic disciplines, but it was effectively developed for use with x rays. Magnetic resonance imaging originated in methods used for chemical analysis; but its adaptation to imaging, and the huge investments needed for this, depended on the prior success of computed tomography and hence on that of x rays.

At the root of sophisticated 21st century medical imaging we find a chance discovery in a 19th century physics laboratory. In transforming physics and later revealing the secrets of biological molecules x rays were the common root of the two great branches of 20th century science.

And for medicine the discovery led to an array of visualisation and interventional techniques that permeate modern practice and continue to astonish. Without x rays, doctors, like Röntgen, would be working in the dark.

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Hybridoma cells producing a monoclonal antibody

Making magic bullets

D Michael Kemeny, Paul A MacAry

Continuing developments in our understanding of antibodies are taking us into a future of limitless and highly specific treatments

Since the discovery of vaccination at the end of the 18th century our understanding of the immune system has advanced in leaps and bounds, and we now know how vaccination endows us with the capacity to fight invading pathogens. We appreciate too that our immune system has been shaped by the challenges of dealing with diverse infectious organisms and that similar immune mechanisms underlie conditions such as autoimmunity, allergy, transplant rejection, and tumour immunity, even though these may not involve invading pathogens.

Understanding of how the immune system distinguishes host cells from “foreign” cells leapt in 1958, when the French medical researcher Jean Dausset described the first of many human histocompatibility antigens (HLA antigens). Our immune system uses the pattern of HLA antigens on the surface of cells as a biological signature—one that is almost unique to each of us. Whenever the immune system does not recognise the pattern of HLA antigens on a cell it creates antibodies and other substances to attack and destroy it. This is the main mechanism for immune recognition of infectious organisms. It also explains why our immune system attacks transplanted tissues and organs.

Transplantation to monoclonal antibodies

In the 1950s a Boston based team of doctors led by Joseph Murray transplanted a kidney from a 23 year old man into his seriously ill identical twin. In the following years Murray (who won the 1990 Nobel prize for medicine) and international colleagues were able to show that by matching as many HLA antigens as possible between organ donors and recipients, and by adding therapies to reduce the immune response, organ transplantation was feasible. Since then bone marrow, kidney, liver, skin, heart, and lung transplants have saved more than 400 000 lives.

Greater understanding of the biological weapons that make up our immune system has resulted in antisera and monoclonal antibody technology. This has had a major effect on disease diagnosis and is emerging as an impor-

tant area for therapeutics. Two early pioneers of antibodies were Emil von Behring (Nobel prize for medicine, 1901) and Paul Ehrlich (who won the prize in 1908), who described the development and standardisation of antisera treatment against diphtheria toxin. Karl Landsteiner (Nobel prize for medicine, 1930) used von Behring and Ehrlich’s theories on antisera in 1909 to develop the A, B, AB, and O blood group antigen system, thus leading to the widespread use of blood transfusion.

In 1978 two scientists based in the Laboratory for Molecular Biology in Cambridge, Césaire Milstein and Georges Köhler, showed that single clones of cells that produce antibodies could be formed by fusing individual plasma cells with immortalised B cell myelomas, thus producing millions of identical progeny secreting a single type of antibody. These monoclonal antibodies have revolutionised the diagnosis of disease through their application in immunoassays. Harnessing the sensitivity of radioisotopes and enzymes, monoclonal antibodies are used to diagnose and monitor human disease, to ensure the quality of food and other biological materials, and to test for trace amounts of drugs and toxins. They have enabled scientists to visualise the outside and inside of cells, stimulating new imaging technologies such as flow cytometry (used to analyse fluorescently tagged blood and tissue cells) and confocal microscopy (for investigating the interior of our cells).

Initial use of monoclonal antibodies to treat disease in humans was limited, because the molecules were produced in mice and induced an anti-mouse response in the human host. Later, Gregory Winter and Michael Neuberger at the Laboratory for Molecular Biology discovered how to engineer the combining site of the mouse monoclonal antibody into the human immunoglobulin gene. The resulting chimeric antibodies, called humanised antibodies, could now be given to patients with little or no anti-mouse response.

The benefits of humanised monoclonal antibodies in the treatment of otherwise intractable diseases have been dramatic. Monoclonal antibodies to an inflammatory protein have been administered to over a million people

with rheumatoid arthritis, with a spectacular reduction of symptoms. An antibody that depletes B cells shows remarkable efficacy in treating autoimmune diseases such as systemic lupus erythematosus. Monoclonal antibodies have helped reduce organ transplant rejection by inactivating the T cells that drive the host’s response to the transplant. Passive vaccination with monoclonal antibodies may be used to fight new infections such as bird flu. The applications appear endless and include use in cancer, where monoclonal antibodies can target radioactive and other cytotoxic agents precisely to the tumour, in the so called magic bullet approach.

Limitless possibilities

Where will all this end? It is not really clear yet. Because monoclonal antibodies are so incredibly diverse, new and remarkable properties of antibodies continue to emerge. Some antibodies can mimic the action of specific ligands such as hormones; others can block or inactivate receptors on cell surfaces. For example, a monoclonal antibody has been generated that binds to the human IgE receptor and displaces the patient’s own IgE without triggering the hypersensitive response of mast cells and basophils and thus blocks the allergic attack. The number of antibodies produced by mice is as many as 10^9 , and a complete recombination of variable genes performed ex vivo (when there is no elimination of self reactive clones) yields as many as 10^{12} different combinations. Thus the properties and specificities of antibodies that can be selected are effectively limitless. Indeed, it is estimated that more than a third of all drugs currently being developed by drug companies are monoclonal antibodies, and hence antibody technology will enable many more medical milestones to be reached in the foreseeable future.

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The simple solution for saving lives

Olivier Fontaine, Paul Garner, M K Bhan

A simple and cheap oral solution, tested in refugee camps in the 1970s, has prevented millions of deaths among children with diarrhoea

Each day at the height of the monsoon season in the early 1970s 6000 starving refugees from the India-Pakistan war poured into refugee camps: a cholera epidemic was inevitable. The sheer volume of patients meant that the government of India, the state government of West Bengal, and non-governmental agencies simply could not provide enough intravenous saline solution or staff to administer it, and 30% of patients died within a few days.

One witness to the tragedy was Dilip Mahalanabis, who, as a member of staff of the Johns Hopkins Center for Medical Research and Training in Calcutta, had helped develop a new oral rehydration solution to replace the water and electrolytes lost through vomiting and diarrhoea. Oral rehydration therapy had been discovered a few years earlier simultaneously in Kolkata (Calcutta) by N F Pierce and in Dhaka by N Hirschhorn but had only ever been used by paediatric specialists in tertiary referral hospitals. Mahalanabis seized on the idea that the therapy might work in this dire catastrophic context too. His team weighed out the ingredients in Kolkata, tipped them into plastic bags with simple instructions, sealed them with a hot iron, and rushed them to the camps. Relatives, parents, and health staff urged patients to drink large volumes of solution in the early stages of their illness. Over eight weeks mortality fell to less than 1%.

An amazing discovery

However, the medical establishment was sceptical about these dramatic results and rejected Mahalanabis's paper reporting them. It took a visit from Dhiman Barua, a cholera specialist from the World Health Organization, for the enormity of the discovery to be realised. He was amazed by what he saw: basic health orderlies, parents, and relatives all treating cholera successfully with just oral rehydration solution. Barua understood then that not only could the solution treat cholera but it also had the potential to completely revolutionise the community management of diarrhoea in children.

His vision led to the creation in 1978 of WHO's diarrhoeal disease control programme, which has popularised this treatment throughout the world. It is simple and it works—and a systematic review in the Cochrane Library has shown that even in developed countries there are no clinically important differences in effectiveness and safety between oral and intravenous fluid replacement. In 1970 Mahalanabis had to prepare his own packets; now close to 500 drug companies produce oral rehydration solutions, the formulation of which was recently improved for greater effectiveness.

In the 1980s nearly five million children under 5 years old died each year from diarrhoea. In 2000 this figure had dropped to 1.8 million. Oral rehydration is central to the package of measures that has helped ensure this fall in mortality. At the beginning of an episode of diarrhoea the child is given increasing amounts of fluid prepared at home, to prevent dehydration. If the child is already dehydrated, oral rehydration solution is given at home or in healthcare centres, and if this fails intravenous fluid replacement is given. Feeding and breast feeding continue during the illness and are increased after the episode, and antibiotics are used only when appropriate, such as when the child has bloody diarrhoea or shigellosis.

Diarrhoea as a cause of death in young children has fallen from 33% of deaths to 18% since the 1980s, and this decline is largely responsible for the fall in total mortality in young children over this period. David Sack, director of the International Centre for Diarrhoeal Disease Research in Bangladesh, said, "To save the life of a person with diarrhoea is probably the cheapest health intervention you can think of."

Fifty million children's lives saved

Without oral rehydration treatment, and with a roughly static incidence of three episodes of diarrhoea every year, children in poor countries are faced with a potentially life threatening infection every four months; and in families of four children, every month of the year the parents would be likely to have a



Oral rehydration has saved millions of young lives

"To save the life of a person with diarrhoea is probably the cheapest health intervention you can think of."

child with an infection that has the potential to kill. With the proper use of oral rehydration therapy these risks become almost zero. Because more than 50 million children's lives have been saved over the last 25 years, thanks to oral rehydration, a large chunk of the adult population in developing countries is alive today.

What does the future hold? Vaccines against rotavirus could be important but are currently expensive. Oral rehydration solutions have been improved since the early days: the formula was adjusted after a Cochrane Library systematic review in 2001 showed that a less concentrated solution had better outcomes. And the treatment strategy now includes giving zinc for a couple of weeks, as this not only reduces the severity and duration of the episode but also protects the child from further episodes in the following 2-3 months.

These improvements will make management of diarrhoea even more successful. But the great challenge is how to reach all children who are still suffering and dying from diarrhoea and who belong to the poorest section of the population. It is a tragedy that 1.8 million preventable deaths from diarrhoea occur every year just because children do not have access to this cheap, easily prepared solution. There is still a desperate need worldwide to promote and distribute this life saving intervention and help parents use it when their child becomes sick with diarrhoea.

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GESA KERKMAN

The pill gave women contraceptive autonomy

Emblem of liberation

Carl Djerassi

The pill is one of the few drugs to have remained essentially unchanged decades after its synthesis—testament to its enduring value

“What sort of pill?” is a question that very few readers seeing the topic of this article would ask themselves.

Surely, that already tells us something about the popularity of an oral contraceptive that I, an organic chemist, would call 19-nor-17 α -ethynyltestosterone (norethindrone, or some other closely related progestogen) combined with 17 α -ethynylestradiol. What single procedure or vaccine would be known by the equivalent labels of “the operation” or “the jab?” The answer is none. Yet does the persistent popularity of “the pill” warrant adding the invention of the oral contraceptive to the list of 15 greatest medical milestones since 1840? To justify my affirmative answer, I first need to define what in my view does not qualify as a medical milestone.

Clean drinking water and effective sewage disposal are of enormous benefit to public health, but in my book they are not a medical milestone because only the consequence, and not the originator, is medical in nature. Lifestyle changes such as stopping smoking, with its fantastic health benefits, still would not qualify for me. Also, basic research advances that are far from the actual medical application won't qualify, because then we would also have to include important chemical synthetic reactions and analytical methods that make possible many chemical syntheses of substances that eventually become drugs.

Making waves around the world

Nevertheless, there is such a mass of truly important, practical, and medically unambiguous milestones that have affected millions of people that selecting the 15 most important seems to me patently impossible. For instance, how would I compare the eradication of a global scourge such as smallpox or polio with the importance of oral contraceptives? Such disease eradication should win hands down, since other types of birth control always did and do exist. So why did I agree to make a case for the inclusion of the pill among the 15 exalted milestones? The

primary reason is that no other milestone has had as many societal, “non-medical” consequences; the pill is a stone thrown into water that has produced ripples and waves way beyond any reasonable expectation, for the following reasons.

- The pill and intrauterine devices raised the expectations for contraceptive effectiveness to an extraordinarily high level, with enormous favourable consequences for millions of women.
- The pill offers women the ability to decide on their own, in private, whether or when to become pregnant, thus undermining the historical dominance of men in all matters relating to sex and reproduction. The consequences range from cultural to economic, professional, and educational aspects, most of them positive.
- The pill and intrauterine devices introduced reversible birth control that was independent of the sex act, completely changing the nature of sexual intercourse, which now ranges from unworried pleasure to undisciplined promiscuity.
- The pill was the first potent drug to be consumed for years by millions of “healthy” people, thus raising questions of defining safety and the risk-benefit balance in the long term that were quite distinct from those for other drugs taken over long periods (such as cholesterol lowering drugs), where the “benefit” was the prevention of a medical condition. The more serious the disease, the higher the tolerance for side effects, cancer being a classic example. In the case of the pill the “disease” is an unwanted pregnancy, for which the level of tolerance of side effects is very low. The discipline of epidemiology has probably been improved in depth and sophistication more through the thousands of studies of the pill than of virtually any other drug.
- No other drug has had such an enormous effect on religion. For instance, Catholic couples, faced with their church's opposition to contraception, often make family planning a higher priority than avoiding “mortal” sin.

If these examples are not convincing, adding more to the list—such as that the pill is the preferred method of reversible contraception in more than half the countries in the world, that more than 80% of women in the US have at one time used the pill, or that about 100 million women worldwide at any one time are on the pill—would probably be overkill.

An enduring classic

Considering this implied panegyric, you might think that current research into even better methods of birth control would be flourishing. Nothing could be further from the truth. Of the 20 largest drug firms in the world, only three are active in modest efforts to improve the pill. The very long development time (about 12–15 years, because of the need to study the side effects from long term use), the fear of litigation, and the current emphasis on blockbuster multibillion dollar drugs aimed primarily at elderly people make research in this field highly unpopular. In fact, desired demographic changes, whether in “paediatric” countries (those where population growth is undesirable) in Africa, Asia, and parts of Latin America or in the “geriatric” countries of Europe and Japan (where the opposite holds), now depend much less on changes in contraceptive “hardware”—the actual means of birth control—than on “software” considerations, the legal, economic, cultural, educational, and public health conditions in each country. As a result, the active ingredient of the pill, though seemingly sold under hundreds of labels worldwide, is still limited to about half a dozen slight chemical variants of the first oral progestogen, norethindrone, which was synthesised in a small Mexican company in 1951. The fact that norethindrone is still being consumed by millions of women is one of the relatively rare examples (aspirin being the most famous) where the original chemical is still being used in unmodified form decades after its original synthesis.

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All done and dusted

Simon Chapman

Two landmark studies in the 1950s led to a growing body of evidence for the harmful effects of tobacco and a decline in the prevalence of smoking, despite the efforts of the tobacco industry to fight back

After tobacco was introduced from America to Europe in the 16th century and then to the rest of the world, its detractors lost little time in condemning the practice, which was popularly reputed to benefit health. Early medical reports, including the French physician Nicholas Andry de Boisregard's 1701 warning that people taking too much tobacco could suffer a withering of their "noble parts," presaged later epidemiology on smoking and erectile dysfunction. In 1771 the *Encyclopaedia Britannica* recorded "a person who through excess of smoking had dried his brain to that degree, that after his death there was nothing found in his skull but a little black lump, consisting of mere membranes."

Serendipitous research

Fumophobic tracts from luminaries such as Robert Baden-Powell and Henry Ford were imbued with the language of moral turpitude. A generation grew up hearing that smoking might "stunt your growth." But the real risks of smoking became clear only after a serendipity in 1950: two major case-control studies on smoking's harms were published, one by the Americans Ernst Wynder and Evarts Graham in the *Journal of the American Medical Association* and the other by the United Kingdom's Richard Doll and Austin Bradford Hill in the *British Medical Journal*.

These findings triggered an avalanche of research. Where results were publicised by the media and governments the prevalence of smoking began to fall. Although in the 1950s most countries reported a prevalence of smoking among men of more than 60%, today smokers are typically outnumbered by more than three to one in areas where tobacco control is taken seriously. In California just 9.8% of people smoke daily.

People smoking 20 cigarettes a day for 40 years will baste their lungs with a toxic, carcinogenic fog 2.9 million times. In compelling them to do this, nicotine has caused unparalleled mortality. Unlike their forebears before 1950, advocates of tobacco control now have the dismal luxury of "great" statistics on which

to make their case: worldwide about five million people die each year from tobacco related illness. Among risk factors for disease, only hypertension and malnutrition kill more people than does tobacco.

In developed countries alone, between 1950 and 2000 smoking caused about 62 million deaths or 13% of all deaths (20% of deaths in men and 4% in women). It has been estimated that tobacco will cause about 150 million deaths worldwide in the first quarter of this century and 300 million in the second quarter. In the United States each smoker loses on average 13 years of life. The World Health Organization estimates that by 2020 "the burden of disease attributable to tobacco will outweigh that caused by any single disease."

These are numbers to die for. Yet too often the hazards of smoking fail to create a sense of urgency among the media, policy makers, and the public. The statistics are so stratospheric that they have become almost banal. As Stalin said, "A single death is a tragedy; a million deaths are a statistic." The number of deaths from cancer arising from the 1986 Chernobyl nuclear reactor meltdown is predicted to rise to 16000 by 2065. The International Agency for Research on Cancer stated that "tobacco smoking will cause several thousand times more cancers in the same population." Few news bulletins picked up on that comparison.

Tobacco control and falling cancer mortality

For all the money poured into cancer research in recent decades, most of the progress in reducing cancer mortality has been due to deaths avoided through successful tobacco control.

The American Cancer Society recently examined how much the decline in smoking had contributed to the decline in deaths from all cancers in the US. It concluded: "Even our most conservative estimate indicates that reductions in lung cancer, resulting from reductions in tobacco smoking over the last half century, account for about 40% of the decrease in overall male cancer death rates."

"A more realistic straight line projection of what lung cancer rates might have become



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Cigarettes: now a mark of social disadvantage?

suggests that, without reductions in smoking, there would have been virtually no reduction in overall cancer mortality in either men or women since the early 1990s. The payoff from past investments in tobacco control has only just begun."

In the early 1980s, while the tobacco industry was still reeling from growing public awareness of the dangers of active smoking, the second horseman of the industry's apocalypse rode into view: the emerging epidemiological evidence for the harmful effects of secondhand smoke. This broadened the ethical foundations of tobacco control: harming oneself invites paternalistic advice, but harming others justifies laws to protect the community. A Rip van Winkle awaking from a 20 year sleep would be astounded by the cultural transformation of the status of smoking from a pleasant, mannered pastime to a badge of low education, social disadvantage, and ostracism. Cigarette packets have metamorphosed from elegant boxes to pathology museum exhibits.

At the end of the 1990s the tobacco industry was further undermined by the release under the US Master Settlement Agreement of more than 60 million pages of its internal documents. This effectively halted the industry's longstanding public denials of the dangers to health of smoking, designed to undermine public awareness campaigns.

Smoking may well continue to be a major health problem in much of the world. However, the world's first legally binding health treaty, the World Health Organization's Framework Convention on Tobacco Control, entered into force in February 2005. Now ratified by 140 nations (but not, notably and disgracefully, by the US), it will unleash unprecedented worldwide controls on the vector for tobacco related disease: the tobacco industry. The force of these events, first set loose by researchers in 1950, means that the end game for smoking may well be just 20 years away in the vanguard of nations where smoking is currently in free fall.

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Demonstration model of sanitary fixtures (1895)

At some time in the 1780s the Industrial Revolution began—firstly in Britain then in other European countries. Technical and commercial advances enabled European societies to break through their pre-industrial production ceiling. Expanding industry attracted labourers and their families to towns and cities, which grew rapidly, at the expense of rural areas. In terms of economic output these transformations were an immense success; in terms of human well-being they were not. Unplanned urbanisation, appalling working conditions, and low wages led to a deterioration in the health of much of the population.

Infectious diseases exacted a huge toll in morbidity and mortality, among them tuberculosis, diphtheria, measles, smallpox, typhoid, and typhus, as well as the “enteric fevers,” whose causes were hotly disputed. We now know that dysentery is caused by ingesting food or water contaminated with faecal micro-organisms in environments where sanitation and access to clean water are inadequate. But at the time popular explanations included the “miasma” theory that fevers were caused by foul damps arising from decaying organic material.

It was cholera, another consequence of economic progress, particularly the increase in international trade and transport, that “concentrated people’s minds.” The second, third, and fourth pandemics reached Western Europe in the 1830s, 1850s, and 1860s. Observations on the spread of cholera, as in John Snow’s studies around London’s Broad Street pump, improved understanding of the causes of enteric disease. His pragmatism (turning off the pump in the face of general disbelief among his peers that water was the source of cholera) has rightly become famous. And the psychological effects of cholera epidemics, which threatened poor and rich people, fostered a collective response.

The British sanitary revolution

As with the Industrial Revolution, Britain also led Europe in the “sanitary revolution,”

Pragmatism works

Johan P Mackenbach

Despite erroneous theories of disease causation and the lack of an evidence base, new sewage disposal and water supply systems in the 1800s revolutionised public health in Europe

although some ideas came from France. Edwin Chadwick was its champion, neither a medical doctor nor a sanitary engineer but a lawyer who had designed the 1834 Poor Law Amendment Act and who wanted to cut the costs of poor relief by preventing a major cause of poverty: acute infectious diseases that killed male breadwinners.

Chadwick believed that these diseases were caused by air contaminated as a result of poor urban drainage. He developed a comprehensive solution: new technologies (sewers rinsed by water, his main reason for bringing piped water to individual homes) and the legal and administrative structures needed to build these expensive works.

Britain took decades to implement these measures, and they spread only slowly to the rest of Europe, but in the end they had a major effect on mortality. In the Netherlands, for example, the first large municipality with piped drinking water was Amsterdam (1854), followed by Rotterdam and The Hague in the 1870s. By the end of the century around 40% of Dutch people had piped drinking water, and in the early 20th century sewerage systems covered more than half the population. Between 1870 and 1970 age standardised mortality in the Netherlands fell by almost 75%. An important contribution to this decline was a fall in the numbers of deaths from infectious diseases, including deaths from respiratory tuberculosis (down 15%), acute respiratory diseases (11%), and acute digestive diseases (8%). Between 1901 and 1970, when a more accurate classification of causes of death was used, a fall in mortality from “diarrhoea and dysentery” accounted for 12% of the overall decline in mortality in the Netherlands. Similar figures were reported for England and Wales.

Paradoxically, what is probably one of the major breakthroughs in public health lacks the empirical underpinning we now think is essential for evidence based health policy. Not only were the theories incorrect, but empirical evaluations have produced less than convincing results. Contemporaneous studies were often too crude to produce reliable evidence. More sophisticated studies

that retrospectively related mortality to better water supply and sanitation have produced conflicting results. Perhaps the strongest support comes now from poor countries, where evaluation studies, although still beset by methodological problems and inconsistencies, support a substantial effect of improved water supply and sanitation.

One review showed that morbidity and total mortality from diarrhoea among children were reduced by about a fifth. Better water quality seems to have had less effect than better water availability or disposal of excreta. The global burden of disease study ascribed 1.8 million deaths in 2001 in low and middle income countries to diarrhoeal disease. Unsafe water, sanitation, and hygiene accounted for 88% of these deaths, indicating that substantial health gains can be achieved by extending the global coverage of adequate water supply and sanitation.

The causation paradox

Improved water supply and sanitation are often held up as exemplars of how best to improve public health, not only in the past but also now and in the future. Of course, it is easy to read too much into a single historical event; and that Chadwick succeeded despite his defective theory of disease causation may have been good luck. Nevertheless, we can still draw three lessons from this tale.

Firstly, effective intervention does not always need accurate knowledge of disease causation. Secondly, environmental measures may be more effective than changing individual behaviour (piped drinking water and sewerage systems worked better than educating the public to improve hygienic practices).

And thirdly, universal measures may be better than targeted measures in reducing health inequalities. These lessons have become part of the “collective consciousness” of public health, and this tale can still inspire us to always search for pragmatic solutions to population health problems.

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Solving the mysteries of viruses

Yvonne Cossart

Tissue culture methods have played a major part in the work of more than a third of the winners of the Nobel prize for medicine since 1953, and without it gene therapy and stem cell research would be impossible

Tissue culture entered mainstream medicine in 1949 when the US scientists John Enders, Thomas Weller, and Frederick Robbins reported that they had grown poliovirus in cultured human embryonic skin and muscle cells. This achievement soon led to methods for measuring immunity to polio and to the award of the Nobel prize for medicine to the three scientists in 1953. Fifty years on we are on the brink of eradicating polio by using vaccines derived from cell cultures, and cells are grown on an industrial scale to yield vaccines, antibodies, and other biological products such as recombinant factor VIII for haemophilia.

In his Nobel lecture Enders described the technical difficulties encountered before the second world war in efforts to grow viruses in culture and how, after the war, antibiotics were used to keep bacterial contamination at bay. The new accessibility of tissue culture methods ushered in the golden era of virus discovery. It also revived many previously unattainable ambitions in medical science, having a crucial role in no fewer than 18 of the 52 subsequent Nobel prize winning discoveries, including RNA interference (the 2006 winner), the nature of oncogenes (1989), monoclonal antibodies (1984), tumour viruses (1975), and virus genetics (1965).

An old dream is realised

Although short term survival outside the body of the beating heart and twitching muscle was known to the ancients, serious attempts to achieve lengthy tissue survival in vitro were possible only in the second half of the 19th century. Among the pioneers were embryologists, who studied the early development of amphibian and avian eggs and began to experiment on “organisers,” soluble messengers that directed organ development. With the advent of cell culture the nature of these growth factors could be elucidated. Modern stem cell research is the most exciting and controversial descendent of this work.

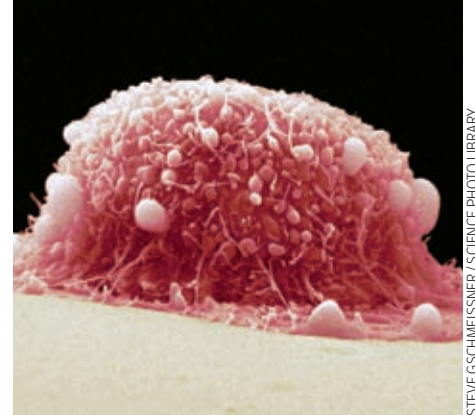
Surgeons had dreamt of organ transplantation since the Middle Ages. In the 1920s and

1930s Alexis Carrel, a French surgeon working at the Rockefeller Institute in New York, collaborated with the aviator Charles Lindbergh to overcome the technical challenges of organ perfusion. Their tissue survival studies attracted enormous public interest, fuelled by newspaper reports such as “birthday” notices for one culture of chick embryo cardiac muscle cells. Before the second world war Thomas Strangeways and Honor Fell in Cambridge used cell culture as part of their multidisciplinary approach to bone and joint disease, paving the way for the recognition of tissue specific markers, which are now so widely used in diagnostic pathology.

After the second world war, the serial subculture of cells was achieved through the use of trypsin to produce single cell suspensions, antibiotics to control contamination, and better growth media, such as the famous “199” with its 64 ingredients. The finite number of divisions achievable in the culture of normal cells contrasted with the “immortality” of cancer cell lines.

HeLa, the most famous of these, was derived from the cervical cancer that killed Henrietta Lacks in 1951. Continuous lines were used to develop convenient in vitro methods for testing the efficacy of potential anticancer drugs and the carcinogenic effects of drugs and chemicals. The demonstration of integrated viral genes in many tumours and of similar homologues in normal cells revolutionised concepts of growth regulation. The discovery of mutations in these homologues—the cellular “oncogenes”—in cancer tissues and in the normal cells of family members with an inherited risk of cancer had applications in cancer diagnosis and screening.

By the 1960s, cell culture technology was well established in virology and cancer research. The time was right for the interaction between cell biology and genetics that gave birth to molecular biology. Study of the chromosomes of dividing cultured cells spawned the new discipline of cytogenetics, while work on gene expression began to explain the mechanisms involved in differentiation, which could now be observed



A HeLa cell (scanning electron micrograph)

in vitro. This ultimately produced skin cultures that could be used for grafting, but its more profound consequences resulted from elucidating the functions of T cells as they proliferated in vitro after stimulation with antigens.

Exquisitely specific antibodies

Fusing cultured benign and malignant cells provided important insight into the control of cell division, and the technique was spectacularly exploited to generate “hybridomas” between myeloma cells and B cells to produce monoclonal antibodies.

Immortalised cell lines now provided a potentially unlimited source of antibodies of exquisite specificity for enzyme linked immunosorbent assay and radioimmunoassay, and monoclonal antibodies are now being used in the treatment of haematological malignancies.

The ability to transfect cultured cells with DNA gene sequences has allowed us to assign functions to different genes and understand the mechanisms that activate or redress their function. Gene therapy has yet to fulfil its promise, but it may ultimately overtake the many other medical applications of cell culture.

Without cell culture we would lack vaccines against measles, mumps, and rubella and would still be dependent on much more expensive and reactogenic vaccines for polio, rabies, and yellow fever. We would be unable to karyotype patients with suspected genetic disorders or to perform in vitro fertilisation. Antibodies for diagnostic or therapeutic use would be derived from immunisation of whole animals—with much greater variation in titre and specificity than products derived from cells. Our concepts of growth, differentiation, biological ageing, and malignant transformation would be simplistic; and gene therapy and the use of stem cells to repopulate damaged organs or to clone individuals would be beyond imagination.

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"Cowpox battling the medical profession" (plaque)

Louis Pasteur's introduction in July 1885 of a rabies vaccine that contained a laboratory attenuated live virus deserves the title of the greatest medical milestone for three reasons. First and foremost, Pasteur's innovation introduced the laboratory modification of micro-organisms by attenuation, to render them less pathogenic but still immunogenic. Vaccines have saved hundreds of millions of lives and spared generations the suffering and long term consequences of infections. Although this reason alone would make Pasteur's work the leading medical milestone, two other reasons make the case for vaccines unanswerable.

Pasteur's rabies treatment was the world's first medical breakthrough to be recognised and celebrated in the public domain. Pasteur was hailed in the press as a great benefactor of humanity and to have opened a new era in medicine. Finally, his high profile and the support he gained garnered funds to establish the Pasteur Institute in Paris, the world's first purpose built medical research institute and the model for others that were established soon after, such as the Robert Koch Institute in Berlin, which opened in 1891, and what became the Lister Institute, opened in London in 1893.

Milkmaids and cows, children and dogs

It can be argued that the breakthrough with vaccines actually occurred a century earlier, with Edward Jenner's introduction of vaccination against smallpox in 1796. Jenner was a country doctor in Gloucestershire who had noticed that patients, especially milkmaids, who had suffered from cowpox (also known as vaccinia) were subsequently immune to the deadly smallpox. He first trialled and then promoted inoculation with small doses of vaccinia pustules, which he assumed carried the poison, as a preventive measure—terming the inoculation "vaccine." Although it attracted much scepticism, news of Jenner's innovation spread rapidly round the world. Smallpox was greatly feared, and it seemed miraculous that so many thousands of lives could be saved; indeed, such was the standing of "vaccine"

that Pasteur named his own methods after it. However, Jenner's innovation was a one-off, and subsequent attempts at emulation, such as inoculating material from syphilis sores to treat infection, failed. By comparison Pasteur's breakthrough was grounded in knowledge and techniques that have been the basis for all the vaccines we have today.

Pasteur, who was not a doctor, shifted his attention from vaccines for anthrax, sheep pox, and rabies in animals to those for human disease, because of medical interest in the new microbiology and because of the possibility, in the case of rabies, of building up immunity during the long incubation period. Pasteur announced his breakthrough in October 1885, giving graphic accounts of the cases of two children, savagely bitten by rabid dogs, who faced certain death until treated in his clinic. Medically, an untreatable disease had been conquered. Such was the excitement this generated that some doctors and scientists immediately looked to the eradication of major communicable diseases.

At this moment all things seemed possible for medicine, and the next decade seemed to prove this. Frightening killer diseases could be cured, as Pasteur's coworkers contributed to the development of antitoxic sera for diphtheria and tetanus; but they could also be prevented, as protective vaccines using inactivated micro-organisms were developed against cholera, typhoid fever, and the plague.

In the 20th century vaccines for many more bacterial and viral infections were introduced. To imagine a world without vaccines is to imagine a world threatened with smallpox, which was eradicated in the 1970s largely through vaccination campaigns. In the United Kingdom today only older generations will remember the predations of childhood diseases made rare by jabs now taken for granted: diphtheria (1923), whooping cough (1926), measles (1963), rubella (1969), polio (1958 and 1961), and measles, mumps, and rubella (1969). For example, from 1920 to 1940 between 40 000 and 70 000 cases of diphtheria were notified each year in the UK, but by the 1990s the number was around 10

Conquering untreatable diseases

Michael Worboys

Vaccines have saved hundreds of millions of lives. All modern innovations can be traced back to Pasteur's 1885 breakthrough with rabies vaccine

a year. In the 1950s as many as 7500 cases of polio were reported in a year; in the whole of the 1980s there were only 25. The incidence of tuberculosis—the principal cause of death in adults a century ago—was reduced by the BCG vaccination, introduced in 1927. Many elderly people now receive flu shots every year, as do high risk workers, who also receive hepatitis A and B vaccines. And would we have the same confidence about travelling overseas if it weren't for yellow fever jabs or modern versions of the vaccines introduced in the 1890s?

New delivery systems and new targets

There is no reason to suppose that the future of vaccines will be any less remarkable than their past. The greatest benefit to humanity would be for all current vaccines to be made available in all countries and to all groups across the world. Greater diffusion should be aided by new delivery systems—aerosols and skin patches—and by the move away from vaccines that need cold storage.

Molecular biology means that we can look forward to preventive and therapeutic vaccines for common infections such as those from staphylococci and pneumococci, for parasitic diseases such as malaria and schistosomiasis, for recent infections such as HIV, viral haemorrhagic fever, and severe acute respiratory syndrome, for autoimmune diseases, and even for infective cancers. Indeed, a vaccine against human papillomavirus and thus against cervical cancer was approved very recently and could be seen as a medical milestone in its own right.

Although Pasteur brought the great benefits of medical innovation to the public's attention and pioneered the institutionalisation of medical research, it is because of the present and future potential for vaccines to save lives and prevent suffering that we can consider his 1885 discovery to be the greatest medical milestone.

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I've got a little list

Jeffrey P Koplan

We all enjoy top 10 lists or other numerical variants, be they selections of riverside pubs, classic rock guitarists or neurosurgeons, the world's best beaches, or the Mann-Booker shortlist. Such lists allow us to focus our own views and congratulate ourselves for our good taste or astute judgment: "The list seems valid, as they chose Mark Knopfler, Jeff Beck, and Eddie Van Halen." They also permit us to scoff at the ignorance or lack of taste of the compilers: "Where are Joe Perry, Dickie Betts, and Stephen Stills?" But I digress.

Rarely do these lists have the explicit quantitative criteria that would satisfy a Cochrane collaborator. But the fun—and frustration—is in the subjectivity of the choices. If readers find themselves in agreement with over half the list then some modicum of satisfaction is achieved. Thus all *BMJ* readers will have turned, with a sense of anticipation mixed with scepticism, to the list in this supplement of the top 15 (egregious inflation of the more decimally traditional 10 or the more familiar dozen) medical milestones of the past 166 years. The list was developed by inviting nominations from readers, and then a final selection was made by a panel of experts—a quasi-democratic cum oligarchic process that is highly likely to lead to an untidy outcome. Unlike pubs, guitarists, or novelists, a medical milestone may mean quite different things to different people. It certainly would include leaps forward in diagnosis and treatment, but it also permits the inclusion of methodological or experimental advances that are far upstream from their bedside application. The impact in numbers of lives saved or diseases averted or controlled could be a factor in identifying a milestone but is not so clearly stated or universally accepted.

Let's look at the *BMJ*'s top 15. In the diagnostic category we find imaging. Several therapeutic advances are listed: anaesthesia, antibiotics, oral rehydration therapy, and chlorpromazine. Now we move across the menu to items that can be lumped into preventive measures (the pill, vaccines, sanitation), theories (the germ theory), technology (computers), basic scientific discoveries (the structure of DNA), epidemiological discoveries (risks of smoking), approaches to medical science (evidence based



JEFF ROBERSON/AP

medicine), major disciplines of bioscience (immunology), and a laboratory technique (tissue culture). This is a most interesting and varied group of milestones, certain to stir debate and elicit reflection. One common feature of all these milestones is that their existence and significance were likely unforeseen when the *BMJ* was established in 1840, but they have all had a major effect on the length and quality of life.

I'll admit to some bias. In 1999-2000 I initiated, at the US Centers for Disease Control and Prevention (CDC), a top 10 list of public health achievements of the 20th century in the United States. Although this exercise was specific to the US, other high income countries have had similar achievements. A considerable overlap exists between the CDC's list and the *BMJ*'s final 15 milestones: half the items on the CDC list (effective and reliable birth control, antibiotics, vaccines, recognition of the risks of tobacco and the institution of effective tobacco control programmes, and water and sanitation) are also represented on the *BMJ* list. But the missing five items merit discussion here: improving safety and reducing hazards in the workplace; providing safe and nutritionally enriched foods; preventing motor vehicle injuries and deaths; improving oral hygiene; and recognising the risks for coronary heart disease and instituting actions to reduce morbidity and

Rarely do these lists have the explicit quantitative criteria that would satisfy a Cochrane collaborator. But the fun—and frustration—is in the subjectivity of the choices

mortality from the disease. All these items have had a major and direct effect on quality of life. For example, more and healthier teeth permit a more varied and enjoyable diet and better nutrition; healthier diets and fortified food have eliminated micronutrient disorders such as rickets, goitre, pellagra, and iron deficiency from large populations across the globe. And the items have reduced the number of preventable deaths and injuries: the number of injuries sustained by miners, railway workers, and factory workers fell by 90% in the US from 1933 to 1997; rigorous governmental standards have reduced exposure to toxic substances in most industries; mortality from motor vehicle collisions has fallen, thanks to safety equipment, better highway design, education, and a reduction in associated risk factors such as alcohol use; and millions of life years have been saved through large reductions in the prevalence of smoking in many countries. (A new book by J W Ward and C Warren, *Silent Victories* (New York: Oxford University Press, 2006), describes these achievements.)

These two lists encourage a discussion of the relative contributions of biomedical science and public health. Biomedical science has won more Nobel prizes, while public health has had a greater role in reducing morbidity and mortality and improving our quality of life. Of course, each approach contributes to the other. We need to develop safe and effective vaccines for serious illnesses; and we need to be able to deliver these vaccines to people at risk. Similarly, even as we develop an understanding of the human genome, we must make this knowledge practically useful and economically feasible and must ensure that benefits of research are distributed equitably and ethically.

So, peruse the *BMJ*'s top 15 milestones, consider the pipeline of discovery and experience that led to them, and imagine their future evolution. In another 166 years, which of the items in the list will still be considered milestones? The current list is interesting and provocative but, of necessity in such lists, incomplete. So, where's Eric Clapton?

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