Rediscoveries

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What is discovery? For many centuries it was thought that it was no more than the revelation of the work of an Almighty Creator, a view still held by some among the faithful. Furthermore, until the late Renaissance if discoveries conflicted with the clerical interpretation of the Divine Will as revealed in Holy Scripture then the discoverer might find himself having to abjure his views, as did the aged Galileo when he knelt before the Most Eminent and Most Reverend Cardinals Inquisitor-Generals in 1633 and promised to abandon "the false opinion that the sun is the centre of the world and does not move and the earth is not the centre of the world and moves."¹ Nevertheless, his heretical views were subsequently sustained and, as they were scientifically established, required no rediscovery but confirmation. William Harvey, whose own views on the circulation of the earth around the sun are not known to us, had the good fortune that nothing is said in the biblical record about the circulation of the blood, so that, unlike Galileo, he had to contend only with scientific detractors. His work, too, however, was an example of a discovery so firmly based on the scientific method that it required neither confirmation nor rediscovery.

Divine gifts

Healing has always been associated in the popular mind with the miraculous, and it is perhaps for this reason that medical discovery was for so long thought

to have its origins in the divine. It was considered, for example, that the presence in certain botanical species of substances that might have beneficial effects was a reflection of the beneficence of a Creator who had liberally distributed plants with such qualities throughout the world. Their discovery or rediscovery, not necessarily by medical professionals, was to be achieved as a result of the use by mankind of that intelligence that distinguished the greatest of God's creations from all other species. Similarly, the widespread distribution of mineral waters, whose supposedly beneficial effects were for so long the mainstay of medical treatment, were a divine contribution to the welfare of mankind. Mercifully, unlike bleeding and purging, taking the waters seems to have been for the most part a harmless pursuit, though now virtually outmoded. By contrast, the removal of evil humours from the blood by venesection has an echo of rediscovery in the current vogue for plasmapheresis, which is considered to remove evil immune complexes from the circulation; and purging is reflected in the modern era by the fashion for fibre, whose consumption has been thought, like purging, to remove all manner of evil influences from the colon.

Revealed not created

Much of scientific discovery has always, in fact, been revelatory. The structure of DNA in the cells of the men who created the great cave paintings of Lascaux was presumably no different from our own, and the current surge towards the sequencing of the entire human genome will succeed in showing something that has been present since long before the ancient Greeks, the authors of the hieroglyphic record, Alexander the Great, or Julius Caesar. Whether scientific discovery can be regarded as truly creative, as is often claimed by scientists, is uncertain, as it is axiomatic in science that discoveries should be repeatable. Scientists may share with creative artists similar qualities of imagination, but the production of a symphony by Beethoven, a play by Shakespeare, and a painting by Rembrandt are clearly unique events and can never be repeated by any other person. And if Bach's *St Matthew Passion* had been destroyed in the years after his death, as could well have happened, it would never have been recreated by Mendelssohn and his friends, who rediscovered the music in the nineteenth century. By contrast, much of scientific discovery, so wondrous a process to all who search out the secrets of nature, would, it has been claimed, be revealed sooner or later regardless of individual brilliance. It is for this reason that priority occupies so central a position in the scientific mind. And it is for this reason too that the historical pathway of science, and of medical science in particular, is paved both with discovery and with rediscovery.

Technological masterpieces

The achievements of technology, however, must be considered differently. They undoubtedly do require creative genius, but once discovered they are usually

Frontispiece to "Dialogue on the two chief world systems" (1632) by Galileo. As a result of his views Galileo was brought before the Inquisition on charges of heresy

Taking the waters at the Pump Room, Bath by Humphrey Repton (1789)

not forgotten and rarely neglected. The creation of the steam engine and Arkwright's spinning jenny and the techniques of radiography, computed axial tomography, and nuclear magnetic resonance are all examples of creative technology that has produced inventions that were not already in existence (as is the human genome) waiting to be revealed but which required the genius of unique people to create. Furthermore, there is another important distinction from science. Despite the popular view that the wheel is constantly being rediscovered, once a great technological advance has been made it rarely has to be rediscovered and is usually put immediately to use. Gunpowder needed no rediscovery, nor did any of the great technological advances of our own era, which include the internal combustion engine, powered flight, instant communication throughout the globe, and all of the horrendous apparatus now available to nations for the destruction of each other. Such awesome achievements will not be rediscovered and they have all been used. Perhaps the only major exception to this generalisation is the microscope, which for more than a century after Leeuwenhoek lay scientifically unexploited.

William Withering (1741-99) learnt of the valuable effects of digitalis because of its use in folk medicine

Jenner's rediscovery

In the history of biomedical science, however, there are many examples of rediscovery. During the past three centuries much that came to belong to medical science was in fact a rediscovery of something already existing in the rich underworld of folk medicine. The establishment of digitalis as a cardiac drug in the 1780s owes everything to the recognition by William Withering of its presence in a concoction for dropsy used by an elderly herb woman in Shropshire. Similarly, the earliest methods for preventing smallpox were known in many different parts of the world long before the established profession of medicine discovered them. The first protective measure was the technique of inoculation, in which material was taken from a smallpox vesicle of an afflicted person and inoculated into the skin. A mild and usually non-fatal attack of the disease would ensue, and thereafter there was lifelong immunity. In Europe in the seventeenth century smallpox scabs could be rubbed into the skin, and this was done in areas as far apart as Wales, Poland,

and southern Italy. In 1700 a paper to the Royal Society in London described the Chinese method of inoculation, dating from antiquity, in which crust material was inserted into the nostrils. Yet so far as western Europe is concerned, the technique had to be rediscovered in 1718 in Constantinople by Lady Mary Wortley Montagu, wife of the British Ambassador to Turkey, and it was she who introduced it into Britain. By the second half of the eighteenth century the technique was widely practised as a preventive measure in Britain.²

There are those who argue that the replacement of inoculation at the end of the eighteenth century by Jenner's discovery of vaccination, published in 1798, was a rediscovery, for the idea that cowpox might prevent smallpox was not new. In 1765 Fewster had written a paper entitled "Cowpox and its Ability to Prevent Smallpox." Four years later Bose in Germany called attention to the protection against smallpox enjoyed by milkmaids, as was also well known to Jenner. Nash in 1781 suggested that the inoculation of cowpox might be preferable to smallpox inoculation as

Benjamin Jesty (1737-1816) vaccinated with cowpox 24 years before Jenner

it was neither fatal nor infectious. Perhaps the most important claim to have preceded Jenner was that of the Dorset farmer, Benjamin Jesty of Yetminster, who vaccinated both his wife and his two sons with cowpox material in 1774, 24 years before Jenner's publication.³ There is no evidence that Jenner knew of these attempts. Furthermore, although Jenner's technique may be classed historically as a rediscovery, he was the only investigator of the beneficial effects of cowpox inoculation to have followed up his vaccination with an attempt to inoculate smallpox in the traditional Turkish manner and to show that he could no longer infect his subjects. It was he, therefore, who quite justly received the reward by parliament of £10 000 in 1802 and £20 000 four years later, despite the claims of others.

Slow to catch on

A further example of an eighteenth century medical discovery that was in fact a rediscovery was the

Not the daily tot of rum but lime juice, served on board the "Alert." The Royal Navy was extremely slow to bring scurvy under control

recognition that it was possible to prevent scurvy among seamen. It was truly extraordinary that the Royal Navy was so slow to find out how to deal with the ravages of this often fatal disease. In the early years of the seventeenth century Captain James Lancaster of the East India Company had succeeded in preventing scurvy in his own ship by feeding bottled lemon juice to his crew, whereas the crews of two ships that sailed in company with him suffered severely. Woodall, in his surgeon's log book, had recommended the use of lemon juice in 1617, yet when Admiral Anson circumnavigated the globe between 1740 and 1744 he lost two thirds of his ship's company of 961 men, a deplorable experience that stimulated contemporary physicians and surgeons to inquire into the causes of scurvy. James Lind's pioneering clinical trial of oranges and lemons was carried out in the 50 gun ship HMS *Salisbury* in 1747, but despite his success in showing the virtues of fresh fruit juice conservative attitudes died hard in both the forecabin and in the Admiralty. Not until nearly 50 years later, after the introduction by Gilbert Blane of lime juice for all seamen in naval ships, was the disease brought under control.⁴ Yet it is a measure of the hazards of ignorance that Captain Scott and his colleagues were to suffer from scurvy during their ill fated journey to the South Pole more than a century later.

If these examples of the influence of traditional healing seem to belong to the past it is well to recall that the introduction to Britain in 1955 of the rauwolfia alkaloids for treating high blood pressure⁵ was a rediscovery of a remedy long known to Eastern, and particularly Indian, medicine.⁶ They remain of major importance as therapeutic agents, particularly in developing countries.

Discovered before their time

Rediscovery is a particular feature of the clinical practice of medicine. The practice of naming diseases after those who supposedly first described them offers ample evidence that observant clinicians faced with similar clinical problems will inevitably recognise the same things. It is therefore hardly surprising that virtually no disease endowed with an eponym was described by only one person and that diseases are often not described for the first time by the person with whose name the disorder is popularly associated. The recent recognition that the features of Crohn's disease, apparently first published in 1932, were in fact described by Dalziel 20 years earlier provides a particular contemporary example.⁷

There are, however, many reasons why rediscovery has been so much a part of biomedical science. An original discovery may be made long before its importance becomes apparent to other investigators. In addition, technical advances may be essential for the development of new ideas. The emergence of the idea that a certain pressure in the blood is necessary to ensure the adequate perfusion of different organs provides a useful illustration. Stephen Hales carried out his original experiments on the blood pressure of the mare in 1733. Nearly 100 years later Richard Bright did not mention raised blood pressure as being of any importance in his patients who, retrospectively, may be seen to have clearly died because of hypertension. He considered that the hypertrophy of the left ventricle that he found was related to increased resistance in the circulation, and the relation of high blood pressure with human disease had to await a technical advance, the development of the sphygmomanometer.

Other more recent discoveries that were made before their time include that of the giant axon of the squid. In 1909 L W Williams published a work under the auspices of the American Museum of Natural History

1980s

- 1981: The Centers for Disease Control recognises AIDS
- 1989: Identification of the cystic fibrosis gene
- 1989: Medical Research Council announces funding for the human genome mapping project

entitled *The Anatomy of the Common Squid, Loligo Pealii*.⁸ The journal *Nature*, reviewing the book, commented that “we did not expect very much in the way of novelty in a memoir of this kind, but the author is to be congratulated on the important discovery of a pair of giant nerve-cells situated in the pedal ganglion and each giving off a giant fibre.”⁹ According to the author it was the first time that such fibres had been described in any mollusc. Nearly a quarter of a century later J Z Young again described the giant axons of cephalopods in a communication to the Physiological Society.¹⁰ He went on to point out that they provided “very suitable material for study of living nerves.” With Det Bronk, Ralph Gerard, and Keffer Hartline to help him at Wood’s Hole and with the aid of amplifiers and loudspeakers he recorded the action potential discharge of a giant fibre of a squid after the application of a solution of sodium citrate to one end. As he so graphically put it, “out came a buzzzzzzzzzz—one of the best sounds I have ever heard.”¹¹ Cephalopod axons were to prove of vital importance in studying basic models of neurophysiology and elucidating the nature of the nerve impulse.

A more recent example of techniques apparently emerging before their time is the polymerase chain reaction, which was discovered by Kary Mullin, Henry Ehrlich, and their colleagues at the Cetus Corporation in California in 1985. As *Nature* has commented, molecular biologists might “like to dust off the *Journal of Molecular Biology* for 1971,” in which H Gobind Khorana and colleagues had previously suggested a method for the “extensive synthesis of the duplexed tRNA genes” using similar techniques.¹² Nevertheless, it was not until the 1985 article that the now familiar technique really took off.

Unsung heroes

The discovery and rediscovery of biologically important proteins has been an increasingly important feature of modern biological science. The pressor properties of renal extracts were first described by Tigerstedt and Bergman in 1898¹³ and were not rediscovered and reclassified as renin until the 1930s. Nowadays, many important proteins are being discovered, rediscovered, and yet again rediscovered. This situation has arisen because of the remarkable technical advances in cell and molecular biology that have permitted the isolation, sequencing, and cloning of particular substances. Groups working to track down the active principle in a particular biological process are quite likely to discover that the principle is in fact identical to one already known in a process previously thought to be unrelated.

The capacity of modern scientists to forget what has gone before is perhaps no greater than in any other field of human activity. Sir David Weatherall, however, has pointed out:

... modern molecular biology has forgotten classical genetics. If you were to read the now classical papers of David Botstein written in 1980 about how one could use restriction length polymorphisms to make a map of the human genome, you would imagine that molecular biology had discovered linkage. However, the whole idea of mapping the human genome with

linkage markers was set out beautifully in 1927 by J B S Haldane in a marvellous essay called *The Future of Biology* (Sir David Weatherall, personal communication).

Haldane referred to the blood groups that “divide mankind into four classes,” and he went on: “if we had about fifty such characters . . . we could use them, by a method worked out on flies by Morgan in New York and his associates, as landmarks for the study of such characters as musical ability, obesity and bad temper.” He thought that such factors should enter into the considerations of those intending matrimony but was equally doubtful that “the world will be converted into a human stud farm.”¹⁴

Neglect of original work

Other factors that may encourage the neglect of original discoveries include publication in obscure journals and in languages other than English. Furthermore, recognition is more likely to go to those who work in well known and internationally respected institutions. The discovery of insulin by Banting and Best in Toronto in 1922 was the culmination of the work of a whole succession of investigators, including Langerhans, the discoverer of the pancreatic islets, and all those who contributed to the finding that there were both external and internal secretions of the pancreas. There were also many who sought to use pancreatic extracts for the treatment of diabetes before Banting and Best. Zuelzer treated a comatose diabetic patient with pancreatic extract in Berlin in 1906 and E L Scott attempted to do the same in Chicago between 1911 and 1912. But the person most forgotten in the story of insulin was the Romanian, Nicolaus Paulesco, professor of physiology in Bucharest, who reported spectacular decreases in the blood sugar concentration of diabetic dogs after intravenous injections of his own pancreatic extracts. He published his earliest findings in 1920 in French, and further experiments were set out in four short papers published in *Comptes Rendus de Science de la Société de Biologie* between April and June 1921. Romanians have never forgiven the Nobel prize committee for their apparently flagrant neglect of the work of their countryman, particularly as Banting and Best, in their original communication, erroneously referred to Paulesco’s findings as having been “negative.”¹⁵

There are other threats to the recognition of original work. One of these is the blind acceptance of authority, which has bedevilled medical science since the time of Galen. Modern medical science is not immune from Galen-like figures, whose suppositions may have a pernicious influence on scientific opinion that effectively hinders progress. The question, for example, of whether absorption of substances across the intestinal mucosa is an active process perplexed scientists at the end of the nineteenth century. In the early 1900s Weymouth Reid, working in the relative isolation of the department of physiology in St Andrews University, Dundee, published a series of papers that provided compelling evidence that intestinal transport is an active process. His work was largely neglected, and in the 1930s it was the dogmatic views of the Swiss physiologist, Verzar, that dominated contemporary thought. Verzar and McDougall propounded the notion that absorption could be entirely explained on the basis of diffusion and osmosis and that active processes were not involved.¹⁶ Their opinions prevailed until the introduction of new in vitro methods for showing active intestinal transport in the 1950s.

Verzar’s views also influenced the concept of localisation of absorption in the small intestine, which if true would have provided important evidence in favour of active transport. As long ago as 1888

Tappeiner had published data suggesting that the conjugated bile salts are selectively absorbed in the ileum in the dog.¹⁷ Verzar, sufficiently concerned by data that conflicted with his cherished opinions, invited Fröhlicher, one of his research assistants, to repeat Tappeiner's experiments. His observations

entirely supported Tappeiner's, but they were dismissed by Verzar. The concept that absorption in the intestine might be localised was not accepted until it was shown that the physiological absorption of vitamin B-12 is a function of the ileum,¹⁸ at least in species that are carnivorous or omnivorous. The

The Madhouse (1988)

Sergei Chepik (b 1953; Russian)

Surprisingly, this picture, seen in England for the first time last year, was painted by the Russian artist Sergei Chepik in the 1980s, for his style seems to belong to an earlier era. Chepik was born in Kiev in 1953 into an academic family in which the arts had an important role. His grandparents befriended many distinguished artists and writers, including Mikhail Bulgakov, who was also a physician, who died in 1940. It was in this kind of milieu that Chepik spent his formative years; his early training was at the Kiev Institute followed by a course at the Leningrad Academy, where he graduated in 1979. Since 1989 he has lived permanently in Paris.

Until recently there was no such thing as artistic freedom in the Soviet Union. Avant-garde artists were forced to go underground and many starved. By the early 1930s Western style experimentation was not tolerated — artists were encouraged to celebrate the joys of communism in an official style instituted by Stalin that was based on academic socialist realism. Any work that offended the authorities was banned, and this is exactly what happened to Chepik's "Madhouse." In this picture he employs a figurative technique reminiscent of French nineteenth century Romanticism, contrasting the

splendour of the decaying architecture with the grotesque puppet-like figures. Could the badly damaged, almost unrecognisable image of the Virgin and Child be a reference to the Virgin of Vladimir, the most holy icon in the Russian Orthodox Church? This powerful representation of religious and political oppression won Chepik the gold medal at the Salon d'Automne in Paris in 1988 and a special medal in Monte Carlo in 1989. Not only is it an appropriate example for the last picture in this series, given the recent political changes in eastern Europe, it also celebrates the splendid news that he is to have a one man show at the Roy Miles Gallery this month.

CLASSIC OF THE DECADE

1983: David Weatherall (ed). *Oxford Textbook of Medicine* (two volumes). Oxford: Oxford University Press.

absorption of bile acids was then reinvestigated and found to occur in the terminal ileum both in experimental animals and in humans.

There is a further example from clinical gastroenterology that illustrates how deeply held opinions may influence thought. In 1912 in Ceylon Manson-Bahr showed in a careful necropsy study that there was atrophy of the small intestinal mucosa in a patient with intestinal malabsorption due to tropical sprue.¹⁹ Manson-Bahr's observations were summarily dismissed by the leading authorities of the day as mere necropsy artefact. That there are important pathological changes in the small intestine in patients with malabsorption had to be rediscovered by Paulley in 1953²⁰ and subsequently by those who pioneered the use of jejunal biopsy techniques in the 1950s.²¹

Deciding who got there first

In our own era the pace of scientific advance has accelerated dramatically. The potential rewards in terms of fame, fortune, and an invitation to Stockholm have also greatly increased the importance of priority in medical science. As simultaneous technical advances provide so many contemporaries with similar scientific opportunities it is not surprising that the question of priority, of who discovered and who rediscovered, ranks so highly in the scientific consciousness. The recent controversy between the French workers who originally discovered the virus that causes AIDS and investigators at the National Institutes of Health in the United States is a case in point. Although the source of the original discovery is not in doubt, it has required some remarkable scientific journalism, which was published in a recent issue of the *Chicago Tribune*, to give the general reader an understanding of who discovered what and when.²² As the editor of that newspaper has written:

It is a story of commitment and dedication to mankind and of tireless, often brilliant detective work within the magic and marvellous world of medical technology. But it is also a story of cut-throat competition and bare-knuckled politics, of individual ego and national pride, and of the kind of intense pressure on human beings that often brings out the worst in even the best and can result in lying, cheating, and outright fraud.

The pressures of the modern world on younger research workers are particularly fierce. The scientific community is sadly not immune from those who would

seek to advance their position by fabricating data, and the question of fraud in science hangs heavily on the scientific achievements of our age.

We need not wonder that rediscovery is so important a feature of biology and medicine. After all, our entire scientific education is based on a process of repetition of previous experimental work that is, when we first do experiments, rediscovery. Furthermore, life itself is a whole process of rediscovery of what our forebears have known—pain and pleasure, ecstasy and despair, beauty and ugliness. And for even the most modest of those who have had the privilege of working in biomedical science there has been the rediscovery of something that we can share even with Galileo—the excitement of making a discovery.

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World Medicine. A sort of obituary

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downfall came because we were difficult to categorise and couldn't explain to outside managers exactly what we were doing.

I see an ominous analogy between what happened to *World Medicine* at the start of the 1980s and what is happening to the NHS at the start of the 1990s. In 1981 we were taken over by a management that knew a lot about the administration, production, and marketing of magazines yet failed to understand the transaction that went on between us and our readers—the pub-

lishing equivalent of the doctor-patient relationship. When they replaced the editorial staff the publication died. Perhaps our creation carried within it the seeds of its own destruction and, like Brünnhilde (that's the trouble with Wagner, once you let him into an article he keeps coming back like a song), poor old *World Medicine* was destined to end by throwing itself upon the flames.

Yet, while it lasted, it was a great place to be. I hope that someone somewhere is dreaming up a successor, but please don't ask me how to do it. As they'd say in the country where my genes were fashioned, if you know what you're doing before you start you're never likely to begin.