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Three hundred years of Nephrology in Scotland

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Τριακόσια χρόνια Νεφρολογίας στη Σκωτία

Περίληψη στο τέλος του άρθρου

Key words

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Richard Bright
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A remarkable flowering of scientific and philosophical thinking, the Scottish Enlightenment, took place in the second half of the 1700s, centred on Edinburgh. The city's new medical school benefited, developed new integrated teaching methods, exploded in size, and sent its graduates around the world. One was Richard Bright, the creator of the specialty of nephrology. Robert Christison, professor of medicine in Edinburgh, was one of those who prominently extended Bright's observations, but his lasting influence was probably limited by his opposition to women doctors. Almost at the same time, Edinburgh graduate Thomas Latta described the first use of intravenous fluids to rescue patients with terminal shock from cholera. Meanwhile in Glasgow, Thomas Graham was describing the principles of dialysis. Scotland took up dialysis and transplantation as treatments for renal failure a hundred years later. Dialysis for AKI from 1959, and the first successful transplant in the UK was performed in Edinburgh in 1960. Establishment of early units for chronic dialysis and transplantation followed, still at a time when the viability of neither was assured. Research centred on complications of dialysis, and on immunosuppression. Edinburgh suffered a devastating dialysis-associated hepatitis outbreak in 1969–1970. This was a major but temporary setback to the development of services. It was followed by a remarkable research initiative that created a landmark, early commercially successful recombinant protein product – hepatitis B vaccine.

1. MEDICINE AND MEDICAL EDUCATION IN 18th CENTURY SCOTLAND

For 200 years from the early 1700s, medical education was a dominant activity of Scotland's universities. This was particularly true of Edinburgh, whose medical school was founded in 1726, in a university created by the City, not under the auspices of a religious body.[1]

The founders of Edinburgh Medical School had travelled to Leiden to experience the new approach developed by Herman Boerhaave. After a founding basis in science, this integrated clinical medicine and practice. Previous norms had been largely theoretical teaching, followed by apprenticeship.

With an astonishing array of great minds attracted to the city, Edinburgh's medical school expanded enormously to become the dominant element of the University. Many notable academics were appointed, a new teaching hospital was built, and Thomas Jefferson wrote in 1789 that so far as science was concerned, "no city in the World can pretend to a competition with Edinburgh".[1] From 1801–1850, Scotland produced 7689 medical graduates to the rest of the UK's 302. By 1895, many new schools had been founded but medical students still comprised half of the 3000 matriculating students at Edinburgh University.[1]

This was far more doctors than Scotland could employ, and Edinburgh's medical graduates, swelled by the growth of other Scottish schools, took the medical-scientific revolution not only to the rest of the UK, but to the limits of the British Empire, and beyond. Edinburgh graduates established medical schools in many nations in North America, South Asia, and China, exporting their mode of instruction too. The Scottish Doctor became a trope in literature and film.

2. WILLIAM CULLEN, TOP TEACHER 1755–1790, ON DROPSY

William Cullen was one of the key attractions to studying in Edinburgh. Like many students, he studied in Edinburgh

for only part of his undergraduate medical education, with the rest of his learning and apprenticeship in Glasgow. There he established an impressive reputation as a clinician and teacher, but he was attracted back to Edinburgh as professor of Chemistry in 1755. His prowess as a teacher was recorded in the diaries and letters of students at the time, but his clinical skills are notably demonstrated in the carefully preserved records of his extensive consultations by correspondence.[2,3]

Many of those writing were doctors seeking advice. Although renal disease was not clearly recognised at that time, beyond renal stones and infection, dropsy and anasarca (local or general fluid retention) were. *Ischuria renalis* (anuria) was recognised, but little intervention was possible if it was not caused by bladder outlet obstruction.

Cullen wrote famously, but gloomily, in 1784, on the dropsy suffered by the leading intellectual figure of Samuel Johnson.[3]

At the age of 74 Asthma and Dropsy are very insurmountable distempers … I am glad to observe that he is in the use of Laudanum as I believe it is the only means of rendering his life tolerably easy. The Vinegar of Squills I judge to be a medicine very well suited to both his Asthma and Dropsy. I hope the coming in of mild weather may be of service to him and if he is to live for another winter he should certainly pass it in a Climate much milder than that of England. I cannot help however telling you that I despair of his having the opportunity for I suspect he has not only water in his limbs but also in his breast.

Contemporary treatments were of limited effectiveness and often difficult to tolerate, relying on purgatives, emetics, and diaphoretics (to induce sweating) to remove fluid. Broom tops (*Genista*) were recommended as a diuretic by some, and Cullen recorded in his Materia Medica (1789) "some dropsies have been cured". Digitalis was now also reported to be an effective drug, based on work by Edinburgh graduate William Withering done in the Midlands of England and published in 1775.

Cullen's textbook *First Lines of the Practice of Physic*, and his *Materia Medica* (therapeutics), were standard texts for several decades. His textbook[4] shows that he understood hepatic, cardiac, and local causes for dropsy, and to some extent renal (dropsy caused by *ischuria renalis* is mentioned). However, his cases also show a thoughtful, sympathetic clinician, who knew not to treat when futile. He seems to have been the key medical opinion of his day. His distinction of insipid versus sweet diabetes is just one of his classic and lasting insights.[5]

3. THE BRIGHT ERA

There was little understanding of renal disease in Cullen's era, but in looking for antecedents of Richard Bright, one of those picked out is William Wells (1757–1815), a Scottish-American Edinburgh graduate working in London, who in 1812 described in great detail the oedema sometimes seen in scarlatina. He also made a number of tantalising observations around oedema and proteinuria, and kidney appearance at autopsy, and related some renal disease to exposure to mercury (prescribed for venereal infection). He was so near making a clear, saleable account, that some have wondered why Bright's story is the only one remembered.[6]

Richard Bright himself, widely credited for creating the specialty of Nephrology, studied in Edinburgh 1808–1810. His MD examination in 1813 including scrutiny (in Latin) of his thesis on erysipelas, as well as extended oral examination on clinical cases. But his 1827 "Reports of Medical Cases"[7] from Guy's Hospital reverberated around the world. He meticulously associated proteinuria and dropsy with shrunken kidneys, and the medical world was convinced. Suddenly everyone wanted to test for proteinuria.[8,9]

Bright's most notable colleagues at Guy's were two other Edinburgh graduates, Thomas Hodgkin (who introduced Laennec's stethoscope to London; Bright was an early adopter) and Thomas Addison, whose eponyms lasted even longer than Bright's. Bright's disease was widely used to describe kidney disease, and later more narrowly glomerulonephritis, into the 20th century.[8,9] Bright wrote an impressive textbook of medicine with Addison in 1839.[10]

4. POST-BRIGHT

Two key characters took Bright's work notably further. These were Robert Christison (1797–1882), professor of Medicine in Edinburgh, who received his Edinburgh MD 6 years after Bright in 1819, and Pierre Rayer (Paris). Each produced classic texts, in 1837 and 1839 respectively. The increasing recognition of acute renal disease, and greater understanding of nephritic (haematuric) renal disease from proteinuric, began here. Indeed this information was endorsed by Bright, and included in his 1839 textbook.[10]

Despite making some striking insights, and wide recognition at the time, as described by Cameron,[11] Christison's role in the development of nephrology has been relatively neglected since. Quietness about him seems almost certainly related to his campaign against permitting women to become doctors. He led internal opposition to the progression of the first female undergraduates in Britain, who had been admitted to study Medicine in Edinburgh

in 1869, and this 73-year-old man, 47 years since being appointed a professor, ultimately succeeded in preventing them from receiving medical degrees in Edinburgh. However honorary degrees were awarded to 7 of them in 2019, the 150th anniversary of their matriculation.[12,13] Though the columns of medical journals displayed views on both sides, Christison's stance seems to have been contrary to the prevailing public mood expressed in the wider press. Only a few years later the arguments were won, an 1876 amendment to the Medical Act clarifying that women should be eligible.[12,13] Women's schools sprang up, and it is fascinating that in 1889 Christison's own son Alexander, who had spent most of his medical life in India, took up presidency of Edinburgh's Medical College for Women, very publicly leading a cause that his late father had been prominently opposed to.

5. CHOLERA, INTRAVENOUS FLUIDS, AND BODIES

The profusion of medical students in Scottish cities led to a notorious shortage of bodies for dissection. This led first to grave-robbing, to sell bodies to anatomists, and culminated in the conviction of Burke and Hare, who found it more convenient to create their own bodies. They were believed to have murdered 16 citizens to sell the bodies to anatomists. Burke was hanged in 1828; Christison gave forensic evidence at the trial. The events aroused widespread scandal, and lasting mistrust. In 1831 the anatomy school in Aberdeen (colloquially known as the "Burkin hoose", after Burke) was burned to the ground,[14] and in Liverpool in 1832 "cholera riots" were triggered by the sight of cholera sufferers being taken to hospital, a rumour having spread that they were being abducted for their bodies.[14,15]

"Asian" cholera hit Britain in 1831–1832, but was also the subject of serious scientific enquiry. Based on science showing that red cells became concentrated in blood in cholera, in Leith (Edinburgh's port) in 1832, Dr Thomas Latta demonstrated that patients who were moribund from Asian cholera could be revived by intravenous injection of large volumes of salty water. This was the first reported successful use of intravenous fluids. The pages of the Lancet were filled with excitement and controversy for a short time, as this approach was the opposite of bleeding, which was recommended by some.[16,17]

"She had apparently reached the last moments of her earthly existence ... I feared that I should be unable to get my apparatus ready ere she expired. ... ounce after ounce was injected, but no visible change was produced. Still persevering, I thought she began to breathe less laboriously, soon the sharpened features, and sunken eye and fallen jaw, pale and cold ... began to glow with returning animation; the pulse, which had long ceased, returned to the wrist; at first small and quick, by degrees it became more and more distinct ... and in the short space of half an hour, when six pints had been injected ... her extremities were warm, and every feature bore the aspect of comfort and health."[18]

The debate died down with the epidemic. This was a discovery of much more immediate importance than Bright's, but was neglected for some decades, before returning as a treatment for haemorrhagic and other shock.[19]

6. THOMAS GRAHAM AND THE ROAD TO THERAPEUTIC DIALYSIS

Thomas Graham (1805–1869) meanwhile described the phenomenon of dialysis, distinguished and defined colloids and crystalloids, and semi-permeable membranes, in work commenced in Glasgow and completed in London, published 1830–1861. His 1861 paper described its application to urea in urine, laying the ground for the first attempts at therapeutic dialysis.[20] One of the steps required to implement it was control of blood clotting. Hirudin was purified from leeches by Edinburgh graduate John Haycraft (1857–1922), a physiologist working in Birmingham, England. Semi-permeable membrane (collodion) and hirudin were brought together by John Jacob Abel in Baltimore in 1913.[20] It was another 40 years before Willem Kolff found a way to harness the technique successfully.

7. DIALYSIS AND TRANSPLANTATION

The next hundred years were relatively quiet in Scottish nephrological output, although the astonishing longitudinal studies and impressive, humane *Glomerular Nephritis* (1948) of another Edinburgh graduate, Thomas Addis (1881–1949), working in Stanford, were a highlight.[21,22]

By 1960 selected academic centres around the world, including two in Scotland, picked up on the potential for of dialysis and even transplantation.

Dialysis for acute renal failure was introduced in Edinburgh and Glasgow in 1959. The first successful kidney transplant in the UK was undertaken between identical twins in Edinburgh in 1960 by surgeon Michael Woodruff. A period of leading research in immunology and immunopathology followed. The second use of Azathioprine in transplantation was in Edinburgh in 1962. Production and research into anti-lymphocyte serum followed. The survival in these early transplants was very poor; in the first 14 years, 129 transplants, Woodruff reported that patient survival at

6 months was 29%, but 28 (22%) had survived more than 2 years.[23] But the long term prospects on dialysis were uncertain during most of that period too.

Edinburgh and Glasgow shared many of the alarms and experiences around the potential of dialysis and transplantation. The affordability, uncertainty of long term viability, and new complications, including dialysis disequilibrium, aluminium toxicity, bone disease, and hepatitis.[24,25]

8. HEPATITIS AND HEPATITIS VACCINE

In 1969–1970, the world's worst dialysis-associated Hepatitis B outbreak occurred in Edinburgh.[26] Outbreaks had occurred intermittently in the UK, and similarly across Europe, since 1965. The Edinburgh epidemic killed 7 of 26 affected dialysis patients, and 4 of 12 members of staff, two transplant surgeons and two technicians.[27] The reason for the exceptionally high mortality in this epidemic is not known, but the events had a major impact on the new specialty locally, just at the time that the prospects for long-term patient survival were looking up. After a period of taking on no new patients, a move to more home rather than in-centre haemodialysis was driven by fears of hepatitis, as well as by economic factors.

There were no local presentations about the Edinburgh epidemic for 35 years, it seemed too sensitive a topic (R. Winney, personal communication). However a scurrilous, politically incorrect but darkly humorous novel "The Houseman's Tale" by Colin Douglas (pseudonym for Colin Currie, 1975) was set in a hospital with a hepatitis B outbreak spreading fear amongst its staff. Currie was an Edinburgh student at the time of the outbreak, when there was real concern about who might be affected next.[29]

The experience triggered a remarkable ensuing scientific project in one of the first of the new laboratories of Molecular Biology, that led to sequencing of the virus in 1979, and subsequent marketing of the recombinant vaccine Engerix B in 1986. The husband and wife team of Kenneth and Noreen Murray were central to this. The route to it included founding one of the first biotech companies, Biogen. The Murrays' income from the enormously successful vaccine was fed back into research and education, a benefit in addition to the health benefits for patients and staff everywhere.[28,29]

ΠΕΡΙΛΗΨΗ

Τριακόσια χρόνια Νεφρολογίας στη Σκωτία

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Μια αξιοσημείωτη άνθηση της επιστημονικής και φιλοσοφικής σκέψης, του Σκωτσέζικου Διαφωτισμού, έλαβε χώρα στο δεύτερο μισό του 1700, με επίκεντρο το Εδιμβούργο. Η νέα ιατρική σχολή της πόλης ωφελήθηκε, ανέπτυξε νέες ολοκληρωμένες μεθόδους διδασκαλίας, αναπτύχθηκε ραγδαία σε μέγεθος και έστειλε τους αποφοίτους της σε όλο τον κόσμο. Ένας εξ αυτών ήταν ο Richard Bright, ο δημιουργός της ειδικότητας της Νεφρολογίας. Ο Robert Christison, καθηγητής της Ιατρικής στο Εδιμβούργο, ήταν ένας από εκείνους που επέκτειναν εμφανώς τις παρατηρήσεις του Bright, αλλά η μόνιμη επιρροή του ήταν πιθανώς περιορισμένη από την αντίθεσή του προς τις γυναίκες γιατρούς. Σχεδόν ταυτόχρονα, ο απόφοιτος του Εδιμβούργου Thomas Latta περιγράφει την πρώτη χρήση ενδοφλέβιων υγρών για τη διάσωση ασθενών με κυκλοφορική καταπληξία από τη χολέρα. Εν τω μεταξύ, στη Γλασκώβη, ο Τόμας Γκράχαμ περιέγραφε τις αρχές της αιμοκάθαρσης. Η Σκωτία ξεκίνησε την αιμοκάθαρση και τη μεταμόσχευση ως θεραπείες για τη νεφρική ανεπάρκεια εκατό χρόνια αργότερα. Η αιμοκάθαρση για την οξεία νεφρική βλάβη από το 1959 και η πρώτη επιτυχημένη μεταμόσχευση στο Ηνωμένο Βασίλειο πραγματοποιήθηκαν στο Εδιμβούργο το 1960. Ιδρύθηκαν πρώιμες μονάδες για χρόνια αιμοκάθαρση και μεταμόσχευση, ακόμα σε μια εποχή που η βιωσιμότητα κανενός δεν ήταν εξασφαλισμένη. Η έρευνα επικεντρώθηκε στις επιπλοκές της αιμοκάθαρσης και στην ανοσοκαταστολή. Το Εδιμβούργο υπέστη καταστροφικό ξέσπασμα ηπατίτιδας που συνδέεται με την αιμοκάθαρση το 1969–1970. Αυτή ήταν μια σημαντική αλλά προσωρινή παύση της ανάπτυξης των υπηρεσιών. Ακολούθησε μια αξιοσημείωτη ερευνητική πρωτοβουλία που δημιούργησε ένα ορόσημο, πρώιμο εμπορικά επιτυχημένο προϊόν ανασυνδυασμένης πρωτεΐνης – εμβόλιο ηπατίτιδας Β.

Λέξεις ευρετηρίου: Ηπατίτιδα αιμοκάθαρση, Ιατρική εκπαίδευση Εδιμβούργο, Richard Bright, Robert Christison, Σκωτικός διαφωτισμός, Thomas Graham, Thomas Latta

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