BIOGRAPHY BIOFPATIA

Leonard George Rowntree (1883–1959) A near-forgotten father of North American nephrology

Canadian physician Rowntree's crucial participation in the first in vivo haemodialysis in 1913 at the Johns Hopkins Hospital Baltimore US, under the direction of John Jacob Abel, was only one of Rowntree's several major contributions to Nephrology. He had already pioneered, aided by John T. Geraghty, a renal function test using injection of phenolsulphonephthalein (PSP) and its detection in the urine, which was used clinically for half a century. Rowntree used a dye dilution technique also to study plasma volume in normal circumstances and in patients, including those with renal disease. He moved to Minneapolis in 1915 and there worked on water overload and hyponatraemia, and on the hydrogen ion concentration in the blood using a buffer method that he set up. Then, late in the First World War, he worked in France on aviation medicine, assessing physiological and psychological suitability in potential pilots. After the war, of several choices, he accepted the chair of medicine in the prestigious Mayo Clinic, to supervise and set up new clinical research programmes. There, early on, he participated with Osborne in the first use of iodide to obtain X-ray images of functioning kidneys (the intravenous urogram, IVU), which is still in use, later studying the clotting of blood in extracorporeal circuits, described the histology of acute lupus nephritis with Norman Keith, and worked on oedema in renal and other patients. Finally, he did early work on adrenal cortex extracts and was a pioneer of the treatment of Addison's disease, hitherto fatal. During this time at the Mayo Clinic from 1921 to 1932, he used his experience from the Johns Hopkins Hospital to organise and staff eight subspecialty medical units, including one in renal medicine, all of whose contributions remain outstanding today. However, he fell out with the Mayo clinic, left in 1931 and returned to Philadelphia University, near where he had started from. During the Second World War, he served as director of a unit assessing men for service in the armed forces as well as their rehabilitation - work for which he received a Presidential citation from Harry S. Truman in 1946. Throughout his whole working life, he continued to publish steadily on clinical and research subjects, for example the more than 100 papers in the 1920s whilst at the Mayo clinic, a remarkable record for the period. His last paper appeared shortly before his death in 1959, 50 years after he had first published as a general practitioner in Camden, New Jersey.

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Leonard George Rowntree (1883–1959): Ένας σχεδόν ξεχασμένος πατέρας της βορειοαμερικανικής Νεφρολογίας

Περίληψη στο τέλος του άρθρου

Key words

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Leonard George Rowntree
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Renal function tests

1. INTRODUCTION

The founders of 20th century North American renal medicine can be debated, but the names of Osler, van Slyke, Christian, Fishberg, Addis and of course Homer Smith come to mind. But one individual who has perhaps the right to join the pantheon is almost never mentioned – Canadian Leonard George Rowntree (1883–1959).

Rowntree wrote a rambling, diffuse, part-autobiography

part history of early 20th century medicine, which is a major source of information about him, but obviously biased and not impartial. Others have hitherto provided only brief biographies. ^{2,3}

2. LIFE AND WORKS

Rowntree was born on April 10th 1883 into a family of eight children of a successful businessman in London,

Ontario in Canada. He was educated locally in Medicine at the University of Western Ontario, graduating in 1905 with the gold medal. Very early his wide curiosity and considerable ability was evident, but at the suggestion of an uncle, a community physician in Camden, New Jersey (a suburb of Philadelphia across the river Delaware) Rowntree joined him, and then practised there solo. The account in his autobiography of his time in general practice is vivid, with infections dominating practice – his first paper in 1908 was on endocarditis. He however acquired an attachment to treating patients rather than diseases, and at heart remained a general practitioner throughout his working life, as reflected in the broad range of his lifelong interests and contributions.

But he became dissatisfied with general practice "I was so immersed in general practice I had no time to think" and also wanted to do clinical laboratory research. His life changed when, in 1907, he approached the famous fellow Canadian (Sir) William Osler for advice about his career, after Osler, on a visit to the USA from Oxford, had spoken to a local medical society. Osler wrote and suggested Rowntree go to the Johns Hopkins Hospital in Baltimore (where Osler had been chair of medicine from 1889 to 1905) and study - for 6 years. During this time, he would not be paid, but Osler judged "if you have brains... and enough cash to keep you floating – which I believe you to have" it could be a success. Rowntree accepted with alacrity and after a short period of biochemistry working on guanine nucleotides, began work in the Laboratory of pharmacologist John Jacob Abel (1858-1935) in 1909 (fig. 1).

Abel suggested "as medicine needs a new ... laxative" that he study a promising group of new compounds, the phenolsulphonephthaleins. With the help of John T. Geraghty, he dived into this project, assessing their lack of toxicity, then absorption and elimination of PSP (as the compound's unwieldy name was abbreviated). Apart from its use as a laxative, which persists today, he realised that it was almost exclusively and rapidly excreted by renal tubular secretion, and could be measured simply by adding alkali, which produced a ruby red colour, easily quantitated photometrically. He realised that they had an easy, cheap and safe renal function test completed in as little as half an hour, and the "PSP test" or "Rowntree test" 5.6 was used clinically worldwide for the next half century.

Meanwhile, Rowntree also studied the elimination of phenoltetrachorphthalein (PTCP), which turned out to be almost exclusively excreted through the liver. In parallel with the studies on renal function using PSP, he also designed a test of hepatic function using PTCP. This did not last as long



Figure 1. Leonard George Rowntree as a young man, at the Johns Hopkins Hospital around 1910. Later he habitually wore eyeglasses (Rowntree family photograph; photographer unknown).

as the PSP test, since the dye Congo red proved equally specific and easier to measure in body fluids. However, this gave Rowntree a lifelong interest in hepatic function and diseases, which persisted through his time at the Mayo clinic and beyond.

Abel started Rowntree on a salary after the successful work of phthaleins, and had sent him to Europe and to visit Strauss in Berlin, von Pirquet, van Noorden, and the incomparable Friedrich von Müller in Munich, who became a sort of long-distance guru for Rowntree. Amongst other influences, August Krogh of Copenhagen played a similar role as well.

This summer working holiday European trip was repeated in each of the following four years, with variations, and accompanying family members including sisters and cousins. 1913 however was different. This time he was accompanied by Abel himself, and their "vividiffusion" apparatus, which they demonstrated in London at an international medical meeting, and in Groningen in the Netherlands – the first *in vivo* haemodialysis. This was called in London by an anonymous newspaper reporter of the London *Times* of August 11th 1913 an "artificial kidney". This important story I and others have related elsewhere, and will not repeat it all here, except to quote Rowntree himself "Dr Turner made the glass fittings, I made the collodion tubes, the leech extract, and conducted the experiments. Dr Abel conceived the idea, and made the chemical analysis."

In his autobiography, unfortunately Rowntree – the only clinician in the team – didn't elaborate as to the potential

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value of haemodialysis in clinical renal failure. Certainly, in 1913 in London and elsewhere Abel presented the apparatus as a means of isolating and analysing amino-acids and other solutes in the blood. But equally in their earliest written account of their work, in the Transactions of the presentation to the American College of Physicians (ACP) meeting⁷ that same year (1913), held in Washington DC on May 5–8 1913, and thus earlier than the visit to London on August 11th, the preamble to the paper clearly states the potential value of blood purification in disease states such as renal failure. This perhaps indicates that Rowntree and not Abel (a pharmacologist and chemist) may have written and given this oral paper, being a member of the ACP, and was better aware than his mentor of its wide applications. Later, Abel followed this trend and referred to dialysis as a treatment for renal failure, but only after it had been done in humans during the 1920s in Germany.

In the 1911 and 1912 trips, finding "time on my hands" in London, Rowntree undertook a study of the surgeon James Parkinson, at that time a man of mystery and of whom still no authentic portrait has been identified. The paper he published⁸ still remains one of the principal sources of information on Parkinson.

Following on the renal function study, with Norman Keith (also Canadian), he used a dye again, this time to measure blood volumes in normal circumstances and in patients,⁹ and later wrote a book on the subject.¹⁰ Again, this test was a standard in clinical medicine, until radioactive isotopes replaced the dye. Meanwhile, Abel's interest in haemodialysis had waned and returned to earlier experiments of withdrawing blood and then returning it. Rowntree and Turner again performed the experiments on dogs,¹⁷ showing how the blood could be centrifuged, and the plasma modified *in vitro*. Abel called this procedure "plasmapheresis" a name which, unlike "vivdiffusion" has survived.

Now with salary as an attending physician at the Johns Hopkins, summer work back in Camden in general practice, and family resources, he felt able to marry, to Katherine Campbell of Camden NJ in 1914. They had 44 years together.

In 1916, ever restless and ambitious, now 32 and seeking promotion, he left the Hopkins and took a Chair of medicine post in Minneapolis, despite a decided deficit in the local facilities for clinical research. Even so, there he began a lifelong interest in water metabolism, studying polyurias and water intoxication, ¹² and perhaps stimulated by Krogh, he also designed a buffer indicator method to measure hydrogen ion concentrations in dialysates of blood

that he studied,¹³ including during renal failure. He wrote a book on this subject, which ran to 16 editions.

Then World War I intervened for Americans, and he spent the latter two years of the war in the military studying aviation medicine and assessing service pilots, serving in the Allied Expeditionary Force in France through most of 1917–1918. This subject again remained a lifelong interest. Demobilised, rather than return to Minneapolis he was in the happy position of having several offers of chairman posts to choose from. He chose the Mayo Clinic, the graduate school of the University of Minnesota, rather than one of several other universities eager to have him, and went to Rochester, Min in 1920. He was now 37 years old. His thirteen years at the Mayo were his apogee.

Rowntree had reason to be grateful to the Mayo brothers. He had had a number of ailments throughout his life¹ suffered with an almost Panglossian cheerfulness, but a perforated gastric ulcer in 1918 threatened his life. He was operated on by William J Mayo, who saved him.

Rowntree's responsibilities at the Mayo were vast, as chief of medicine and Professor of medicine. By 1922, he was elevated to Chief of the Department of Medicine. His task was to add laboratory and clinical investigation in medicine of world quality to the unparalleled clinical service provided by the clinic, which started with surgery as its predominant activity but spread to internal medicine under his aegis. To achieve this, he had in his mind the images of the great clinics he had seen in Europe, such as that of Friedrich von Müller, as well as his experience from the Johns Hopkins.

He persuaded and appointed men of talent (no women of that standing were available to him in the early 1920s) to form a stellar team incorporating almost every area of medicine, amongst the first being his fellow Canadian Norman Keith to head a division in what would later be called Nephrology. Alongside them were two other colleagues from the Hopkins - Dr Samuel Amberg of Chicago and Dr Reginald Fitz of Boston. Henry Helmholz was attracted to head up paediatrics. Gastroenterologist Walter Alvarez of San Francisco and Nobel winner-to-be rheumatologist Philip Hench also joined the team, along with Drs Russell Wilder already on the staff, George Brown, Stanley McVicar, George Brown, Carl Greene, Jay Bargen and Albert Snell. Each was given space and postgraduate students from the university, and recruited further talent from within and outside Mayo. Rowntree headed 8 divisions, all doing clinical investigation as well as clinical medicine, and Dr Henry Plummer (still with the title also of Chief of Medicine) seven.

What of Rowntree's personal contribution to clinical and investigational medicine during his time at the Mayo? During his time there, he published 107 papers in medical journals. Nor did he simply put his name on work done in his many departments; each was a personal contribution. He continued the major interests of his Hopkins days in liver disease, ¹⁴ kidney disease, plasma volume and oedema and acidosis, writing a book on plasma volume in health and disease with colleagues at the Clinic Drs George Brown and GM Roth *The volume of the blood and plasma*. ¹⁰ He returned to study directly clotting of blood in artificial circuits made from collodion, and pointed to the involvement of platelets in this process, as well as the inability of hirudins and the newly introduced heparin to totally arrest this process. ¹⁵

But there were also new projects to pursue. Early in his time at the Mayo Clinic, in 1923 he collaborated with Osborne, a pioneer of the use of iodide in radiology, using urinary excreted iodide as a tool for imaging the anatomy of the kidney and the urinary tract. ¹⁶ This became known as the intravenous urogram (IVU), and is still in use today, using improved contrast media. With Norman Keith, he gave the first detailed description of severe lupus nephritis, including photomicrographs. ¹⁷ His work on the adrenal cortex later in the 1920s was groundbreaking, and led to a further book, *A clinical study of Addison's disease* with Dr Albert Snell, which included data on the first successful use of adrenal extracts to maintain patients with Addison's disease long-term.

Newly developed interests included hypertension, for which at that time there were few ineffective medicines, although salt restriction was clearly important. Rowntree was probably the first who set out deliberately, in 1925, to follow Leriche and do lumbar sympathectomy for severe hypertension with success, 19 but did not follow this early attempt with long-term studies although further cases were treated, although it remained a standard method of treating severe hypertension for more than three decades. He did however also persuade "his" surgeon Dr Alfred Adson to do in addition a nephrectomy in a patient with unilateral renal disease and severe hypertension, again with success. This was before the experiments of Golblatt were performed.

However, his time at the Mayo Clinic ended somewhat acrimoniously in 1931–1932. John Graner, an alumnus²⁰ suggests that the Mayo tradition of maintaining a generalist stance in medicine –an idea which Rowntree himself advocated lifelong– became incompatible with the increasingly specialist interests of the "Rowntree group", who drifted apart as their many individual contributions blossomed. Rowntree himself also spent less and less time

seeing patients whilst pursuing and supervising the many projects his departments were engaged in. Graner remarks "Rowntree never became assimilated into the Mayo Clinic's structure and routine" and his new academic style did not suit many of the existing, more senior, staff. Rowntree also in his autobiography felt that he was "losing control of his time"," and his personal life was affected adversely with overwork. Moreover, other members of his staff were "suffering from chronic exhaustion"."

He resigned, but was invited to stay on by W.J. Mayo (as he emphasises strongly in his autobiography), with an increased salary – but with conditions and restrictions, including a public guarantee never to leave the Clinic; Rowntree declined this offer, and so he left after 13 ½ very successful years. Graner²⁰ quotes Dr Nelson Barker "Perhaps Leonard Rowntree's greatest contribution was the fact that he stimulated in his associates, first assistants and fellows a strong and lasting interest in clinical investigation and research". The clinic remains a centre of excellence with a worldwide reputation for both clinical medicine and clinical investigation and innovation. Much of this was begun by Leonard Rowntree.

He left for a less demanding role in his adopted home town of Philadelphia, becoming Director of the Philadelphia Institute for Medical Research. Nevertheless, in the next few years he published a further 37 papers on his several interests. He became more interested in endocrinology after his success with the adrenal cortex, but sadly achieved little with both pineal and thymus extracts and implants.

His medical career was then interrupted by the entry of the USA into World War II. Rowntree volunteered, wishing to continue his work in aviation medicine begun in the previous conflict. Probably because he was nearing 60 and had enormous administrative and medical experience, he was appointed instead as head of the Medical Service of the Selective Service System (popularly known as "the draft") in August 1940. He quickly became an expert in public health and constantly revised and improved criteria for clinical assessment for service in the armed forces.²¹ For this work, he was awarded a Presidential Citation in 1946 by US President Harry S. Truman.²²

After the war, he retired with his wife to Florida, but was far from inactive, helping to set up the University of Miami School of Medicine in 1952. His last publication, in 1958, was a case report in JAMA, just 50 years after his first paper. In that year, he also had the pleasure of watching a dialysis done for acute renal failure in a patient under the care of Dr George W. Schreiner of Georgetown University. He died aged 76 in 1959.²³

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Like all too many individuals who contributed notably to medicine and medical science and were not recognised Rowntree's contribution has been largely lost to notice. Only at the Mayo Clinic has he been remembered. In Nephrology, he is now only known –if at all– as part of the "et al." in Abel's landmark work on *in vivo* haemodialysis, to which he contributed so much. Perhaps this article can help to alter this neglect by medical historians.

ΠΕΡΙΛΗΨΗ

Leonard George Rowntree (1883–1959): Ένας σχεδόν ξεχασμένος πατέρας της βορειοαμερικανικής Νεφρολογίας

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Η κρίσιμη συμμετοχή του Καναδού ιατρού Rowntree στην πρώτη *in vivo* αιμοκάθαρση το 1913 στο νοσοκομείο Johns Hopkins της Βαλτιμόρης των ΗΠΑ, υπό την καθοδήγηση του John Jacob Abel, ήταν μόνο μία από τις σημαντικές συνεισφορές του Rowntree στη Νεφρολογία. Ήταν ήδη πρωτοπόρος, με τη βοήθεια του John T. Geraghty, στη χρήση μιας δοκιμασίας νεφρικής λειτουργίας με έγχυση φαινολοσουλφονυλοφθαλεΐνης (PSP) και την ανίχνευσή της στα ούρα, η οποία χρησιμοποιήθηκε κλινικά για μισό αιώνα. Ο Rowntree χρησιμοποίησε μια τεχνική αραίωσης χρωστικών για να μελετήσει τον όγκο πλάσματος σε κανονικές συνθήκες και σε ασθενείς, συμπεριλαμβανομένων εκείνων με νεφρική νόσο. Μετακόμισε στη Μινεάπολη το 1915 και εκεί εργάστηκε πάνω στην υπερφόρτωση ύδατος και την υπονατριαιμία καθώς και στη συγκέντρωση ιόντων υδρογόνου στο αίμα, χρησιμοποιώντας μια μέθοδο ρυθμιστικών που δημιούργησε. Στη συνέχεια, προς τα τέλη του Πρώτου Παγκοσμίου Πολέμου, εργάστηκε στη Γαλλία στον τομέα της αεροπορικής ιατρικής, αξιολογώντας τη σωματική και ψυχολογική καταλληλότητα υποψήφιων πιλότων. Μετά τον πόλεμο, μεταξύ πολλών προτάσεων που του έγιναν, δέχθηκε την έδρα της Ιατρικής στην περίφημη Κλινική Mayo, με στόχο την επίβλεψη και δημιουργία νέων προγραμμάτων κλινικής έρευνας. Εκεί, από νωρίς, συμμετείχε με τον Osborne στην πρώτη χρήση ιωδιδίου για τη λήψη ακτινολογικών εικόνων των λειτουργικών νεφρών (ενδοφλέβιο ουρογράφημα, IVU), το οποίο εξακολουθεί να χρησιμοποιείται και σήμερα. Αργότερα, μελέτησε την θρόμβωση του αίματος σε εξωσωματικά κυκλώματα, περιέγραψε την ιστολογία οξείας νεφρίτιδας του λύκου μαζί με τον Norman Keith και εργάστηκε πάνω στο οίδημα σε ασθενείς με νεφρικές παθήσεις και άλλους. Τέλος, ήταν ένας από τους πρώτους που ασχολήθηκαν με τα εκχυλίσματα φλοιού των επινεφριδίων και ήταν πρωτοπόρος στη θεραπεία της νόσου του Addison, που ήταν θανατηφόρα μέχρι τότε. Κατά τη διάρκεια αυτής της περιόδου στην Κλινική Mayo, από το 1921 έως το 1932, χρησιμοποίησε την εμπειρία του από το Νοσοκομείο Johns Hopkins για να οργανώσει και να στελεχώσει οκτώ ιατρικές μονάδες υποειδικοτήτων, συμπεριλαμβανομένης μιας στη νεφρική Ιατρική, οι συνεισφορές των οποίων παραμένουν εξαιρετικές και σήμερα. Ωστόσο, καθώς οι σχέσεις του με την Κλινική Μayo ψυχράθηκαν, αποχώρησε το 1931 και επέστρεψε στο Πανεπιστήμιο της Φιλαδέλφειας, κοντά στον τόπο από όπου είχε αρχίσει. Κατά τη διάρκεια του Β΄ Παγκοσμίου Πολέμου, υπηρέτησε ως διευθυντής μονάδας αξιολόγησης ανδρών για θητεία στις ένοπλες δυνάμεις καθώς και για την αποκατάστασή τους - έργο για το οποίο έλαβε Προεδρική μνεία από τον Χάρι ΣΤρούμαν το 1946. Καθ΄ όλη την επαγγελματική του ζωή, συνέχισε σταθερά να κάνει δημοσιεύσεις για κλινικά και ερευνητικά θέματα. Επί παραδείγματι, δημοσίευσε περισσότερες από 100 εργασίες τη δεκαετία του 1920, όντας ακόμα στην Κλινική Mayo, ένα αξιοσημείωτο ρεκόρ για την περίοδο. Η τελευταία του εργασία δημοσιεύθηκε λίγο πριν από τον θάνατό του το 1959, 50 χρόνια μετά την πρώτη του δημοσίευση ως γενικός ιατρός στο Κάμντεν του Νιου Τζέρσεϋ.

Λέξεις ευρετηρίου: Αεροπορική Ιατρική, Δοκιμασίες νεφρικής λειτουργίας, Έγχυση phenolsulphonephthalein, Ενδοφλέβιος πυελογραφία, Ιστορία αιμοκάθαρσης, Leonard George Rowntree, Νόσος του Addison

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