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JOURNAL OF PEPTIDE SCIENCE

Historical Essay

The life and work of Guy Newton (1919–1969)

JOHN JONES*
Balliol College Oxford, OX1 3BJ, UK

Abstract: An account is given of the life and work of G.G.F. Newton (1919–1969), joint discoverer with E.P. Abraham (1913–1999) of cephalosporin C. Copyright © 2008 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: Abraham, Sir Edward; Newton, Guy; cephalosporin C, history of; antibiotics, history of; peptide antibiotics, history of

The coupled names Abraham and Newton are very well-known in the peptide antibiotic field for their 1953 co-discovery of cephalosporin C and opening the door to its descendants for the pharmaceutical industry. The total value of the global cephalosporins market, all of it ultimately dependent on the discovery of cephalosporin C, is currently estimated by journalists at around US$ 10 billion p.a.

A great deal has been recorded about the history of cephalosporin C [1–3]. Sir Edward Abraham, although a very modest and self-effacing man, was rightly full of fame when he died in 1999 [4]. But his colleague Guy Newton died prematurely 30 years earlier, and has been all but forgotten except in name. The name itself is very familiar, in Oxford at least, because there are Guy Newton Scholarships and Fellowships, grants are made from a Guy Newton Research Fund, there are Newton–Abraham Studentships, and there is a Newton–Abraham Visiting Professorship. But for information about Newton the man, you have to dig deep, and always in Abraham's shadow. Abraham was clearly the leader, but there were only 6 years in age between them, and their names appear as equals on all the key patents. In everything he later said and wrote about their joint work, Abraham was careful to share the credit with Newton and stress the importance of his contributions. They had a master and apprentice relationship to begin with, but it soon became that of friends and colleagues. Twenty years after Newton's death, Abraham wrote of him 'My admiration for Guy, high at the beginning, continued to grow with the years. He not only became a valued colleague but also a real friend, and his early death left a gap in my life.' [5] And the Visiting Professorship established by Abraham in the late 1970s was thoughtfully named the Newton–Abraham Visiting Professorship [6] by him.

All that is easily accessible about Guy Newton at present is a two-paragraph obituary in *Nature* [7a]. There is a somewhat more expansive obituary in *Chemistry in Britain* [7c], but this is not readily found, and does not surface on database searching. The present article is an attempt to give a fuller account and appreciation of his life and work.

Guy Geoffrey Frederick Newton was born on 11 September 1919, son of Bernard Newton, an English gentleman farmer of Fairfield Bury, St Ives, Huntingdonshire, and Antoinette Gabrielle (née Gerard) his wife, who was French. He had two siblings, a younger brother and an elder sister. There is a strong family tradition of origin from the same stock as Sir Isaac Newton (1642–1727) : this is plausible, as descent can be traced back to the mid-18th century in the numerous Newtons of the Huntingdonshire – Cambridgeshire area, and Sir Isaac Newton was born in nearby Lincolnshire [8]. After prep school [9] on the Sussex coast, Guy Newton was educated, like his father before him, at Oundle School (1933–1938), where he was both sporty and academic. In1938 he matriculated at Cambridge to read Natural Science as a member of Trinity Hall. A leading oarsman, he represented his college in a IV which won the Visitors' Cup at Henley Royal Regatta in 1939. He did well in his first year exams, but his undergraduate studies were interrupted by the War. Generally, chemistry was a reserved occupation, and many chemists remained civilians. But Newton had had military initiation in the Officers' Training Corps at Oundle, and applied without hesitation to join up in September 1939. The Recruiting Board recommended him for a commission, and he joined the Royal Artillery (RA). He still spent the Phoney War term in Cambridge, but was called to training in December, and commissioned 2nd Lieutenant in September 1940. He served as a Lieutenant in the 127th Field Regiment of the RA through 1941 in England, and travelled by sea via the Cape to India in mid 1942. There he was posted to the 14th Regiment of the Royal Horse Artillery, with whom he served in India, Iran, Iraq, Syria and Egypt. He kept a very private journal in the first 2 years of the War, complaining frequently to himself of boredom and inactivity, recording his sometimes troubled thoughts about being tested under fire, doubts about leaving

* Correspondence to: John Jones, Balliol College, Oxford, OX1 3BJ, UK; e-mail: john.jones@balliol.ox.ac.uk

Cambridge (wondering whether he would ever return), and entering manhood. He discovered two things about himself during these reflections: '... one that my heart was in organic chemistry with a Biochemical bias & two that my heart was in the river...'; but warned himself that 'it would be disasterous to my career as a chemist and an oarsman if I was to fall in love seriously' [10].

In 1943 he volunteered for attachment to the Raiding Support Regiment (RSR), an élite special force. The RSR had a three-fold role: to support regular raiding forces; to bring heavy weapons to the aid of resistance groups in Greece, Albania and Yugoslavia; and to carry out irregular warfare such as blowing up bridges, roads, fuel and ammunition dumps. After tough commando-style training in Palestine, including parachute-jumping, he was engaged in various operations in the islands of the eastern Mediterranean, and with partisan groups behind enemy lines on the mainland. In December 1944 he was in Crete, and in April 1945 he took part in the fierce fighting to drive the Germans out of north eastern Italy. He won an immediate Military Cross as a Lieutenant in command of an amphibious artillery unit supporting Operation Impact Royal. This was a 3-day push by 9 Commando to frustrate demolition of vital bridges over a canal near Lake Comacchio by the retreating forces. Newton was ordered to engage closely with the enemy in advance of the main assault. The MC recommendation [11], approved by Field Marshal Alexander, concluded :

> During the whole of this Operation, when plans changed with alarming rapidity and we were subject to constant enemy shell, mortar and machine gun fire, Lt NEWTON organised his section and shot his guns with such skill and effectiveness that he was instrumental to a large degree for the success of the Commando's Operation.

He was demobbed as a Captain, and resumed his studies and rowing at Cambridge in January 1946. In the May Races he was in the Trinity Hall crew which rowed Head of the River, and he rowed at Henley again that year, partnering his brother-in-law the Olympic oar Humphrey Warren DFC AFC in the Double Sculls.

Figure 1 Guy Newton the Cambridge oarsman at bow in a coxless IV.

Figure 2 Guy Newton's trophy oars.

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Figure 3 Guy Newton the newly commissioned soldier.

Figure 4 E Battery RSR officers at Ramat David Parachute School Palestine, January 1944. From the left, Lt. Guy Newton, Maj. Pat Hill, Capt. John Bethel with Capt. Peter Munden in front.

But in 1947 he resigned as Captain of Trinity Hall Boat Club, declined an invitation to train for the Oxford and Cambridge boat race, and cut back on rowing to concentrate on his chemistry. After his finals he returned to the water, rowing in a Trinity Hall IV which won the Visitors' Cup at Henley again [12]. GW Kenner [13], another great name of peptide science, a young Fellow of Trinity Hall at this time, was one of his tutors.

In 1947, Newton obtained a place for postgraduate work in the Sir William Dunn School of Pathology at Oxford. He had second thoughts about that when he got Third Class Honours in Part II of the Natural Science Tripos (Chemistry), but Sir Howard Florey [14], Head of the Dunn School, admitted him anyway, and he became a member of University College Oxford. While a graduate student at Oxford he was invited to train for the boat

Figure 5 Lt. Guy Newton the veteran (front left) when his unit entered Athens at the liberation, late 1944. The other two prominent soldiers in RSR berets are his comrades L/Sgt. Parsons (with the dog), and Sgt. Bloxham.

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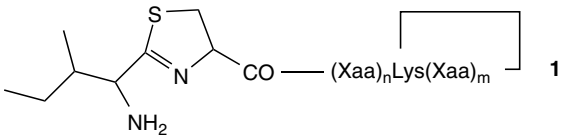
race again, now on the Oxford side, but declined again. Kenner wrote to Abraham after Newton's death [15]:

> I first knew Guy in I think 1946 when he returned to Trinity Hall from war service in Greece and other places...his knowledge of chemistry was inevitably rusty and it was a hard task for him to take Part II of the Tripos in one year. If he had spent two years over it, he might have done himself justice, but the result at the end of one year was not a fair reflection of his ability and, and therefore I was delighted that you found a place for him in your laboratory. Events since then certainly proved the soundness of your judgement...I formed an enormous respect for him and we maintained a true friendship despite the infrequency of contact...

Newton's DPhil thesis [16], for which Abraham was supervisor, was entitled *Biochemical investigations of naturally occurring antibacterial substances*. It was concerned with peptide antibiotics produced by *Bacillus subtilis* and *Bacillus licheniformis*, in particular with the complex mixture then known as ayfivin, which was resolved by counter-current distribution into at least seven peptidic components, three of them antibacterial, one of which was inseparable from bacitracin. He made incidental practical and theoretical contributions to the development of counter-current distribution. The examiners considered the thesis worthy of publication as it stood, and commented on his 'considerable aptitude for independent original research'.

In the 20 years of their association, Abraham and Newton published about 50 papers together. There were numerous reviews and preliminary notes in various journals, but the definitive papers all appeared in the *Biochemical Journal*; they are listed in the Appendix. Of their collaboration, Abraham wrote in 1969 [7c]:



Partial stucture of bacitracin A

> Guy Newton was an unusually conscientious man of absolute integrity who paid meticulous attention to detail, and he entered a field of research in which these qualities proved highly rewarding. He incorporated unselfishness and a complete lack of pretentiousness in a personality which had a positive and unforgettable flavour. A succession of colleagues are indebted to him for his help in the laboratory; and the writer also for the great good fortune of a friendship and untroubled collaboration which lasted for 20 years.

It was completely overshadowed by the cephalosporin discovery, but Abraham and Newton also did important work on the bacitracin family of peptide antibiotics, following on from Newton's DPhil work, first suggesting [17] the presence of a thiazoline ring in bacitracin A (**1**).

They worked on the nisin group too [18], and attempted to isolate the peptide hormone secretin from crude material supplied by Eli Lilly & Co., using counter-current distribution machines built to Newton's specifications. Up to 10^5-fold purification was achieved, but they were just beaten to the pure hormone by Jorpes *et al.* [19] and it was decided to leave further investigations to them [20].

Cephalosporin C was found in the complex antibiotic mixture produced by a species of *Cephalosporium* [21] flourishing near a sewage outfall off Sardinia. Cultures

Figure 6 The Sir William Dunn School of Pathology, Oxford.

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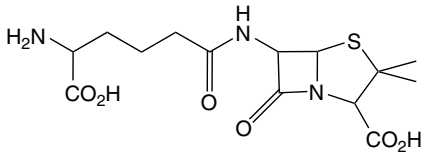
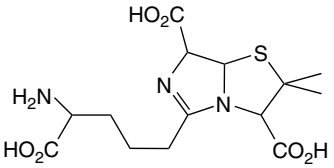


2

Cephalosporin N



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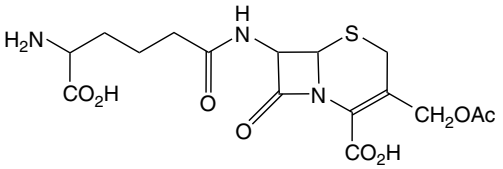
Penillic acid N



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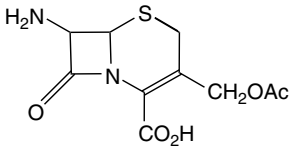
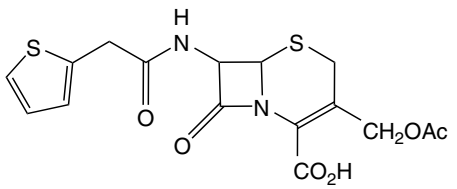
Cephalosporin C



5

7-Aminocephalosporanic acid, 7-ACA

of this mould had been investigated there by Giuseppi Brotzu [22] during the War. As his own facilities were limited, and he could not interest anyone else in Italy, after the War he asked COS Blyth Brooke [23], whom he had met as a British medical officer during the allied occupation, to explore possibilities for further research. Brooke approached the Medical Research Council (MRC), who suggested contacting Florey, which he did, and Brotzu sent Florey a culture of his fungus in August 1948. Florey gave it to NG Heatley [24] who with his Dunn School colleague Kathleen Crawford made preliminary investigations [25], and collaborated with the MRC Antibiotics Station at Clevedon [26] in Somerset. They produced larger amounts of the antibiotic material, which was shown to be a complex mixture. It was then passed to Abraham, who investigated the hydrophobic fraction first. It was terpenoid, comprising the multi-component cephalosporin P (P for gram-positive activity). Newton was not involved at that stage. But when he had finished his DPhil work, he was retained on MRC support, and stayed with Abraham to work on the hydrophilic



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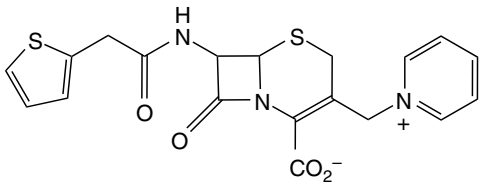
Cephalothin



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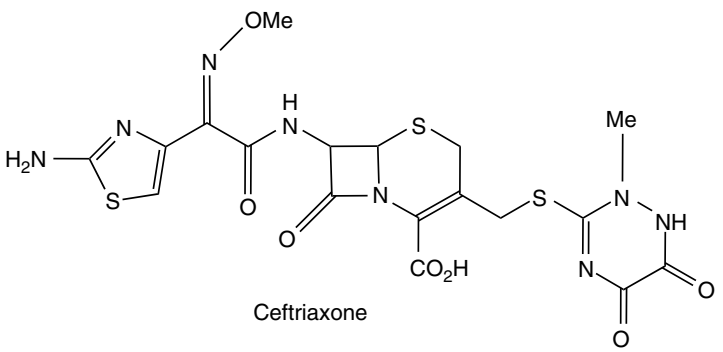
Cephaloridine



8

Ceftriaxone

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fraction of the culture. The major component of that fraction, cephalosporin N (N for gram-negative activity), was recognised as probably of the penicillin type, and was therefore judged to be worth exploring in depth. The compound responsible for the activity observed by Brotzu, it did eventually turn out to be a new penicillin (**2**) [27]. But its purification was difficult. Newton was seconded to Clevedon in early 1952 to help in the development of its production. There was some success, and, in the few months he was there, improvements were devised. These resulted in a patent [28] in his name together with Clevedon staff. The preparation was still not completely pure, however.

The structure of cephalosporin N had not been nailed down when Newton returned to Oxford. With a view to obtaining a more easily purified and characterised derivative, in September 1953, Abraham suggested converting the crude cephalosporin N to the corresponding crude penillic acid by mild acid treatment, which is a general isomerisation of penicillins, and purifying that.

When Newton performed this experiment, he was indeed able to isolate the penillic acid (**3**) pure by ion-exchange chromatography, but he did not stop the column, and in the later fractions he found a minor ninhydrin-reactive component with λ_{max} 260 nm which had come through from the crude antibiotic mixture unchanged by the acid treatment. It was put aside for a while to concentrate on cephalosporin N, which was the main focus of Florey's interest at this time. On returning to the minor product, it was found to have some similarities of chemical properties to the penicillins, but also some marked differences; and a broad spectrum of low antibiotic activity, but with resistance to penicillinase. This material, which was also later isolated with difficulty from the original antibiotic mixture, crystallised easily as a sodium salt. It was arbitrarily named cephalosporin C [29]. The inactivity of penicillinase against cephalosporin C was of importance, because bacterial strains causing infections which did not respond to penicillin therapy were evolving, and becoming problematic. Further investigation was therefore undertaken, now with strong encouragement from Florey, who did the first *in vivo* experiments. He showed it was not toxic to mice, and cured otherwise fatal artificially inflicted streptococcal infections, and reported these results [30] in April 1955. He was closely informed thereafter, but he did not put his name on any of the subsequent cephalosporin papers or patents, as many laboratory heads would have done at that time [31].

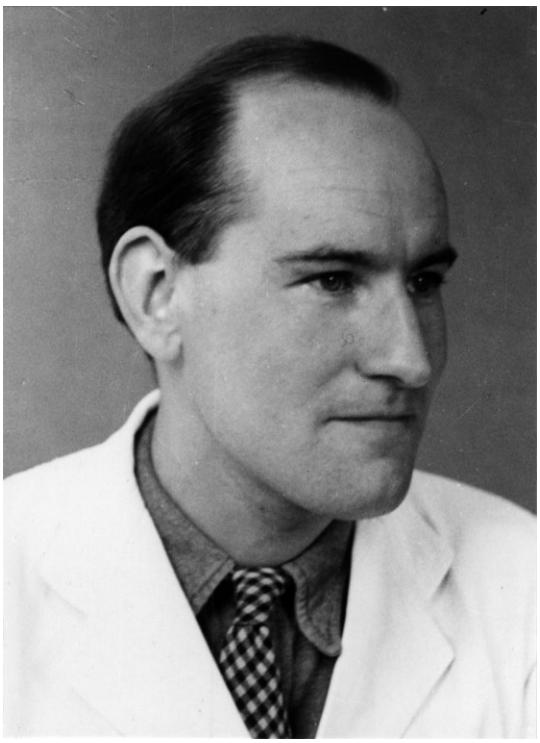

Figure 7 Guy Newton the scientist.

There was considerable feeling after the War that patenting opportunities had been missed with penicillin, and Great Britain had lost out [32]. This sparked the formation of the National Research Development Corporation (NRDC), which had a brief to help see that inventions in British universities were protected and commercially developed. Steps were taken by the NRDC to obtain patent cover [33] for cephalosporin C, and stimulate industrial interest as soon as its possible potential was appreciated. Several companies in the pharmaceutical industry were interested at an early stage, but Glaxo Laboratories Ltd. was the keenest. They were licensed to produce the antibiotic in cooperation with the Oxford and Clevedon workers [34]. Guy Newton was instrumental in helping Glaxo to get going, and made numerous visits to them; in return Glaxo produced more than 100 g of pure cephalosporin C for work at Oxford. This gave Glaxo a lead in the cephalosporin business, and contributed to the continuation of their rise from being a producer of mundane health products to being a sophisticated international drug company, which is now part of GlaxoSmithKline [2,35].

Abraham and Newton's cephalosporin C structural analysis reads as a mixture of old and new science; much depended on the study of degradation products, careful observation and colour reactions, but IR, UV and even infant NMR data were also used – it was probably the first application of NMR to an important natural product problem anywhere. What would now call for a few milligrammes of pure material and a few days with advanced instrumentation needed multigramme quantities and took 5 years. It was not until around April 1959 that the structure (**4**) was firmly established, with first public disclosure in August 1960 [36] and a full *Biochemical Journal* paper in 1961 [37], followed by Dorothy Hodgkin's X-ray confirmation

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[38] as the next paper in the same issue. Having been in disagreement 18 years previously with Robert Robinson over the structure of penicillin [39], and then eventually been proved in the right, Abraham had a similar experience over the cephalosporin C structure, albeit less protracted, with R.B. Woodward. Since these two Nobel Laureates were arguably the greatest organic chemists of all time, to have bettered them both in turn was no mean feat.

Abraham and Newton also established in principle that the peptidyl side-chain could be removed and replaced by other acyl groups with enhancement of activity – designated modification type A in Scheme 1 [40]; and that the acetoxy group was susceptible to nucleophilic displacement – designated modification type B [41].

These observations, which were also patented [43], opened the way for the pharmaceutical industry, which soon became hyperactive, to breed a whole family of valuable antibiotics based on the bicyclic cephalosporin C core, 7-aminocephalosporanic acid, 7-ACA (**5**). Typical early cephalosporins derived by making modification type A, or modifications types A and B together, are cephalothin (**6**) and cephaloridine (**7**) respectively. Cephalosporin C itself had a few clinical successes [44], but attention soon shifted to the next generation such as **6** and **7,** which were being marketed by Eli Lilly & Co. and Glaxo respectively by late 1964. Ceftriaxone (**8**) is an example of one (of the 'third generation') currently in widespread use. The number of cephalosporins which have been marketed is now very large [45].

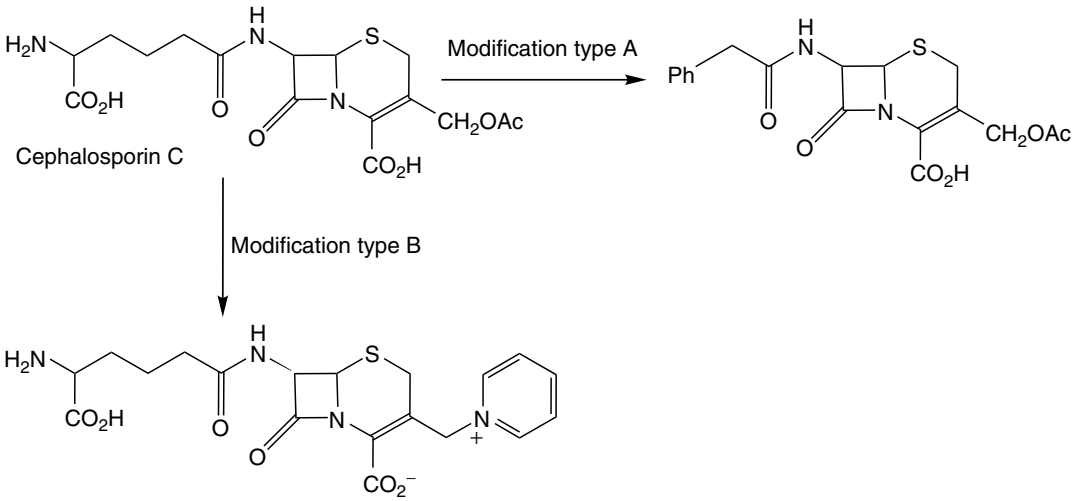
With the essentials defined, and the pharmaceutical companies vigorously engaged, further development of derivatives for marketing and use in medical practice was largely left to them. But the chemistry and biochemistry (especially mapping the biosynthetic pathways) of cephalosporin C and its simple derivatives remained the main thrust of Abraham and Newton's interests for the rest of Newton's life; see the titles of their main papers in the Appendix.

Through the 1950s Newton was an MRC external member of staff, on a succession of insecure appointments. In 1958, the MRC began to take the view that the University of Oxford should do the decent thing and take Newton onto its payroll, and in 1960 Florey urged that this should be done. The uncertainty, he wrote, was

> .....very upsetting not only to me and Newton but also to Abraham, for Newton and Abraham work together admirably and during Newton's stay here they have turned out a succession of first class pieces of chemical work on substances of biological interest, which has won for them wide recognition not only in this country but in the United States. This work culminated in particular in the demonstration of a new antibiotic, cephalosporin C, which I feel quite confident will in one form or another reach medical practice.

The MRC had, somewhat grudgingly it seems, agreed to support Newton until October 1962, but, Florey continued,

> ... this is however of only limited value in settling the problem with which Newton, Abraham and I are confronted,



Scheme 1 The modification of cephalosporin C. *Conditions for modification type A* [40]: partial hydrolysis with dilute HCl to give 7-ACA in very low yield followed by acylation with, in this example, $PhCH_2COCl$. The product had 100-fold enhanced antibiotic activity versus *Staphylococcus aureus*. Developments in the Eli Lilly & Co. Research Laboratories in Indianapolis a little later [42] enabled 7-ACA to be produced in good yield, giving easy access to diverse semi-synthetic cephalosporins. *Conditions for modification type B* [41]: aq. pyridine. The product in this example had enhanced activity versus *S. aureus* and also versus *Salmonella typhi*, but the relative activities were different from those of cephalosporin C. Other heterocyclic bases also reacted, giving products with varying spectra and levels of activity.

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> for Newton rightly says that at the age of 40 he cannot in the interests of his family, if not for himself, go on in a state of uncertainty... Already he has had several tentative offers from industry in this country and from at least two firms in the United States...it would redound to nobody's credit in this country if some form of permanent employment cannot be found for Newton in the academic sphere for which he is peculiarly fitted.

In the face of such pressure from such a man, it is difficult to see how the University could have evaded its responsibility, so Newton was duly taken on, and after the usual 5 years of probation he was given tenure until retirement as a Senior Research Officer [46].

For the last 15 months of his life, Newton was a Fellow of the new-born St Cross College, which was created by the University of Oxford in 1965 to give a collegiate base to the established academics, by then many of them, who were entitled by seniority and status to expect one, but who had not been absorbed into the traditional college system. Establishment Oxford outside the Dunn School was slow to give Guy Newton proper recognition.

The University of Oxford had no policy in the 1950s regarding the patenting of inventions by its staff. Abraham was a University employee, but when cephalosporin C was discovered, Newton was on the MRC payroll, albeit notionally part time. So, although the patents were in the joint names Abraham and Newton, and they had agreed to an equal split, the revenue-division between them was unequal, the MRC taking part of Newton's share [47]. The NRDC, which later became the British Technology Group (BTG), took half of all the income as it had been the investor of time, trouble and money in the business side of it all, and the cephalosporins were its biggest early success. Abraham and Newton could both have become rich from the discovery, but much of what they could have taken as personal wealth was laid down voluntarily in charitable trusts to support the Dunn School, Lincoln College, the University of Oxford, medical, chemical and biological science, the Royal Society and King Edward VI School Southampton. Between them the Charities they created [48] now have capital approaching £200 million, and benefactions to Oxford chemical and biomedical science probably now total around £50 million, and are ongoing.

A fit and lean man all his life, Guy Newton died on New Year's Day 1969 in the Radcliffe Infirmary, shortly after suffering a massive heart attack while chopping a tree down in the garden of his family home, 'Windrush', on Shotover Hill, Oxford.

In 1953 he married Rosemary Enid Stowers, daughter of Dr Raymond Stowers MC, of the Royal Army Medical Corps in World War I. She survived him for nearly 30 years with their two daughters, now Mrs Frances Anderson and Mrs Joanna Oulton, who are warmly thanked for their help in compiling this late memoir.

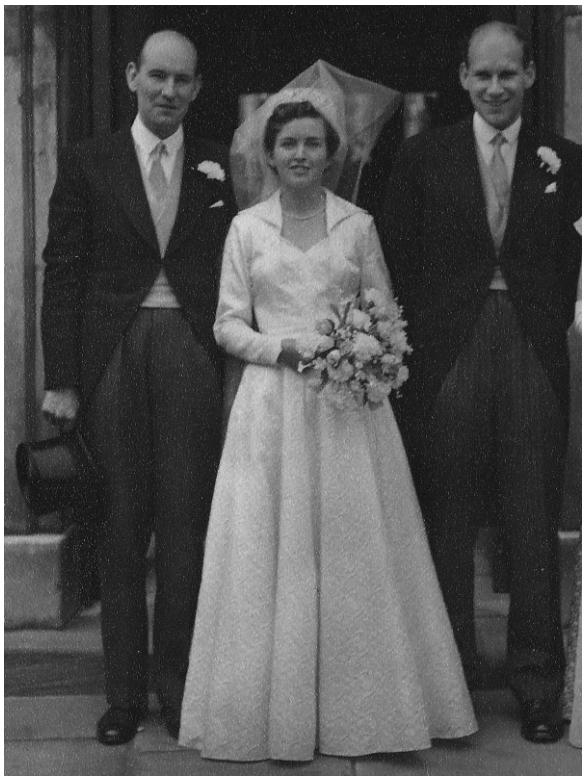

Figure 8 Guy Newton (on the left) on his wedding day, with his bride and brother Anthony.

Figure 9 Guy Newton the family man, with Rosemary Newton and their daughter Frances.

For many years after penicillin entered medical practice, the role of Norman Heatley attracted little attention, although the isolation of workable quantities

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of penicillin was largely dependent on his ingenuity and skill. There is an analogy for us here which I owe to one of Guy Newton's last young associates, who shall have the last word [49]: 'Newton is to cephalosporins as Heatley was to penicillins, viz the unsung hero'.

Acknowledgements

I began this memoir in almost complete ignorance of Guy Newton. Indeed, the blankness of the accessible record about him was why I took the task upon myself. Many people have contributed facts or clues, or been willing stepping stones to useful sources. I am especially grateful to Harry Bennett, Head of Humanities at the University of Plymouth, for providing a large relevant section of the memoirs of Sgt. Walter Jones (RSR) which he is editing. Research at the National Archives, Kew was undertaken by Roger E. Nixon, Military and Historical Searches, London. Thanks for information are also due to Sir Henry Harris FRS, Regius Professor of Medicine Emeritus, Oxford; [David]Anthony Newton, Guy Newton's brother; ex-Bdr. William Osborne (RSR); ex-Maj. Pat Hill (RSR); Janet Hurst of the Society for General Microbiology; Valerie Boasten, Secretary to the Trustees of the three Charities arising from cephalosporin C; Simon Dawkins, grandson of Sgt. Robert Parkes (RSR); Jeremy Hamilton-Miller, Emeritus Professor of Medical Microbiology, Royal Free and University College Medical School, London; Eric Sidebottom, Archivist, Sir William Dunn School of Pathology Oxford; Robin Darwall-Smith, Archivist, University College Oxford; Jacqueline Cox of the University Archives, Cambridge; Stephen Forge, Archivist, Oundle School; John Pollard, Fellow Archivist, Trinity Hall Cambridge; Simon Bailey, Alice Millea, and Cara Downes of the University Archives, Oxford; Colin Harris of the Bodleian Library; and my son Peter Jones of the Royal Hospital, Brisbane.

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5. Abraham EP. Fax to R Marston, 25 October 1990. Bodleian Library EP Abraham Papers, H.195.
6. There is Trustees' material concerning the foundation of this prestigious chair in the Bodleian Library EP Abraham Funds Papers A.115–A.118, but this collection is effectively closed until 2050.The corresponding University Offices file (PAT/10/3,file1) survives only in microfiche, of which there is a copy in the University Archives. The first incumbent of the chair was AJ Birch FRS; his successors have included Nobel Laureates James Watson, Konrad Bloch and Jean-Marie Lehn.
7. Obituaries: (a) Anon. *Nature* 1969; **221**: 885–886; (b) Anon. *J. Antibiotics* 1969; **22**: 135; (c) Abraham EP . *Chemistry in Britain* 1969; **5**: 368. The basic biographical information given in this essay is derived from these obituaries, amplified by the helpfulness of many archivists and others. The first two obituaries were in fact by Abraham, much reduced editorially. In 1990 he wrote [5] of the one in *Nature* : "In retrospect it seems rather colourless, but it is the kind of thing that was asked for".
8. A pedigree is in possession of the family. Independent checking corroborates it back to William Newton, great-great-grandfather of Guy Newton; he was living in Ramsey Huntingdonshire at the time of the 1851 census, recorded as a retired farmer, aged 81, born at Manea Cambridgshire.
9. Seafield School, Bexhill-on-Sea (now defunct); a POW camp during WWII.
10. Newton GGF. Private journal ca 1940–1942; In possession of the family.
11. Military Cross recommendation for WS/Lt 148684 Guy Geoffrey Frederick Newton, May 1945, National Archives, in WO 373/13. Operation report on Operation Impact Royal, National Archives, WO170/4.825. Newton's section for this action was No.4 Sec. 12 Tp. 'E'. Bty R.S.R. Professor Harry Bennett is editing the memoirs of Sgt. Jones, who was with Newton's section at Lake Comacchio, for the University of Plymouth Press; provisional title *Sergeant Jones's War: A Memoir of Life with the Raiding Support Regiment in the Mediterranean 1943–1945*.
12. Swann JT. *The Trinity Hall Boat Club 1928 to 1949*. Cambridge, 1950; 58–59.
13. Todd AR. George Wallace Kenner 16 November 1922–26 June 1978. *Biogr. Mem. Fellows R. Soc.* 1979; **25**: 390–420.
14. Abraham EP. Howard Walter Florey, Baron Florey of Adelaide and Marston 1898–1968. *Biogr. Mem. Fellows R. Soc.* 1971; **17**: 255–302.
15. Kenner GW. Letter to Abraham, 4 February 1969; Bodleian Library EPAbraham Papers, H.192.
16. Newton GGF. DPhil Thesis, Oxford, 1950 Work TS, Woods DD. *Examiners' Report to the Board of the Faculty of Medical Sciences*, Oxford University Archives, in FA 4/9/2/11, Oxford, 21 June 1950.
17. Newton GGF, Abraham EP. Observations on the nature of bacitracin A. *Biochem. J.* 1953; **53**: 606–613.
18. (a) Berridge NJ, Newton GGF, Abraham EP. Purification and nature of nisin. *Biochem. J.* 1952; **52**: 529–535; (b) Berridge NJ, Newton GGF, Abraham EP. Sulphur-containing amino-acids of nisin. *Nature* 1953; **171**: 606.
19. Jorpes JE, Mutt V, Magnusson S, Steele BB. Amino acid composition and N-terminal amino acid sequence of porcine secretin. *Biochem. Biophys. Res. Commun.* 1962; **9**: 275–279.
20. Newton GGF. *Report on Period of Office as Senior Research Officer*. Oxford University Archives: FA/9/2/640; FGB/NEWTON GGF, 1966.
21. *Cephalosporium acremonium* was the name assigned then, *Acremonium chrysogenum* is the correct name now.
22. Giuseppi Brotzu (1895–1976), Professor of Hygiene, University of Cagliari (Rector 1936–1945).
23. Charles Owen Swithin Blyth Brooke (*c*.1900–1971) sometime Medical Officer of Health, Finsbury.

24. Norman George Heatley OBE (1911–2004). Obituary: *The Guardian* 8 January 2004 See also: Hamilton-Miller JMT. Dr Norman Heatley. *J. Antimicrob. Chemother.* 2004; **53**: 691–692.
25. Crawford K, Heatley NG, Boyd PF, Hale CW, Kelly BK, Miller GA, Smith N. Antibiotic production by a species of *cephalosporium*. *J. Gen. Microbiol.* 1952; **6**: 47–59.
26. This MRC unit was set up about 1949 to screen for new antibiotics, make research quantities and develop fermentation methods for their production. For three or four years before that it had been a modest scale penicillin plant run by the Distillers' Company. Florey was a leading figure in establishing and steering it until it closed about 1961. Its last important contribution was the isolation of a fungal strain which gave a much higher yield of cephalosporin C, which was then taking off. There are several files on the Clevedon Station in the National Archives, class FD; see especially FD 1/86 for its activities in the early fifties. See also Carlile M. A strange episode in the history of antibiotics. *Microbiol. Today* 2004; **31**: 9.
27. Newton GGF, Abraham EP. Degradation, structure and some derivatives of cephalosporin N. *Biochem. J.* 1954 **58**: 103–111. The antibiotic was later called penicillin N; it was also found to be identical with an antibiotic isolated in the USA; Abraham EP, Newton GGF, Schenck JR, Hargie MP, Olson BH, Schuurmans DM, Fisher MW, Fusari SA. Identity of cephalosporin *N* and synnematin *B*. *Nature* 1955; **176**: 551.
28. Miller GA, Kelly BK, Newton GGF. *Cephalosporin N Production*. 1958; US 2831797, assigned to the NRDC.
29. (a) Newton GGF, Abraham EP. Cephalosporin *C*, a new antibiotic containing sulphur and D-α-aminoadipic acid. *Nature* 1955; **175**: 548 [submitted 3 February 1955, the day after the Patent Application was made; publication date 26 March 1955]; (b) Newton GGF, Abraham EP. Isolation of cephalosporin C, a penicillin-like antibiotic containing D-α-aminoadipic acid. *Biochem. J.* 1956; **62**: 651–658.
30. Florey HW. Antibiotic products of versatile fungus. *Ann. Intern. Med.* 1955; **43**: 480–490. [The James D Bruce Memorial Lecture, delivered in Philadelphia, 25 April 1955].
31. Florey did accept 0.5% of the revenue arising from a complex agreement of 1967 between Abraham, Newton and the NRDC but this concerned all the patents in the cephalosporin field, including cephalosporin N.
32. Sheehan JC. *The Enchanted Ring; the Untold Story of Penicillin*, Chapter 6, MIT Press: Cambridge Massachussetts, 1982; 161–197.
33. Abraham EP, Newton GGF. *Cephalosporin C*. 1959; GB 810196, assigned to the NRDC. Application 2 February 1955.
34. National Archives, FD23/1929 is the MRC file "Collaboration between Oxford, Clevedon, NRDC and Glaxo for production of Cephalosporin C", 1955–1958.
35. Jones E. *The Business of Medicine. The Extraordinary History of Glaxo, a Baby Food Producer, Which Became One of the World's Most Successful Pharmaceutical Companies*. Profile Books Ltd.: London, 2002.
36. Abraham EP, Newton GG. Degradation of cephalosporin C. Oral presentation at Canberra on 22 August 1960, at session CS3 of the IUPAC International Symposium on the Chemistry of Natural Products. Abraham's annotated copies of the Symposium Handbook and Abstracts Book are in Bodleian Library EP Abraham Papers, F.2; the text he prepared for the presentation is in E.37.
37. Abraham EP, Newton GGF. The structure of Cephalosporin C. *Biochem. J.* 1961; **79**: 377–393.
38. Hodgkin DC, Maslen EN. The X-ray analysis of the structure of cephalosporin C. *Biochem. J.* 1961; **79**: 393–402.
39. Curtis R, Jones J. Robert Robinson and penicillin: an unnoticed document in the saga of its structure. *J. Pept. Sci.* 2007; **13**: 769–775.
40. Loder B, Newton GGF, Abraham EP. The cephalosporin C nucleus (7-aminocephalosporanic acid) and some of its derivatives. *Biochem. J.* 1961; **79**: 408–416. On the history of the cephalosporin penicillin nuclei see; (a) Rolinson GN, Geddes AM. The 50th anniversary of the discovery of 6-aminopenicillanic acid (6-APA). *Int. J. Antimicrob. Agents* 2007; **29**: 3–8; (b) Hamilton-Miller JMT. Development of the semi-synthetic penicillins and cephalosporins. *Int. J. Antimicrob. Agents* (in press).
41. Hale CW, Newton GGF, Abraham EP. Derivatives of cephalosporin C formed with certain heterocyclic tertiary bases. The cephalosporin C_A family. *Biochem. J.* 1961; **79**: 403–408.
42. Morin RB, Jackson BG, Flynn EH, Roeske RW. Chemistry of cephalosporin antibiotics. I. 7-Aminocephalosporanic acid from cephalosporin C. *J. Am. Chem. Soc.* 1962; **84**: 34501–33402.
43. (a) [Modification type A] Abraham EP, Newton GGF, Boothroyd B. *Derivatives of Cephalosporin C*. 1964; GB 953695, assigned to the NRDC. Application 4 August 1959; (b) [Modification type B] Abraham EP, Newton GGF, Hale CW. *Cephalosporin C Compounds*. 1962; GB 912541, assigned to the NRDC. Application 17 March1958; (c) [Modifications types A and B together] Abraham EP, Newton GGF. *N-acyl Derivatives of 7-aminocephalosporanic Acid and Related Compounds*. 1964; GB966221, assigned to the NRDC. Application 20 January 1960. Numerous other patents followed on from these.
44. Walker HM. Letters to Abraham, 1 November 1961 and 7 June 1962. Bodleian Library EP Abraham Papers, in C.884 and C.886.
45. A useful survey of the range in 1983 is given in the following: Knothe H, Dette GA. The current state of cephalosporin antibiotics. Microbiological aspects. *Infection* 1983; **11**(Suppl. 1): S12–S15. The comment is made that 'An increasing number of new cephalosporins continue to become available in the clinic, so that the clinician requires something akin to Ariadne's thread to work through the labyrinth of confusing names and product claims'. The choice is even wider now; *embarrasse de richesse* comes to mind. For a history of the development and four-generation proliferation see; Sneader W. Antibiotic analogues. In *Drug Discovery. A History*. John Wiley & Sons: Chichester, 2005; 319–340.
46. Personnel file on Newton. Oxford University Archives FA/9/2/640, FGB/NEWTON GGF.
47. Abraham EP. Letter (copy) to HH Turner of NRDC, 24 June 1955. Bodleian Library EP Abraham Papers, C.525.
48. There are three charities, all of them registered with the Charity Commission and independent of the University of Oxford: the Edward Penley Abraham Research Fund (1967,309659); the E. P. A. Cephalosporin Fund (1970,309698); and the Guy Newton Research Fund (1967,309696). In capital terms the last is the smallest at about £8 million, but this is because Guy Newton's share of the money was partly taken by the MRC and he died so prematurely. The three charities have a common origin in joint discovery and philanthropy.
49. Hamilton-Miller JMT. Email to the author 31 August 2007.

APPENDIX

A List of Full Papers by Abraham and Newton *et al.* in *Biochem. J*

1950

1. Ayfivin and bacitracin: resolution of crude products into similar series of peptides.

1952

2. Purification and nature of the antibiotic nisin.

1953

3. Some properties of the bacitracin polypeptides.
4. Observations on the nature of bacitracin A.

1954

5. Purification and some properties of cephalosporin N, a new penicillin.
6. Degradation, structure, and some derivatives of cephalosporin N.
7. Synthesis of D-δ-amino-δ-carboxyvaleroylglycine (a degradation product of cephalosporin N) and of DL-δ-amino-δ-carboxyvaleramide.

1955

8. The *N*-terminal and sulphur containing residues of bacitracin A.

1956

9. Isolation of cephalosporin C, a penicillin-like antibiotic containing D-α-aminoadipic acid.
10. Experiments on the degradation of cephalosporin C.
11. A comparison of the action of penicillinase on benzylpenicillin and cephalosporin N and the competitive inhibition of penicillinase by cephalosporin C

1960

12. Further degradation products of cephalosporin C. Isolation and synthesis of 2-(4-amino-4-carboxybutyl) thiazole-4-carboxylic acid.

1961

13. The structure of cephalosporin C.
14. Derivatives of cephalosporin C formed with certain heterocyclic tertiary bases. The cephalosporin C_A family.
15. The cephalosporin C nucleus (7-aminocephalosporanic acid) and some of its derivatives.
16. Deacetylcephalosporin C.

1962

17. Behaviour of some derivatives of 7-aminocephalosporanic acid and 6-aminopenicillanic acid as substrates, inhibitors, and inducers of penicillinases.
18. Incorporation of acetate into cephalosporin C.

1965

19. Production and purification of bacilysin.

1967

20. Biosynthesis of penicillin N and cephalosporin C. Antibiotic production and other features of the metabolism of a *Cephalosporium* sp.
21. Use of α-aminoadipic acid for the biosynthesis of penicillin N and cephalosporin C by a *Cephalosporium* sp.
22. The role of valine in the biosynthesis of penicillin N and cephalosporin C by a *Cephalosporium* sp.

1969

23. Behaviour of α-aminoadipylcysteine and glutamylcysteine in the presence of intact and disrupted mycelium of a *Cephalosporium* sp.

1970

24. Products of aminolysis and enzymic hydrolysis of the cephalosporins.

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