Hospital Radiopharmacy in the UK

17

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The first great expansion in nuclear medicine took place around 1970 with the introduction of the $^{99}Mo/^{99m}Tc$ generator and kit preparations, allowing convenient on site production of radiopharmaceuticals. That being said, I would be remiss if I did not begin by mentioning the seminal work of Stephen Garnett (much later my PhD supervisor) in development of the ^{51}Cr EDTA technique for determination of glomerular filtration rate [1].

In the early days, hospital radiopharmacy usually fell under the remit of medical physics and regulation was somewhat informal. The Medicines Act 1968 was the first legislation to classify radiopharmaceuticals as drugs. In the early 1970s, the Medicines Control Agency (MCA, later Medicines and Healthcare Products Regulatory Agency, MHRA) took an interest in improving the standards for practice of radiopharmacy but at this point theirs was only an advisory role. An early guideline on preparation of radiopharmaceuticals in hospitals was published by the British Institute of Radiology in 1975 [2]. With the loss of Crown Immunity in 1991, radiopharmacy came under the full scrutiny of the MHRA and standards have been continually tightened since then. Indeed, the UK led the world in this, for which the world does not thank us.

Hospital radiopharmacy is now one of the most heavily regulated specialties imaginable. Radiopharmaceuticals are drugs (MHRA) but also radioactive materials (Environment Agency), sources of radioactive exposure (Health and Safety Executive), for which patient exposure must be optimized (Care Quality Commission) and which must be transported safely (Office of Nuclear Regulation). Moreover, these different regulatory agencies can have conflicting requirements. For safety of the operator, radioactive materials should be handled under negative

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R. McCready et al. (eds.), *A History of Radionuclide Studies in the UK: 50th Anniversary of the British Nuclear Medicine Society*,
DOI 10.1007/978-3-319-28624-2_17

air pressure but for safety of the patient these procedures should be under positive pressure. For safety of the operator in case of contamination there should be a sink nearby, but sterile pharmaceuticals must not be handled anywhere near a sink. One issue they all agree on is that disposable gloves and gowns are a good idea. As such a specialist area, few of the agency inspectors have full understanding, which can lead to disastrous outcomes. A classic case occurred some 15 years ago when an MHRA inspector insisted that a radiopharmacy sanitise its kits with chlorine based disinfectants rather than the usual alcohol; the next day all the products failed because ^{99m}Tc labeling requires reducing conditions but the residual chlorine was an oxidant.

It is believed that the first hospital radiopharmacy in the UK was established at the Liverpool Clinic in the late 1950s. Most radiopharmacies at major teaching hospitals were set up in the early 1970s. Radiopharmacy as a specialty became recognized under the Regional Pharmacists Committee and the first formal meeting of radiopharmacists took place on 26 January 1977 at a pub in Cambridgeshire. In attendance were Malcolm Frier (Nottingham General Hospital), Stuart Hesslewood (City Hospital, Birmingham), Penny Hill (Bristol Royal Infirmary), Colin Lazarus (Guy's Hospital, London), Bill Little (Royal Liverpool Hospital), and Teresa McCarthy (Addenbrooke's Hospital, Cambridge). The Regional Radiopharmacists Subcommittee eventually morphed into the UK Radiopharmacy Group (UKRG) under which name it is still going strong (www.ukrg.org.uk). UKRG remains a public sector organisation (there are no commercial members) with broadly geographical representation and includes members from PET, IPEM, MHRA, and academia.

Since the 1990s the UKRG has held an annual workshop open to the radiopharmacy community and industry in January at The Beeches conference centre in Bourneville, Birmingham. Attendance has grown to about sixty, the capacity of the venue. In the mid 1990s, UKRG published the UK Radiopharmacy Handbook, which was updated in 2002. Much of the content in the original handbook is now easily accessible via the internet, but certain sections remain on the UKRG website as Radiopharmacy Information Resources. UKRG has also published guidance documents on a variety of issues.

Also since the 1990s an annual postgraduate lecture course in radiopharmacy has been held at King's College London under the auspices of the UKRG. Originally set up by Tony Theobald (KCL) and Stephen Mather (St Bartholomew's Hospital, Queen Mary University, Cancer Research Campaign), it has latterly been organised by Jim Ballinger (KCL, Guy's and St Thomas' Hospital). This is open to anyone interested in the field and is offered for credit to students on the MSc in Nuclear Medicine Science (KCL), MSc in Pharmaceutical Technology and Quality Assurance (PTQA; originally at the University of Leeds, now at University of Manchester), and the new MSc in Clinical Pharmaceutical Science (University of Manchester). Annual attendance varies between 20 and 45. UKRG has also co-sponsors with KCL a biannual practical course in radiochemical purity testing; laboratory space limits attendance to 20.

The UKRG has maintained a database of adverse reactions and product defects. For many years annual summaries were published in the European Journal of Nuclear Medicine blue pages and the plan is for this tradition to resume.

Throughout the years, UKRG members have played an important role in such UK organisations as the British Nuclear Medicine Society (BNMS) and the Administration of Radioactive Substances Advisory Committee (ARSAC), as well as the European Association of Nuclear Medicine (EANM). The biannual European Symposium on Radiopharmacy and Radiopharmaceuticals has been hosted in the UK on three occasions.

Charles Sampson (Addenbrooke's Hospital, Cambridge) edited the Textbook of Radiopharmacy in 1990. It is now in its fourth edition, edited by Tony Theobald, and renamed Sampson's Textbook of Radiopharmacy in Charlie's honour.

There have been many developments in Positron Emission Tomography (PET) in which the UK has played a major role, with the original two PET centres at the Hammersmith Hospital and the University of Aberdeen, and the first clinical PET centre at Guy's and St Thomas' Hospital. However, this development has largely been in parallel with hospital radiopharmacy rather than part of it; both fields have been poorer because of this missed opportunity.

The presence in the UK of one of the largest radiopharmaceutical companies, Amersham International, now part of GE Healthcare, meant that a number of new ^{99m}Tc labeled radiopharmaceuticals were first put into humans in UK nuclear medicine departments. These include cerebral perfusion imaging with ^{99m}Tc HMPAO (Ceretec) at the Middlesex Hospital [3] and Aberdeen [4], myocardial perfusion imaging with ^{99m}Tc tetrofosmin (Myoview), based on chemistry developed at the University of Cardiff, also at Aberdeen [5], and hypoxia imaging with ^{99m}Tc HL91 (Prognox, never marketed) at Guy's Hospital [6]. Mention must also be made of the development of cell radiolabeling techniques by the group under the direction of Michael Peters at the Hammersmith Hospital, leading to ^{111}In tropolonate [7] and ^{99m}Tc HMPAO [8] becoming standard labeling methods worldwide. This is now being extended to subpopulations of cells [9]. Over the last 50 years we have witnessed great changes within the radiopharmaceutical industry, as I have chronicled elsewhere [10]. At times the radiopharmaceutical divisions have suffered as minor cogs in the big wheel of a pharmaceutical or chemical company.

Within pharmacy, radiopharmacy has suffered by being classified as a technical service when in reality it is among the most clinical of specialties. The radiopharmacy is often embedded in a clinical nuclear medicine department where it is impossible to avoid patients even if one wanted to. Where else can one see the full gamut — from raw materials to injectible product to clinical results — all within a matter of minutes to hours? I'm still amazed every time I see a beating heart on the processing monitor. But pharmacy is only one route into radiopharmacy, and the lack of a defined career path has created problems in recruitment and succession planning. Finally in 2013 Health Education England set up a scientist training programme in Clinical Pharmaceutical Science which will lead to state registration with the Health and Caring Professions Council (HCPC). Finally, formal recognition of radiopharmacy.

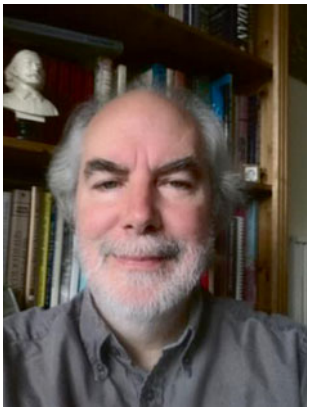
In summary, the practice of hospital radiopharmacy has become much more tightly controlled over the last 50 years. Ensuring high standards has been expensive both in terms of operating and capital costs. Ironically, this has protected NHS

radiopharmacies by making the UK unattractive for commercial radiopharmacies. But this has also slowed the implementation of new procedures which are virtually routine elsewhere; witness the limited availability of ^{68}Ga labeled peptides in the UK. My greatest sadness is that the diversion of human resources to regulatory issues has virtually killed hospital based radiopharmaceutical research and development in the UK. Despite this, members of the UK community continue to play an important role nationally and internationally in advancing the practice of hospital radiopharmacy.

References

1. Garnett ES, Parsons V, Veall N. Measurement of glomerular filtration-rate in man using a ^{51}Cr-edetic-acid complex. Lancet. 1967;1:818–9.
2. Taylor DM, Brock M, Frier M, Joshi VK, Jewkes R, Keeling DH, Hughes D, Little WA, Smith PH, Trott NG, Watson IA, Whately TL, Wood EJ. Guidelines for the preparation of radiopharmaceuticals in hospitals. London: British Institute of Radiology; 1975.
3. Ell PJ, Jarritt PH, Cullum I, Hocknell JM, Costa DC, Lui D, Jewkes RF, Steiner TJ, Nowotnik DP, Pickett RD, et al. Regular cerebral blood flow mapping with ^{99m}Tc-labelled compound. Lancet. 1985;2:50–1.
4. Sharp PF, Smith FW, Gemmell HG, Lyall D, Evans NT, Gvozdanovic D, Davidson J, Tyrrell DA, Pickett RD, Neirinckx RD. Technetium-99m HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. J Nucl Med. 1986;27:171–7.
5. Higley B, Smith FW, Smith T, Gemmell HG, Das Gupta P, Gvozdanovic DV, Graham D, Hinge D, Davidson J, Lahiri A. Technetium-99m-1,2-bis[bis(2-ethoxyethyl)-phosphino]ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. J Nucl Med. 1993;34:30–8.
6. Cook GJ, Houston S, Barrington SF, Fogelman I. Technetium-99m-labeled HL91 to identify tumor hypoxia: correlation with fluorine-18-FDG. J Nucl Med. 1998;39:99–103.
7. Peters AM, Saverymuttu SH, Reavy HJ, Danpure HJ, Osman S, Lavender JP. Imaging of inflammation with indium-111 tropolonate labeled leukocytes. J Nucl Med. 1983;24:39–44.
8. Peters AM, Danpure HJ, Osman S, Hawker RJ, Henderson BL, Hodgson HJ, Kelly JD, Neirinckx RD, Lavender JP. Clinical experience with ^{99m}Tc-hexamethylpropylene-amineoxime for labelling leucocytes and imaging inflammation. Lancet. 1986;2:946–9.

9. Lukawska JJ, Livieratos L, Sawyer BM, Lee T, O'Doherty M, Blower PJ, Kofi M, Ballinger JR, Corrigan CJ, Gnanasegaran G, Sharif-Paghaleh E, Mullen GE. Real-time differential tracking of human neutrophil and eosinophil migration in vivo. J Allergy Clin Immunol. 2014;133:233–9.
10. Ballinger J. News and views. Nucl Med Commun. 2014;35:218–20.



James R. Ballinger I retired in 2015 after spending 31 years in clinical radiopharmacy, half of that time in Canada, the remainder in the UK. Born in Toronto, I obtained my BSc in Pharmacy from the University of Toronto in 1976, followed by an MSc in analytical toxicology. I was then persuaded to undertake a 1-year residency in radiopharmacy at Chedoke-McMaster Hospital in Hamilton, followed by a PhD in PET radiochemistry, where my project involved synthesis and evaluation of ^{18}F-fluoronicotine for regional cerebral perfusion studies and investigation of the nicotinic acetylcholine receptor. In 1984 I took a position as radiopharmacist at Ottawa Civic Hospital where I developed a profile as an independent researcher. I moved to the Ontario Cancer Institute and Princess Margaret Hospital in Toronto in 1990 and continued research in multidrug resistance to chemotherapy and hypoxia imaging. In 1999, perhaps unwisely, I migrated against the rotation of the earth to take a post at Addenbrooke's Hospital in Cambridge. My final move was in 2003 to Guy's and St Thomas' Hospital and King's College London, where I was involved in setting up and teaching on the MSc in Radiopharmaceutics and PET Radiochemistry. I am a fellow of the Royal Society of Chemistry. I have published more than 110 peer reviewed scientific papers, 20 invited reviews, 12 book chapters, and have given invited lectures in North America, Europe, and Japan.

I served lengthy terms as newsletter editor, first for the Canadian Association of Radiopharmaceutical Scientists (CARS) and later the UK Radiopharmacy Group, and a shorter term as News and Views editor for BNMS. I was chair of the Canadian Society of Nuclear Medicine and a member of the radiopharmacy committee of the European Association of Nuclear Medicine, the radioactive drugs committee of the British Pharmacopoeia, and the Administration of Radioactive Substances Advisory Committee. In the latter role I contributed to two reports on future provision of ^{99m}Tc. I represented the UK on a three person delegation to lobby the European Parliament during the drafting of the Clinical Trials Regulations.

My outside interests include music, theatre, and literature. In my retirement I intend to drink less coffee and more wine.