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Review Article

Amersham Radiochemistry to GE Healthcare†

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Abstract: I was invited by Professor John R. Jones (University of Surrey) to write a paper to celebrate 50 years of the Journal of Labelled Compounds and Radiopharmaceuticals. The aim of this paper is to outline *briefly* the history of radiochemistry from The Radiochemical Centre at Amersham in the 1940s to the acquisition by General Electric in 2004 and the formation of GE Healthcare. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: radium; carbon-14; The Radiochemical Centre; Amersham; tritium; GE Healthcare

Part 1: A brief history of Amersham

The forties[1]

The birth of radiochemistry at Amersham, Buckinghamshire, UK, was started by a 26-year-old organic chemist, Dr Walter Patrick Grove CBE (1915–1986), at the onset of World War II in a country dwelling known as Chilcote House (Figure 1).

Chilcote House became synonymous with the extraction of pure radium from radium concentrates and played a crucial role in the war effort. A large amount of radium concentrates were obtained from a shipment from Portugal, which was destined for Germany's war effort. These radium concentrates were impounded at the London docks by the British Government to prevent their transportation to Germany. The pure radium was used to manufacture luminous paint which could be used for creating self-illuminating instrument dials and aircraft gun sights. Today, Chilcote House serves as the reception area for the manufacturing facility now located on the site.

In 1940, Dr Patrick Grove (Figure 2) and the 'Chilcote' team carried out their first experiments to measure the radium content in the concentrates using gamma-ray emission in conjunction with radium standards supplied by the National Physical Laboratory. When

Figure 1 Amersham's birthplace: Chilcote House, Amersham, Buckinghamshire.

Figure 2 Dr Walter Patrick Grove, CBE – Amersham's founder.

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†Fiftieth Anniversary Special Issue, In memoriam John Jones.

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Dr Grove visited one of the Chilcote laboratories at night he noticed that the glass beakers were glowing in the dark and recalled the following: 'It was quite unexpected and the impact upon me must have been almost as great as it was on the Curies 40 years earlier when they saw the phenomenon for the first time.'[1]

'This gave us even greater confidence and we pushed ahead with the crystallizations until we were ready to seal the first 250 milligrams of pure radium bromide on October 17 – some three months from the start of refining.'[1]

The major concern of the British Government was that the Chilcote team was only producing 1 g of pure radium per month and this was an insufficient quantity to develop luminous materials for the war effort. The requirement was for the production of half-gram quantities per week and the radium shortfall had to be met from Canadian stocks. By 1944, the total production of pure radium refined from all sources at Chilcote was approximately 35 g; this included 18 g from radium concentrates. All the refined radium produced over 500 kg of luminous materials.

The war years at Chilcote produced other radioactive materials, such as neutron sources for the determination of the neutron yield in the fission of uranium. The Chilcote team made many contacts with other leading scientists and in particular with the Nobel Laureate Professor James Chadwick FRS, who discovered the neutron. Chadwick's support for the idea that a national centre for radioactive materials production should be set up at Amersham, Buckinghamshire, UK, was instrumental in its eventual creation.

An important milestone was reached in May 1946 when it was decided by the British Government that a single national centre for natural and artificial radioisotopes should be formed. The new centre would be under the direction of the Ministry of Supply and operated by the agency Thorium Limited.

In September 1946, the Ministry purchased the premises, plant and equipment of Chilcote House from Thorium for the sum of £40 000. The Ministry extended the buildings with Thorium Ltd managing the whole site. Hence, 60 years ago, the national centre for the processing and distribution of radium, radon and artificial radioactive substances required for scientific, medical and industrial purposes was born.

The Ministry stated that the site at Amersham should 'provide radioactive substances, however and wherever they may be needed by doctors, engineers and research workers, at home and abroad – and to do so in a business-like way as a commercial enterprise.'

The site at Amersham was originally intended to be temporary, but due to the expanding need to produce other radium devices to meet hospital requirements, an additional nine acres of land was purchased. New laboratories were constructed and equipped to standards recommended by the Medical Research Council. The site became home to the first radiochemical laboratory. It also housed the first fully operational radon extraction plant. This was used to supply tiny capsules of radon gas to treat tumours.

By March 1949, the site at Amersham had grown to 70 scientific and administrative staff under the leadership of Dr Patrick Grove. On 3 March 1949, a test tube labelled with the initials JRC (John R. Catch) contained the first carbon-14 compound prepared at Amersham (Figure 3). The compound was the sodium salt of [1-^{14}C]acetic acid (0.50 mCi, 41 mg).[2] On 11 May 1949, the site was designated 'The Radiochemical Centre (TRC), Amersham'.

The fifties[3]

The new status of TRC as a Government establishment staffed by civil servants brought physicists and chemists together, and in 1948 an isotope division was set up with new responsibilities. TRC became an outstation of the UKAEA (UK Atomic Energy Authority) linked to Harwell, and the contract with Thorium Limited was terminated on 31 March 1950.

TRC was to process the material irradiated by the Harwell reactors. The establishment was responsible for purification, standardization and synthesis of labelled compounds, together with the manufacture of radiation sources and the despatch of radioactive materials to customers.

TRC produced radioactive materials for over 40 countries and became an established distributor to

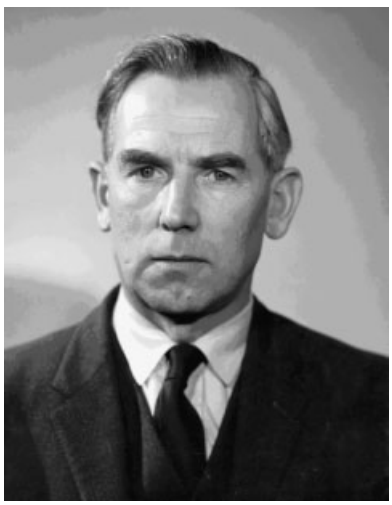

Figure 3 Dr John R. Catch – Chemist behind Amersham's first carbon-14 compound.

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the USA and Japan. Isotopes from Amersham were either artificially produced from materials in the Harwell reactors or came from natural radioactive elements such as radium. These isotopes found early application almost exclusively in medicine and science. In medicine, isotopes and radium-based applications benefited therapy, diagnosis and research. One example involves radio-tracers emitting signals, enabling the path of an investigative substance to be plotted inside the human body.

At TRC, pioneering work was carried out on producing organic compounds incorporating the radioisotope carbon-14.[4] This radioisotope was the most widely used in research, with a half-life of 5730 years. In the 1950s, some 200 carbon-14-labelled research compounds were synthesized. The first tritium-labelled chemicals were introduced, and the biosynthesis of vitamin B-12 with cobalt-58 was also developed.[5]

The latter half of the fifties also saw radioactive isotopes coming into wide use in industry, for instance, using beta and gamma rays in the continuous control of thickness in the production of paper and plastics. A new laboratory was opened on 1 November 1957, fitted with enclosures that allowed operators to stand outside to remotely manipulate these radioactive materials in a safe environment.

As the second decade came to a close, the UKAEA widened the scope of the centre to make it a single comprehensive organization for producing and marketing radioisotopes. Amersham made over £1 million in sales for the first time, with medical products taking 50%, industry 15% and research 35%.

Tritium chemistry: Dr E. Anthony Evans[6]

Dr E. A. Evans' first post (1955–1958) was as an Atomic Energy Research Establishment research fellow at Amersham, working on the synthesis of radioactive polycyclic aromatic hydrocarbons. This was followed by an appointment to the Organic Department of TRC. Up until then the department had only concentrated on carbon-14. This was about to change with the arrival of Dr Evans whereupon a major project was designed to introduce a whole range of compounds that were labelled with tritium ($t_{1/2} \sim 12.5$ years).[7] The tritium project very quickly became a commercial success involving colleagues such as Dr Vic Chambers and Dr David Warrell.

A vital academic link was formed between Professor John Jones of Surrey University and Dr John R. Catch, who was at that time the Head of Organic Chemistry at TRC, and Dr E. A. Evans (Figure 4). Their long-term collaboration was to develop and establish tritium nuclear magnetic resonance (NMR) as an analytical tool.[8] Dr Evans was also involved at the early stages in the formation of the International Isotope Society. He served as its first President and his many contributions to tritium chemistry were recognized by his receiving the Melvin Calvin Award in Toronto in 1991.

The sixties[9]

TRC (Figure 5) was now a single Government organization for the exploitation of radioactive products and the 1960s brought continued product demand for radiolabelled materials. The Centre was regularly producing close to 1000 catalogue items, over 100 primary radioisotopes and more than 530 labelled compounds. This included more than 330 sources of alpha, beta, gamma and neutron radiations.

The Centre was dealing with some 60 countries, the principal buyers being in Germany, USA, France, Canada and Japan. The Amersham cyclotron was installed and commissioned in the mid-1960s and

Figure 4 Dr E. Anthony Evans – Tritium pioneer.

Figure 5 The site at Amersham today.

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was the first machine of its kind in the world to be designed and operated for isotope production. Hitherto, the radioisotopes were derived from nuclear reactors and produced by neutron irradiations. The range of cyclotron isotopes was achieved with the bombardment of metallic targets by the high-velocity electrically charged atomic particles generated by the cyclotron. The cyclotron produced a wide range of isotopes including sodium-22, cobalt-57, arsenic-74, cadmium-109 and many more. The supply of radon for its use in radiotherapy came to an end on 31 March 1968 when it was replaced by grains of gold-198 from Harwell.

Enjoying world status, the staff at TRC published 'The Radiochemical Manual' and it was well received by the scientific community.[10] Its purpose was to provide information for the individual user to choose the right material for a particular application.

A senior chemist, who joined TRC in 1965, recalls that in the late 1960s Amersham was the first company to supply carbon-14-labelled compounds at close to 100% isotopic abundance. At about the same time, Amersham was starting to offer a custom preparation service for carbon-14 and tritium compounds.

In 1967, the UKAEA and TRC were jointly awarded the Queen's Award for Industry for export achievement, and also for technical innovation in the production for sale of radioisotopes. Interestingly, TRC produced products that were used in the 1960s, such as smoke detectors containing americium-241, carried aboard the Apollo 11 spacecraft.

The seventies[11]

The first 25 years had been a period of steady expansion in production, sales and profitability. The Atomic Energy Authority Act 1971 transferred the functions of the UKAEA to private companies. TRC became a limited company, taking control from the UKAEA on 1 April 1971, with full responsibility for the Centre together with its relevant assets and liabilities. TRC Limited now has a board of directors headed by the chairman Sir Charles Cunningham, with Amersham's founder Dr Patrick Grove as its managing director.

By the mid-1970s, with growing sales and staff levels exceeding 1000 it was decided by Sir John Hill (the creator of the limited company status and succeeding chairman) that Cardiff should be the location for an additional UK radiochemical manufacturing site. This attractive location with a promising (planned) motorway route to London Airport was well positioned for collaboration with the university and hospital institutions of that area. The Cardiff project was stalled pending a public inquiry on TRC's planning application.

Manufacturing capacity at the USA and German subsidiaries added modest support to that of Amersham, and a small but important specialist unit was in operation at Gloucester for large-scale freeze drying of non-radioactive diagnostic products.

The first subsidiary companies were established outside Britain, each subsidiary carried the name of the Company's home town within its title, Amersham Corporation in the USA, Amersham Buchler in Germany, Amersham France and Amersham Australia in the 1970s.

TRC became a major world supplier of radioactive materials. As the 1970s drew to a close with no relief in pressure on production, staff and facilities at Amersham and Gloucester, it was top priority to get the Cardiff site operational. Preliminary work on the green field site began in the summer of 1976.

Solid-phase technology Amerlex™ was launched to provide a precise and reliable method for analysing trace components in biological samples. This was the first use of a trade name whose preface ensured immediate identification with the 'Amersham' site name. In addition to this, the technetium-99m sterile generator won a Design Council award presented to the Company by the Duke of Edinburgh.

In May 1979, after 39 years spent guiding Amersham, Dr Grove retired. 'His inspiration and leadership made the business what it is today,' Sir Charles Cunningham, the chairman, noted. He was succeeded as chief executive by Dr Stuart Burgess, whose own service started at Amersham as a development chemist in 1953.

The eighties[12]

During the 1980s, the company continued to grow. In May 1981, The Radiochemical Centre Limited became Amersham International Limited. This name change followed the first move towards the Company's privatization. On 17 February 1982, Amersham International plc ceased to be owned by the British Government and was the first state-owned company to be fully privatized under the Prime Minister Margaret Thatcher.

In the Amersham area, the Group headquarters relocated to Amersham Place. A new manufacturing facility opened at Cardiff under the direction of Dr John Maynard as its first general manager (Figure 6). Cardiff Laboratories offered a bespoke service in the synthesis of radiolabelled drugs or advanced intermediates containing carbon-14 and tritium. Amersham also

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produced a wide range of radiolabelled products for its catalogue, assisting researchers around the world.

Today, the Custom Preparations Group at Cardiff is a world leading supplier of high-purity labelled compounds prepared to customers' exact specifications. Many of these radiolabelled compounds support the development of new pharmaceutical and agro–chemical products by reproducing an absolute duplication of the drug or compound with the inclusion of a radioactive label.[13] Over 20% of all new drug approvals have previously been radiolabelled by the *Amersham Radiolabeling Service* (Figure 7).

Cardiff Laboratories became the Company's principal life science manufacturing site when it began operations in 1980. The facility gained ISO 9002 registration in 1993 and produced Amersham's range of advanced research products for the use in the life science and healthcare markets.

William (Bill) Castell became Chief Executive of the Amersham International Group in 1989 setting a new course for the company by expanding its product portfolio. The Healthcare (nuclear medicine) business, under Dr John Maynard, would gradually move towards branded, innovative diagnostic and therapy products. The Life Sciences business, led by Ron Long, would add a new technology base in genomics and extend its market to include the pharmaceutical industry as well as academia.[2]

The nineties[14]

On 5 August 1997, Amersham International merged its Life Science division with Pharmacia and Upjohn's Pharmacia Biotech in a (55:45) joint venture, forming Amersham Pharmacia Biotech. Three weeks later, Amersham International merged with Nycomed to form Nycomed Amersham plc and the Nycomed Amersham Imaging business. Following completion of the mergers, Nycomed Amersham plc and its two businesses, Nycomed Amersham Imaging and Amersham Pharmacia Biotech, further refined the strategy for enabling molecular medicine. The ultimate goal was to enable personalized medicine – providing predictive diagnostic and screening products along with gene-based therapies, tailored to the individual patient's genetic profile.

The new millennium: GE Healthcare

On 15 October 2001, the business changed its name to Amersham plc and operated as Amersham Health and Amersham Biosciences.[15] Amersham Laboratories was renamed The Grove Centre in recognition of Dr Patrick Grove's significant contributions to radiochemistry and Cardiff Laboratories was renamed The Maynard Centre

Figure 6 Dr John Maynard, OBE – Cardiff's first General Manager.

Figure 7 The Cardiff site today.

(TMC) in recognition of John Maynard's achievements during his 40 years of service. Then on 8 April 2004, The General Electric (GE) Company acquired Amersham plc combining it with its GE Medical Systems business unit to create a $14 billion industrial leader under the leadership of Sir William (Bill) Castell, who was Knighted in June 2002 for his services to Life Sciences.[16] General Electric's acquisition of Amersham plc married GE's medical imaging and healthcare informatics equipment with Amersham's medical diagnostics and life sciences business units. Together, the companies formed the new GE Healthcare, one of the diverse range of business units that makes up GE, and the only one of which headquartered outside the USA at the old Amersham offices at Pollards Wood near Amersham.

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The GE Company traces its beginnings to Thomas A Edison, who established Edison Electric Light Company in the USA in 1878. In 1892, a merger of Edison general Electric Company and Thomson–Houston Electric Company created General Electric Company, known today as GE. Worldwide, GE Healthcare employs more than 43 000 people who are committed to serving healthcare professionals and their patients in more than 100 countries. GE Healthcare offers a broad range of services for improving productivity in healthcare to enable better diagnoses, treatment and the management of patients with conditions such as cancer, Alzheimer's and cardiovascular diseases.

In February 2005, The Royal Society of Chemistry named the Grove Centre, formerly Amersham Laboratories, as a Historic Chemical Landmark.[17] The Grove Centre was selected for its pioneering work in the life sciences as a major centre for the development of the medical and industrial applications of radioactivity in the UK during the past 60 years. The Grove Centre and TMC have received over 14 Queen's Awards to date, nearly half of which were for Technological Innovation.

Part 2: Radiochemistry highlights

Carbon-14

In the same year that the Chilcote team was setting up the radium refinery at Amersham, Melvin Calvin in Berkeley, California, was making his Nobel Prize (1961) winning discovery on the properties of carbon-14. This was the radioactive isotope of carbon, discovered by Martin Kamen at Berkeley, which helped Calvin unravel how plants use carbon dioxide in the process of photosynthesis.[18]

By substituting a particular carbon atom in a molecule with carbon-14, scientists introduced a 'label' by which they could follow its fate no matter what chemical changes that the molecule itself might undergo. This was the principle of radiotracing, which allowed the scientist to follow the complexity of a biochemical pathway. Amersham assisted in developing the concept of isotope tracing and provided the novel chemistry needed to synthesize complex organic molecules, starting from the simplest 'building blocks' such a carbon dioxide for carbon-14 (Scheme 1).

Tritium

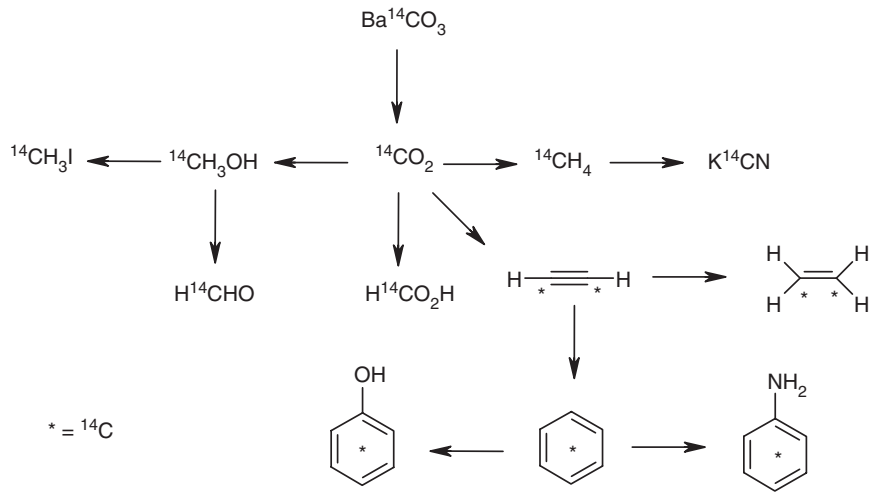
In the 1950s, Amersham began to work with another radioactive label, tritium. This weak beta-emitter proved to be easier to introduce into some of the increasingly complex biochemical substrates required as radiotracers. A number of catalytic isotope exchange processes were developed to enable a complete new range of radiolabelled biochemicals.

In 1969, collaboration began with Professor John Elvidge of Surrey University to use NMR spectroscopy for determining the position of a tritium label in compounds.[8]

'Amersham' tritium labelling methods[19]

The tritium laboratories at TMC, Cardiff, have developed many methods to introduce tritium at a specific location in organic molecules:

- tritiation with tritium gas;
- chemical labelling (e.g. Na[^{3}H]BH_4);
- tritiated water exchange.



Scheme 1

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One method is to use homogeneous iridium-catalysed hydrogen/tritium exchange.[20] This is a relatively new technique that provides a fast, non-synthetic route for the labelling of complex organic molecules. The labelling is regiospecific and often associated with high specific activity. The basis of this method is to use an iridium catalyst with tritium gas to enable the exchange of aromatic ortho protons with a suitable activating group such as an amide, ester, ketone, aldehyde or heterocyclic nitrogen. The iridium is thought to form either a 5- or a 6-membered metallocyclic intermediate in such a way that transfer of tritium from the catalyst to the aromatic ring can occur (Figure 8).

TMC is involved in the development of catalysts that offer enhanced reactivity over the commonly used iridium catalyst and also allow labelling of numerous functional groups such as those shown below (Scheme 2).[20]

Radioisotopes

Amersham's expertise led to working with other sensitive radioisotopes such as phosphorus-32. Although first used in the USA, phosphorus-32 was made at Amersham in 1978 in a pure and highly active form. This isotope was incorporated in a wide range of labelled phosphorus-32 nucleotide building blocks for DNA and RNA research.

Amersham's labelled nucleotides – labelled initially with tritium and later with phosphorus-32 and sulphur-35 – helped life science laboratories worldwide to unravel the structure and function of the genetic code. The 1980s led to the development of radiolabelled DNA probes for the diagnosis of several genetic diseases such as sickle cell anaemia, thalassemia, Down's syndrome and cystic fibrosis.[21] Throughout the 1990s, labelled compounds continued to be a cornerstone of modern drug development. The estimated 3000 million chemical 'building blocks' of DNA to be mapped in the correct order together with Amersham's desire to develop highly automated sequencing systems steered the company into molecular biology in the mid-1990s. On 26 June 2000, the completion of the initial sequencing of the human genome by The Human Genome Project and Celera Genomics was announced.[2]

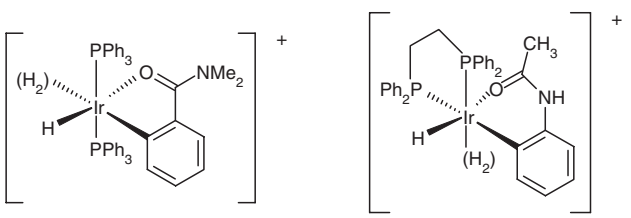
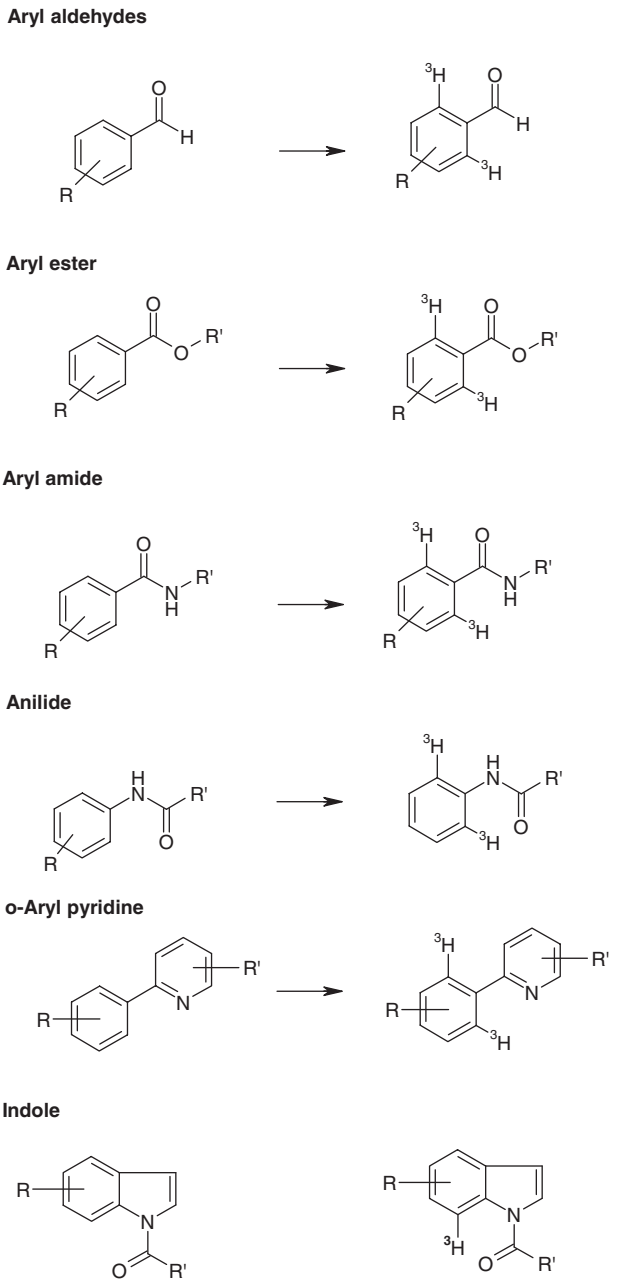


Figure 8 Five- and six-membered metallocyclic intermediates.

Radioactive iodine

In 1960, radioimmunoassay was invented by Solomon Berson and Rosalyn Yarrow (1977 Nobel Laureate). This took the company from making research reagents



Scheme 2

into producing clinical tools such as diagnostic kits. Amersham was approached by biochemists from Cambridge University to find whether it could provide them with iodine-131 labelled insulin for radioimmunoassay (RIA) of insulin levels in the blood of diabetics. The Solomon procedures were not productive and wasted a lot of precious radioactive iodine, but Amersham's method harnessed over 98% of the iodine. In its silver jubilee year, 1965, Amersham launched the world's first commercial RIA kit to measure insulin in blood.[14]

Radioactive iodine provides the perfect example of a 'natural' radiopharmaceutical. Most of the body's iodine accumulates in the thyroid gland in the neck. Iodine-131 not only goes to the thyroid but has the right characteristics to assay the gland's activity and also to treat the gland for hyperactivity and other conditions. Amersham has been supplying doctors with iodine-131 for more than 50 years. Doctors required a selection of short half-life isotopes, and to meet this requirement Amersham inaugurated the world's first commercial cyclotron in 1966 for isotope production. Amersham continued to pioneer commercial cyclotron technology. Amersham's cyclotrons are dedicated to making a number of isotopes for nuclear medicine including thallium-201, used in nuclear cardiology for imaging the beating heart and gallium-67, used for detecting abdominal tumours. The indium-111 oxime complex (which is unique to Amersham) was used for the detection of internal abscesses and also for inflammation following major surgery.[18]

Technetium-99m

Technetium-99m has the ideal properties for many medical investigations and in 1983 Amersham International introduced the Amertec™ technetium-99 generator, replacing earlier models (Figure 9). The generator is vital in nuclear medicine departments throughout the world. It provides the source of precise quantities of radioactivity as the active component for diagnostic agents, such as Ceretec™, used in the diagnosis of brain disease. The Amertec II™ generator won a 1987 Queen's Award.[22]

In 1991, Amersham International acquired iodine-125 Seeds (OncoSeed™) from 3 M and introduced this for the treatment of prostate cancer in the USA.[2] Manufacturing facilities for OncoSeed were also established in the mid-1990s at The Grove Centre.

Myoview™

In 1994, Amersham International launched Myoview™ to be used in cardiology as an imaging agent to study the heart in microscopic detail (Figure 10).[2] This

Figure 9 GE Healthcare Technetium-99m Generator (Drytec).

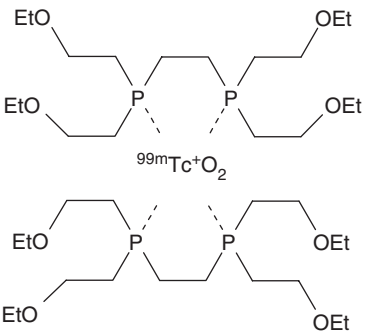


Figure 10 Myoview™.

cardiac imaging agent is labelled with technetium-99m which complexes to a biphosphine ligand tetrofosmin. Myoview™ is useful in the diagnosis and localization of regions of reversible myocardial ischaemia in the presence or in the absence of infarction under exercise and rest conditions. This achievement was recognized by winning the prestigious 1998 Queen's Award for Technological Achievement. One reason for the success of Myoview™ is that it uses the gamma emitter technetium-99m ($t_{1/2} = 6.01$ h) rather than thallium-201 ($t_{1/2} = 73$ h).[23]

Amersham Radiolabeling Service

Today, TMC, Cardiff, is a Centre of Excellence in the custom synthesis of carbon-14 and tritium advanced intermediates and final drug-labelled compounds. *Amersham Radiolabeling Service* offers a wide range of compounds tailored to the needs of our customers. As a company, our radiochemists have accumulated over 3000 people years of experience in the production of radiolabelled compounds. Even today the name Amersham is still synonymous with radiochemistry.

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Conclusion

About 60 years ago, the only radioactive substance known to doctors was the naturally radioactive but rare metal, radium. Nuclear physics provided Amersham with a host of new radioactive materials of different characteristics. Scientists have responded with a wide range of medical products that allow the detection of certain diseases through the life cycle of man. Since the days of Dr Patrick Grove and Chilcote House, the Company has evolved from successive mergers into the present $17 billion plus global company GE Healthcare.[24,25]

Acknowledgements

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