The contribution of medical physics to nuclear medicine: a physician's perspective

Peter J Ell

Abstract
This paper is the second in a series of invited perspectives by four pioneers of nuclear medicine imaging and physics. A medical physicist and a nuclear medicine clinical specialist each take a backward look and a forward look at the contributions of physics to nuclear medicine. Here is a backward look from a nuclear medicine physician’s perspective.

Keywords: Nuclear medicine; Physics; History

“He who does not doubt, does not investigate, does not perceive; and he who does not perceive, remains in blindness and error”

Al-Ghazali (1058–1111 a.C.), theologian, jurist, philosopher, cosmologist, psychologist and mystic

The introduction of radioactive tracers to clinical medicine can be traced to the late 40 s [1-3]. From its inception, physicians and physicists made use of purposely developed detection instruments and radionuclides in order to (a) further the understanding of the underlying mechanisms of disease in man and (b) to investigate the earliest manifestations of pathologies. To diagnose early on and to treat if possible were mutual aims of both physicians and physicists. To underline, the contribution of scientists and physicists to the development of Nuclear Medicine has been not just major but disruptive and of fundamental importance. The very first applications preceded the previously mentioned by half a century (Table 1).

November 12, 1936
Visiting patients at his thyroid clinic at Mass General Hospital, the physician JH Means, M.D., poses a most relevant question. In his mind was already the understanding of the role and importance of iodine metabolism of the thyroid and the possibility to measure it non-invasively in vivo. RE Evans, Ph.D., rose to the challenge with a seminar pronouncement:

JH Means M.D.: ‘Is there a radioisotope of iodine?’
Robley Evans, Ph.D.: Mass. Inst. Techn.: ‘We can make some’.

This seminal encounter possibly marks the development of what was to become known as Nuclear Medicine (Table 2, Figure 1). It is the perfect example of the interdisciplinary thinking which was to permeate and characterise the development of this
speciality. It also represents the ideal setup, where an identified problem, namely, the investigation of thyroid physiopathology, led to the development of a new investigative tool (the radionuclide). It would take many years indeed before another ‘magic bullet’ was to be identified and widely applied. If specificity is intended by such a magic bullet, receptor ligands such as those targeting the dopamine and somatostatin receptors and most recently those ligands targeting the misfolded amyloid protein, are good examples of the progress achieved.

Whilst on the topic of interdisciplinarity, it is opportune to underline that not only physicists greatly contributed to the development of Nuclear Medicine. This equally applied inter alia to engineers, chemists and radiopharmacists. Gopal Subramanian with a degree in chemical engineering introduced \(^{99m}\)Tc labelled phosphonates for bone scanning; Hal Anger as an electrical engineer and biophysicist developed the Anger gamma camera; Roger Ekins, also a biophysicist, developed the saturation analysis/radioimmunoassay methodology (Table 3). Physicists turned physiologist developed and emphasised the need for elegance and simplicity in quantitative measurements.

From the preceding paragraph, it is clear that fundamental discoveries spanned a period of a century. In the space available for this short piece, it is simply not possible to give due consideration to all those many eminent scientists who developed the field. So I shall focus on the three seminal physics developments which fundamentally changed the practice and future of Nuclear Medicine: the introduction of the rectilinear scanner, the development of the gamma camera and, finally, the design of the first single-photon emission computed tomography (SPET), positron emission photography (PET) and PET/computed tomography (CT) instruments.

### Table 1 The pioneers of nuclear medicine

| Year | Discovery | Name | Specialty |
|------|-----------|------|-----------|
| 1895 | X-rays    | Wilhelm C. Roentgen | German physicist |
| 1896 | Radioactivity | Antoine H. Becquerel | French physicist |
| 1898 | Polonium, radium, thorium | Marie Sklodowska Curie | French physicist |
| 1923 | Tracer principle | Georg V. Hevesy | Hungarian chemist |
| 1927 | Circulation times | Hermann L. Blumgart | German doctor |
| 1928 | Counter | Johannes W. Geiger | German physicist |
| 1932 | Cyclotron | Ernest O. Lawrence | American physicist |

| Year | Discovery | Name | Specialty |
|------|-----------|------|-----------|
| 1845 to 1923 |  | Wilhelm C. Roentgen | German physicist |
| 1852 to 1908 |  | Antoine H. Becquerel | French physicist |
| 1867 to 1934 |  | Marie Sklodowska Curie | French physicist |
| 1885 to 1966 |  | Georg V. Hevesy | Hungarian chemist |
| 1895 to 1977 |  | Hermann L. Blumgart | German doctor |
| 1882 to 1945 |  | Johannes W. Geiger | German physicist |
| 1900 to 1979 |  | Walther Mueller | German physicist |
| 1901 to 1958 |  | Ernest O. Lawrence | American physicist |

### Table 2 The early years of nuclear medicine

| Year | Discovery | Name | Specialty |
|------|-----------|------|-----------|
| 1934 | First radioactive \(^{129}\)I | Enrico Fermi | Italian physicist |
| 1936 | Production of \(^{99m}\)Tc | Enrico G. Segre | Italian physicist |
| 1936 | First therapy with \(^{32}\)P | John H. Lawrence | American physicist |
| 1938 | Discovery of \(^{131}\)I | Glenn Seaborg | American chemist |
| 1942 | Therapy of benign thyroid disease | Saul Hertz | American physician |
| 1946 | First therapy of thyroid cancer | S. M. Seidlin | American physician |
| 1949 | First therapy of thyroid Carcinoma in Europe | Cuno Winkler | German physician |
| 1949 | First therapy of thyroid Cancer in Europe | Eric E. Pochin | British physician |

| Year | Discovery | Name | Specialty |
|------|-----------|------|-----------|
| 1901 to 1954 |  | Enrico Fermi | Italian physicist |
| 1905 to 1989 |  | Enrico G. Segre | Italian physicist |
| 1904 to 1911 |  | John H. Lawrence | American physicist |
| 1912 to 1999 |  | Glenn Seaborg | American chemist |
| 1905 to 1950 |  | Saul Hertz | American physician |
| 1907 to 1995 |  | Robley D. Evans | American physician |
| 1895 to 1955 |  | S. M. Seidlin | American physician |
| 1886 to 1995 |  | Leo D. Marinelli | American physician |
| 1919 to 2003 |  | Cuno Winkler | German physician |
| 1909 to 1990 |  | Eric E. Pochin | British physician |
Surface counting had been an important milestone in the clinical development of the radioactive tracer method. It was used early on by Norman Veal and others in mapping the placenta, the thyroid and the pericardium. This was laborious, a manual-driven process and rather time-consuming. It was difficult to perceive much more than the simplest outlines of organs, and yet, quantitative measurements were already taking place.

The relationship between physicists and physicians has always been most interesting. A healthy diffidence between both experts was often present and wonderfully illustrated from the following extract, taken from the outstanding chronology authored by Marshall Brucer, the first President of the Society of Nuclear Medicine (USA) and Chairman of the medical division of Oakridge Institute of Nuclear Studies from 1948 to 1962. And one can read in page 291: ‘...three months after the London meeting (the first meeting at University College London, on 29th July 1950, where data from $^{131}$I.

Table 3 Twenty-five years of seminal discoveries

| Year | Discovery          | Inventor            | Nationality         | Date     |
|------|--------------------|---------------------|---------------------|----------|
| 1951 | Rectilinear scanner| Benedict Cassen     | American physicist  | 1902 to 1972 |
| 1953 | CBF with radio krypton | Niels Lassen | Danish physician | 1926 to 1997 |
| 1958 | Anger gamma camera | Hal O. Anger        | American engineer | 1920 to 2005 |
| 1959 | Radioimmunoassay   | Rosalyn S. Yalow    | American physicist | 1921 to 2011 |
| 1959 | Radioimmunoassay   | Solomon Berson      | American physician | 1918 to 1972 |
| 1960 | Saturation analysis| Roger Ekins         | British biophysicist| b. 1936 |
| 1962 | Tc-99 m generator  | Paul Harper         | American surgeon | 1915 to 2005 |
| 1962 | SPET               | Katherine Lathrope  | American physicist | 1915 to 2005 |
| 1962 | SPET               | David Kuhl          | American physician | b. 1929 |
| 1971 | Polypeptides       | Gopal Subramanian   | American chemist | 1953 to 2000 |
| 1973 | PET                | Michel Ter-Pogossian| American physicist | 1925 to 1996 |
|      |                    | Michael Phelps      | American biophysicist| b. 1939 |
therapy was discussed); Sam Seidling asked: ‘If a metastasis has high uptake, we can destroy it. Now, for God’s sake, when will physicists learn to measure $^{131}$I uptake?’ Leo Marinelli murmured: ‘As soon as physicians decide how much uptake is high’.

Benedict Cassen changed all this with his discovery of the rectilinear scanner in 1950. Born in New York in 1902, he graduated in physics and mathematics from the Royal College of Science in London in 1927. He moved to the California institute of Technology in 1930. Imaging the thyroid, he reported first results in 1950. The radioactive tracer method would forever be linked to imaging, for better or for worse. Single-head, dual-head, 3-inch or 5-inch rectilinear scanners and whole-body scanners became routine imaging instruments for 2D organ imaging and counting, dominating for some 30 years Nuclear Medicine applications well into the late 80s, as new tracers became available.

Whilst brilliant individual scientists made major contributions to medicine, institutions and or societies have a habit of getting it wrong. In the late 40s, much debate and thought went into what role a medical physics department should have in a hospital. To quote an example: ‘...Any one radio-element investigation may be too short lived to justify the provision by the department concerned of the best apparatus for the job’. [4]. Whilst Cassen had already proven that this viewpoint was completely wrong, how would Hal Anger comment on the on the previously mentioned discussion?

**US patent 3,011,057 in 1961**

Nuclear Medicine was to change forever with the mentioned patent, defining the Anger gamma camera. It is truly astonishing that this technology, still in worldwide use today, has outlived over half a century of technological breakthroughs and progress! In modern times, there is probably no other example of such a long lasting instrumentation breakthrough.

Hal Oscar Anger (Figure 2) was born on the 20th of May 1920, in Denver, USA. He graduated as an electrical engineer. His innovative career spanned from radar jamming equipment to radiation detector devices, culminating with his seminal invention of the
imaging device still in use today. His camera was presented at the 1958 meeting of the Society of Nuclear Medicine and led to an explosion of commercial exploitations. The history of the patent itself would merit a separate chapter. He died on October 21, 2005, in Berkeley. No writings can give sufficient justice to Anger’s innovative genius and the impact he has had worldwide on millions of patients investigated with his seminal instrument.

It would take some 30 years before 3D Imaging became an integral part of the development of Nuclear Medicine. And one has to give proper due to a medical scientist, David Kuhl (Figure 3), the originator of single-photon emission tomography. Born in St. Louis, Missouri in 1929, David E. Kuhl graduated in medicine at UPENN in 1955. In 1964, David Kuhl and Roy Edwards developed the Mark II emission tomographic scanner, starting the field of cross-sectional tomographic imaging. Kuhl went to develop the technique of SPET - truly ahead of its time and ahead of the development of the CT scanner (1973). Should one write a history of missed Nobel awardees? Mark II was followed by Mark IV and a number of subsequent improvements.

Single-slice SPET imaging was subsequently superseded by whole-volume SPET imaging, with the introduction of the rotating gamma camera (Anger’s device, shaping de novo the clinical applications of the radioactive tracer method). Without SPET, nuclear cardiology, and less so, neurotransmission imaging would have not risen to the clinical pre-eminence these modalities reached in the last 15 years. SPET became a truly worldwide available technology, supported by a range of useful radiopharmaceuticals.

**Modern technologies (SPET, SPET/CT, PET, PET/CT and PET/MR)**

The beginnings and development trends of positron emission tomography are outlined in Table 4. Again, constraints on space prevent a detailed analysis. Suffice to say that for a physician, interested in patient care and management, it took a rather long time before clinical useful applications began to emerge [5-7]. It would take the development and final availability of $^{18}$F labelled glucose, which made positron emission tomography a clinically useful tool. Between the development of the first PET system in 1973 by

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**Figure 3** David Kuhl (born in 1929, retired in 2011). Image taken during presentation of the 2009 Japan Prize Award, attended by Emperor Akihito. This prestigious prize was introduced in 1985 to award scientists who contribute to the development of science and technology.
Michael Phelps and the approval by the FDA of $^{18}$F labelled glucose, 24 years would have elapsed (Table 4).

To complete this brief review, we end with David Townsend, Ph.D., who gave us the most significant development in medical imaging in the last 10 to 15 years. The PET/CT prototype, attributed to Townsend and Nutt (Figure 4), then President of CPS Innovations, was named by TIME Magazine as the medical invention of the year 2000. A hugely impressive development, bringing human anatomy and biochemistry onto a combined 3D map, this technology was instantly adopted by the medical community as

Table 4 The history of PET

| Year | Event                                                                 | Inventor(s)                  |
|------|------------------------------------------------------------------------|------------------------------|
| 1951 | First use of NaI probes for positron detection in brain                | William Sweet and Gordon Brownell |
| 1963 | First description of radon equations for image reconstruction          | Alan M. Cormack              |
| 1973 | Description of CT scanner                                             | Godfrey N. Hounsfield        |
|      | First PET tomograph                                                    | Michael E. Phelps            |
| 1976 | First commercial PET scanner                                          |                              |
| 1978 | First BGO-based scanner                                               | Chris Thompson               |
| 1977 | $^{14}$C Deoxyglucose                                                 | Louis Sokoloff               |
| 1978 | $^{18}$F Fluorodeoxyglucose                                            | Tatsuo Ido                   |
| 1986 | Present synthesis of FDG                                               | Kurt Hamacher                |
| 1984 | Commercial cyclotron development                                      |                              |
| 1997 | FDA approves FDG as radiopharmaceutical                               |                              |
| 1998 | PET/CT prototype                                                      | David Townsend and Ron Nutt |
| 1999 | Lutetium orthosilicate (LSO)                                          |                              |
| 1999 | Medicare reimburses for staging NSCLC, SPN, colorectal ca, HD and NHD, melanoma, hibernating myocardium and TLE |                              |
| 2001 | PET/CT in UK at INM/UCL                                               |                              |
| 2002 | Health technology assessments (HTA) begin                             |                              |

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an essential tool for early staging and monitoring of human disease. No hospital facility
today can bypass the availability of a PET/CT system for appropriate patient management.

What about PET/MR? Time will tell; its adoption by the medical community will
take much longer. But the input of physics computing and engineering will remain vital
for the future development of this innovative speciality. This will be ever more relevant
as the demands posed by multimodality imaging technologies and the need for true
quantitative and reproducible measurements are widely felt. This is especially relevant
in the increasing need for the monitoring of interventions, being medical, surgical or
pharmacological, applied to an individual patient. Whilst the overtly simplistic aims of
personalised medicine are being reassessed, patient specific interventions will grow,
and with it, the growth of physics in the field is assured.

Competing interests
The author declares that he has no competing interests.

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