

New faces at Cyclomedica



Professor Nabil Morcos Chief Operating Officer & Director of Science

Professor Nabil Morcos has been appointed as the Chief Operating Officer and Director of Sciences at Cyclopharm Ltd. For the year and a half prior to joining our company, he was the Acting Head of the Radiopharmaceutical Research Institute at ANSTO. He holds a Ph.D. in Nuclear and Radiochemistry and a research professor position in the Physics and Environmental Engineering Departments at Vanderbilt University (Nashville TN, U.S.A.). He did several stints at Brookhaven National Laboratory (U.S.A.) in the Chemistry and Radioactive Waste Management Divisions in support of the U.S. Nuclear Regulatory Commission with respect to waste form characterization and performance. He spent a total of twelve years in the Radiopharmaceutical research industry where he developed several products from concept to market and patents including the Squibb Tc-99m generator. He holds about 16 patents in the radiopharmaceutical arena and related medical areas. He also spent the ten years prior to joining ANSTO at the U.S. DOE at INEEL and Hanford working on the Plutonium Production Legacy Waste as a radiochemistry and safety advisor to the DOE. He has authored and co-authored more than 50 peer-reviewed publications, a reference textbook, 2 book chapters, and co-discovered several radioisotopes and isomeric states.

nmorcos@cyclopharm.com.au



Mr Kevin Murphy European Business Development Manager

Kevin has worked in the nuclear medicine field for many years after graduating as a nuclear medicine technologist in Canada. He has worked with Amersham, Mallinckrodt, Sirtex and recently as Sales & Marketing Manager at ARI. Kevin operates from the U.K. and assists with the European markets.

kevin.murphy@cyclomedica.ie



Ms Rhoda Chalaan National Sales & Marketing Executive

Rhoda is new to the nuclear medicine field. She has Masters Degree in Forensic Pathology. Rhoda has over 6 years experience in sales and marketing having worked in the health area where she managed the "Total Health Screening" program.

rchalaan@cyclomedica.com.au



Mr Terry AuYeung General Manager (Asia)

Terry has many years experience in the pharmaceutical field and has extensive exposure to high tech industries in the medical, pharmaceutical and engineering fields. Terry is a Melbourne graduate with a major in Biochemistry. He is responsible for sales and marketing activities throughout the Asia area.

auyeung.terry@gmail.com

If you would like to receive updates and further information please provide your e-mail details to enquiries@cyclomedica.com.au



Contact your nearest representative -

ASIA / PACIFIC / SOUTH AFRICA
Cyclomedica Australia
sales@cyclomedica.com.au
Cyclomedica Asia
auyeung.terry@gmail.com
Tel - +612 9541 0411
Fax - +612 9543 0960

Contact
Australia/NZ - Charles Buttigieg
Tel - +61 418 285 048
Asia - Terry AuYeung
Tel - +852 9229 3761

EUROPE / MIDDLE EAST / NORTH AFRICA
Cyclomedica France
cyclopharma@cyclopharma.fr
Tel - +33 473632700
Fax - +33 473632705

Contact
Jean Louis Claude
Tel - +336 8805 8845

CANADA
Cyclomedica Canada
lynn.mclauchlin@cyclomedica.ca
Tel - +1 905 319 9610
Fax - +1 905 319 0497

Contact
Lynn McLauchlin
Tel - +1905 690 0345
Fax - +1905 690 0553

LATIN AMERICA
Cyclomedica Latin America
mlima@cyclomedica.ar
Tel - +54 11 4585 9172
Fax - +54 11 4586 0251

Contact
Martin Lema
Tel - +54 911 5174 1639

GERMANY
Cyclomedica Germany
info@technegas.de
Tel - +49 (0) 5341 550802
Fax - +49 (0) 5341 550803

Contact
Bjorn Altmann

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Issue 3, June 2007

Introduction

The New Year has ushered a formalisation of our company's new directions in providing products and services to the Nuclear Medicine and Radiology communities. Vita Medical Australia P/L was reorganized as "Cyclomedica Australia Pty Ltd" under a holding company "Cyclopharm Limited" and two new business units were created under the holding company: "Molecular Imaging" and "Turnkey Solutions". The holding company has been listed on the ASX and commenced trading its stock on January 18th, 2007.

"Molecular Imaging" will focus on the development, production and distribution of Positron Emission Tomography (PET) radiopharmaceuticals while "Turnkey Solutions" will provide the necessary hardware and expertise in Australasia to produce PET radiopharmaceuticals and radiotracers including cyclotrons, and automated chemical synthesis equipment for their production. Cyclopharm

has recruited key individuals to support this new business direction.

We are currently under negotiations for cyclotron sites in Sydney and Melbourne to establish our PET imaging radiopharmaceutical production facilities. Our vision is to establish these facilities in close proximity to practicing Nuclear Medicine physicians with the intent on establishing the capability of supporting clinical research in PET imaging during our non-production hours to enhance excellence of care in Nuclear Medicine and support Oncology.

This Newsletter issue brings you a synopsis by Dr. Bill Burch of two attached white papers by Professor Lee Collins (Medical Physics Department, West Mead Hospital, Sydney) on Radiation Dose, LNT and ALARA, and by Professor Paul Roach (Head, Department of Nuclear Medicine, Royal North Shore Hospital, Sydney) on PLOPED and the future of V/Q scan.

Company Announcement

As part of its significant expansion plans, Cyclomedica Australia P/L is pleased to announce the establishment of its new trading name, Cyclopharm Limited, the entity was recently listed on the Australian Stock Exchange.

"This is an exciting development for Cyclopharm," states Professor Nabil Morcos, Cyclopharm's Chief Operating Officer and Director of Research. "No longer will this be a one product company. While Technegas will continue to be marketed by Cyclomedica Australia and remain a market leader in the non-invasive diagnosis of PE, the new product lines of Cyclopharm will compete aggressively in the rapidly expanding cyclotron market and provide complete turn-key solutions to PET radioisotopes production while the Molecular Imaging arena will supply PET radioisotopes and state-of-the art PET imaging biomarkers for diagnostic imaging services to the Nuclear Medicine community."

Mr John Sharman, Managing Director of Cyclopharm, endorsed Professor Morcos'

comments. "Cyclopharm has assembled a strong team and is firmly focussed on providing unequalled products and services to its clients in nuclear medicine. A series of announcements outlining key strategic arrangements will follow and will instil confidence in all stakeholders. Cyclopharm's corporate goal is to become the pre-eminent supplier of radiopharmaceuticals, both established and novel, including the hardware to produce them."



CONTENTS pg

Editorial 1

Company Announcement 1

Bill Burch's Literature Review 2

ICRP Guidelines 3

PIOPED II Critique 4

New Faces 5

Technegas 6

Radiation Dose, LNT and ALARA

In this issue, analysis by Lee Collins, of International Commission on Radiological Protection (ICRP) findings for tissue weighting factors specifically in breast and gonads over the last 30 years, highlights just how sparse is the hard data to validate the figures. Importantly, it brings into focus an effect of adoption of the conservative Linear No Threshold (LNT) hypothesis for creating a radiation protection code based only on high dose-effect data such as atomic bomb survivors. By definition, LNT implies that ANY radiation dose above zero has an adverse effect of some kind, and this, of course is the footing from which those opposed to nuclear-based science launch their campaigns.

We are all used to the “risk versus benefit” exposure modifier for the LNT hypothesis, known as the ALARA principle, “as low as reasonably achievable – social and economic considerations being taken into account” that was introduced by the ICRP in the 1970s. Radiation exposure to patients and staff has been governed by this maxim ever since. The vacillation of a weighting factor for breast tissue from 0.15 in 1976, to 0.05 in 1990, and now back to 0.12 only stresses the importance

V/Q SPECT and PLOPED II

It is important when reading many of the imaging comparisons in the current literature to be well aware of the nature of the comparisons being made. Imaging technology has made such rapid advances in just the last 5 years, that the whole process of comparing the efficacy of one imaging system with another as a diagnostic tool can be completely irrelevant. This is most apparent in US-based reviews that use the PLOPED II trial as a baseline reference. Note for example the following excerpts from the V/Q protocol for the trial “either a xenon gas (133Xe) or a radioactive aerosol (radioaerosol of 99mTc-diethylenetriamine pentaacetic acid [DTPA] or 99mTc-pyrophosphate [PYP] is used. Whenever possible, all V/Q imaging is performed with the patient upright. If upright images are not possible, supine images are acceptable.” Then as a bald statement on the next page “There is no readily apparent difference between the various agents used for ventilation scans from a diagnostic standpoint” with the justification being a citation dated 1984 from the same group!

Thus, when a major paper appears in such a prestigious journal as the New England Journal of Medicine in June of last year, again by the PLOPED team, still using PLOPED II as a reference point for yet more imaging evaluation studies for PE, this time Multidetector Computer Tomography, it should be a cause for real concern.



Bill Burch has retained an Honorary Visiting Fellowship at the John Curtin School of Medical Research within Australian National University since 1976. His background includes stints in Antarctica in geophysics, radiotherapy, and nuclear medicine in Melbourne, the U.K. and Canberra where from 1976 to 1984 he began his quest to find good ventilation agent. He “stumbled” upon Technegas and has been its champion ever since.

of conscious use of ALARA when prescribing tests for patients, and is another strong argument for the use of V/Q in PE diagnosis against the much higher doses generated by the equivalent Radiological procedures, given that their specificity and sensitivity are, at the very worst, comparable.

An excellent discussion of the practical issues of dose and effect at these lower levels, focussed around the Chernobyl accident in the Ukraine, pitched to the intelligent layperson, was a BBC “Horizon” program with the rather off-putting title “Nuclear Nightmares” and first aired in Britain in July 2006. It is the kind of program that should be part of every radiation worker’s training syllabus, teaching primarily the inadequacies of the LNT hypothesis at the kinds of exposure patients and staff are likely to receive in Medical procedures and the consequences of predictions made from it; and leading to the mounting solid evidence for a damage threshold for radiation, much like any other poison. A synopsis of the program may be found at <http://news.bbc.co.uk/1/hi/sci/tech/5173310.stm>

Such publications serve to cement some kind of “Holy Grail” status for PLOPED in the minds of the wider medical community, and especially the referral base for imaging diagnostics for PE. All too frequently, imaging literature discussing PE refers back to PLOPED as some kind of de facto ongoing “gold standard”. In reality, PLOPED should be confined to the historical record of Nuclear Medicine in the same way as is a single posterior view of 133Xe, the ventilation procedure from which it originally sprang.

The best that can be said of the paper is that it highlights just how far from a real screening test for PE is the latest contrast-enhanced Radiology technology. From 7284 patients suspected of having PE, 3019 or almost half were excluded because they could not have the procedure on technical or medical grounds. Note particularly the 595 on ventilatory support. V/Q with Technegas/MAA need not exclude anyone. In fact, one of our Physicians said informally once that he preferred patients with tracheostomy tubes and comatose as he can get good ventilation every time!

Gottschalk A, Stein PD, Goodman LR and Sostman HD. Overview of prospective investigation of pulmonary embolism diagnosis II. *Semin Nucl Med* 2002; 32: 173-182.

Stein PD, Fowler SE, Goodman LR et al. Multidetector Computed Tomography for acute Pulmonary Embolism. *New Engl J Med* 2006; 354: 2317-27.

ICRP Tissue Weighting Factors

Ionising radiation has three known effects on tissue. Deterministic effects involve cell death, which may result in observable harm, the degree being related to radiation dose above a certain threshold. Stochastic effects result from modification of the cell rather than cell death, and may result in later formation of a malignancy or leukaemia with the risk being related to dose. Hereditary effects are a special type of stochastic effect where the damage occurs to cells whose function is to transmit data to later generations.

Much of our knowledge of stochastic effects is based on the epidemiological studies on the survivors of the Japanese atomic weapons explosions. Periodic reviews of the data are undertaken by, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the US National Academy of Sciences “Biological Effects of Ionising Radiation” Committee (BEIR). Interpretation of the data for radiation protection use is performed by the International Commission on Radiological Protection (ICRP). The ICRP, in its “Recommendations”, draws conclusions relevant to application of radiation protection.

Two of the early outcomes of the studies of Japanese survivors (and other data) were that there was a latency period between radiation exposure and the appearance of symptoms of particular malignancies, and that some body tissues appeared to be more radiosensitive than others. Using the available epidemiological data, the ICRP established risk factors for different organs or tissues. In its 1976 recommendations (1) the ICRP introduced the term “tissue weighting factor, WT” to describe this. The weighting factors are used when calculating a person’s effective dose from exposures to individual organs or tissues. The “effective dose” is believed to be linearly related to the risk of stochastic effects and is calculated as the sum of the individual weighted organ doses.

WT for the breast was 0.15, based on assumed risk factor for fatal cancer of 2.5 x 10⁻³ Sv⁻¹. The highest weighting factor of 0.25 was for the gonads, based on assumed risks of hereditary effects as well as tumour induction and fertility impairment. Only 6 organs were allocated specific weighting factors at that time. The sum of all factors was 1 by definition. All factors including breast are gender-averaged.

The 1990 recommendations of the ICRP (2) added 6 further organs to be allocated WT values, resulting in a reduction in the values for gonads and breast to 0.20 and 0.05 respectively. These values are still being used for radiation protection purposes at the present time.

Last year, the ICRP issued a draft revision of its Recommendations. These do not suggest any fundamental change in the system of radiation protection, but do take into account knowledge gained in the last 20 years. Although there has been no evidence that radiation exposure to the parent causes excess hereditary disease in the offspring, the ICRP continues to believe that radiation can cause mutations to reproductive cells but that the risk of hereditary diseases has been overestimated. As a result, the tissue weighting factor for gonads could be considerably reduced.

In January 2007, ICRP released their draft recommendations (3), which may be a final draft after a public comment period on an earlier draft in 2006. In this document, the weighting factors for gonads and breast have been changed to 0.08 and 0.12 respectively.

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3. International Commission on Radiological Protection, “Draft Recommendations of the ICRP – 12th January 2007”, available at www.icrp.org/docs/ICRP_Draft_Recommendations_12_January_2007.pdf, accessed 15/1/07.
4. Stein PD, Woodard PK, Weg JG et al, “Diagnostic pathways in acute pulmonary embolism: Recommendations of the PLOPED II investigators”, *AJM* 119:1048-1055, 2006

What are the implications of this? Firstly, breast is now in the highest weighted organ category, along with red marrow, colon, lung, stomach and “remainder tissues”. Gonads have the second highest weighting. This has the effect of more than doubling the contribution of breast dose to the effective dose, and will particularly affect cases where breast exposure is a significant component. Two good examples of this will be in cardiac diagnosis and treatment, and diagnosis of pulmonary embolism.

Cardiac catheterisation procedures involve sometimes significant doses to organs in a small region around the heart – lung, mediastinal marrow and breast being the most important. There will be a higher emphasis needed on dose optimisation in cardiac x-ray procedures.

CT-based pulmonary angiography (CTPA) is rapidly becoming a preferred technique for pulmonary embolism diagnosis in preference to nuclear medicine V/Q scanning. However the breast, lung and marrow doses are significantly higher in CTPA than for V/Q scans. Even in the case of pregnant patients, where CTPA offers a lower uterine/foetal dose than nuclear medicine, the maternal breast dose is still significant.

There may also be an impact in a third area – that of asymptomatic x-ray screening for breast cancer. Fortunately in both cardiology and breast screening, current technology allows lower doses than even 10 years ago. It is the potential for increased use which is the significant issue.

In the case of pulmonary embolism diagnosis however, the shift in technology increases doses markedly. The recent PLOPED II report (4), recommends CT as the imaging test of choice for patients where D-dimer and clinical evaluation have not ruled out pulmonary embolism. The reviewed dosimetry suggests breast dose from CTPA to be 10 to 50 mGy, and about 0.3 mGy for perfusion scanning (my own calculations suggest 31 and 1.1 mGy respectively). It is the 30- to 150-fold increase in breast dose from CTPA which is of potential concern. It is up to the user to decide if the higher dose is warranted by the diagnostic outcome.

There are no prescribed limits for clinically indicated medical radiation exposure – only so-called reference levels, which are intended as a guide to good practice. The reference levels in radiology are for skin entrance dose, not organ dose, and due to the wide variation in protocols and scanned areas, not an easy concept to use in CT. The underlying principle is that the medical benefit from any patient radiation exposure should outweigh the potential for harm due to the radiation.

The release of the new ICRP Recommendations, while not having a fundamental impact, will pose some questions in how we use radiation in medicine.

A/Prof Lee Collins AM
Medical Physics Dept
Westmead Hospital

Lee Collins is Director of Medical Physics at Westmead Hospital, Sydney, specialising in medical imaging, medical lasers, and radiation safety. He is an honorary adjunct associate professor in the School of Medical Radiation Science at Sydney University and a member of the NSW Radiation Advisory Council. He was made a Member of the Order of Australia in 2003.

PIOPED II and the future of the V/Q scan

A/Prof Paul Roach FRACP Head, Department of Nuclear Medicine Royal North Shore Hospital, Sydney

Increasingly, the ventilation/perfusion (V/Q) scan is being replaced by CT pulmonary angiography (CTPA) as the first line imaging test for suspected pulmonary embolism (PE). There are several reasons behind this change, including the increasing availability and technical improvements of CTPA imaging and the ability of CTPA to demonstrate other pathologies. At the same time, planar V/Q scans have the limitation of a lower diagnostic specificity and clinicians may find reports unhelpful due to the use of probabilities. To add to this, Nuclear Medicine imaging facilities may not always be easily available, a point noted in the British Thoracic Society PE guidelines, for instance (1).

As with other new technologies, the uptake of CTPA into the medical community as a diagnostic modality for PE, has preceded its scientific study. However, in 2006, the PLOPED II investigators published the results of the largest trial to date investigating the diagnostic accuracy of CTPA, in the *New England Journal of Medicine* (2). This was a multi-centre study which compared the diagnostic performance of CTPA (using 4-16 slice scanners) to a composite gold standard which included pulmonary angiography, planar V/Q scintigraphy (with Xe-133 often used as the ventilation agent) and clinical follow-up. Several important points regarding this study, and the diagnostic performance of CTPA, are summarized below:

- Patient exclusions: Of the 7284 subjects originally screened, 23% were excluded due to either co-existent renal impairment or significant contrast allergy (neither of which precludes the use of V/Q scanning) and a further 19% were excluded as patients were considered to be critically ill or required ventilatory support.

- Of the 1090 patients enrolled, 22% were excluded from the final analysis as a final diagnosis could not be confidently established. This subgroup represents the most difficult clinical population, where an accurate diagnosis of PE is often critical. As the final analysis of CTPA’s accuracy failed to take these into account, the true sensitivity and specificity may be different in a clinical population.

- Image quality and reporting: Of 824 CTPA studies performed, 51 (6.2%) studies were inconclusive due to poor image quality. This is usually due to respiratory motion artifact. Although not stated in the final paper, when PLOPED II results were presented in abstract form at the annual meeting of the American College of Chest Physicians meeting in 2004, it was noted that the inter-observer variability rate for CTPA reporting was 7% (3).

- Sensitivity: The overall sensitivity of CTPA was 83%. This varied significantly between enrolling sites, with individual institutions reportedly ranging from 58% to 95% (3). The addition of CT venography to the study protocol increased the sensitivity to 90%, at the expense of increased radiation exposure to the pelvis and abdomen.

- As with the original PLOPED study (4), clinical probabilities were added to scan interpretations to improve overall accuracy. In patients with a discordance between the clinical probability, and the scan result, the CTPA was noted to have a significant false positive and false negative rate.

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What does this mean for Nuclear Medicine and the V/Q scan in 2007?

1. While CTPA clearly has a role to play in the diagnosis of suspected PE, the results of the PLOPED II investigators have demonstrated that CTPA lacks sensitivity, and therefore should be used with caution as a screening test in isolation. As the authors state, “a false negative rate of 17% for CTPA alone indicates the need for additional information to rule out pulmonary embolism”. Consequently, it is important that clinicians and imaging specialists are aware of these limitations, given the increasing tendency to rely solely on CTPA when PE is suspected.

2. In comparison with CTPA, the strength of V/Q scintigraphy is its high sensitivity, and consequently it is ideally suited as a screening test. However, several studies have demonstrated that to maximize sensitivity (as well as improve specificity and reduce interobserver variability), SPECT acquisitions should be done (5-7). In an era of technologically advancing CT technology, it is imperative that the technique of the V/Q scan be optimized thereby maximizing its diagnostic potential. To compare planar V/Q (especially as practiced in the USA where agents such as Xe-133 are still being used) with CTPA obtained on a 4, 16 or 64 slice scanner, is like comparing a 1989 Nissan Pulsar with a 2007 BMW M3. The future for V/Q scintigraphy is made harder by the lack of access to Technegas in the USA and it is therefore imperative that sites in Australia, Europe, and Canada, continue to present data regarding the strengths and accuracy of V/Q SPECT.

3. The advent of V/Q SPECT should also be seen as the catalyst to replace the probability-based reporting perpetuated since the original (planar) PLOPED study of 1990 with more definitive reports where possible. This is important for acceptance by referring clinicians and there would seem to be little value in trying to apply the old planar criteria to V/Q SPECT.

4. There is increasing concern regarding radiation exposure from CTPA. This is of particular concern for pre-menopausal females given the radio-sensitivity of breast tissue. Currently, the medical profession is struggling with the balance between the use of high levels of radiation in some imaging procedures and the potential risks this may expose patients to in the long term. As the profession gains an increased understanding of this concept, it is important that Nuclear Medicine practitioners are aware of relevant radiation safety issues. This will enable imaging tests to be appropriately selected in individual patients.

This is an important time for the future of the V/Q scan. Many clinicians and imaging specialists will have expected that CTPA would have performed better than the results of PLOPED II investigators indicate. As CTPA technology improves, it is likely that its accuracy will continue to improve, however V/Q scintigraphy clearly has an important role to play in the detection of PE. However, as Nuclear Medicine Physicians, we must optimize imaging techniques and patient reports so that the benefits of the test can be fully maximized. This is the challenge for all of us today.