Advancing A Molecular Theory Of Disease
Medicine is based primarily on the cell theory of disease, first proposed by Rudolph Virchow in 1858, and on the germ theory of disease, first proposed by Louis Pasteur and Robert Koch in 1862. This theory led to the development of antibiotics which have made a huge contribution to human welfare.

Molecular imaging can be the foundation of a new molecular theory of disease, and can help characterize mental as well as physical diseases.
The diagnostic process begins with the elucidation of the patient’s symptoms and physical signs. The goal is to predict the presence of pathological lesions in specific organs, tissues or cells. The Clinical Pathological Conference was sacred in my medical school days.

Today, with molecular imaging, we search for measurable micromoles/minute/ml of tissue (4M) that are related to the patient’s problems. If found, we hope they are modifiable (5M).

Time, the 4th dimension, is a key parameter, defining biological processes, not just states.
Genotype plus molecular phenotype are the keys
Histopathology still plays a major role, but cells are so complex, that a molecular theory of disease advances the science of disease.

Why?

Each cell contains 20,000 different kinds of molecules, with 50,000 molecules of each type per cell.

Molecules are the basic units of bodily structures, provide intercellular communication, and control the responses of the body to environmental stresses.

Molecules control the birth, life and death of cells.

Cells are like cities; molecules are like people, inhabiting and running the cities.
In-111 WBC SPECT/CT and MRI in a diabetic patient with an infected foot

Karin Knešaurek, Dov Kolker, Josef Machac, Michael Muzinic, Maria DaCosta, Zhuangyu Zhang, Heiba Sharif

The Mount Sinai Medical Center
New York
24 year old woman with a foot infection. Does she have osteomyelitis?

MRI & In-111 WBC SPECT revealed osteomyelitis as well as soft tissue disease

SPECT/MRI Image of the Year 2008
Three-phase bone scans were performed in 1,475 patients during a one year period, and included patients, who had undergone an extremity amputation or placement of an orthopedic device.

28 scans had regions of increased activity. 27 (96%) had an In-111 white blood cell (WBC) and Tc-99m sulfur colloid study to diagnose or exclude osteomyelitis.

It was concluded that patients should proceed directly to the more definitive and specific In-111 tagged WBC/Tc-99m sulfur colloid examinations, if the diagnosis of osteomyelitis is suspected.

Skeletal scintigraphy provided little diagnostic benefit.
18-FDG PET-CT imaging in patients with transplants

M. Catalano; S. Piccolo; M.L. De Rimini; B. Magliulo; F. Barbato; M. Bifulco; P. Muto

Diagnostic Imaging - Nuclear Medicine Dept. A.O.R.N. Monaldi, Naples - Italy
PET/CT was useful in diagnosis, follow-up, and the monitoring and planning of therapeutic strategies.
Molecular Imaging Of Receptors

Neuroendocrine tumors (carcinoid) imaged with $^{68}$Ga-DOTA-NOC PET (somatostatin receptors)

Castellucci Paolo; Fanti Stefano; Ambrosini Valentina; Tomassetti Paola; Montini GianCarlo; Allegri Vincenzo; Rubello Domenico; Nanni Cristina; Franchi Roberto

Nuclear Medicine,
Azienda Ospedaliero-Universitaria di Bologna, Italy
Molecular Imaging of a somatostatin receptor-expressing tumor in the ear of a 33 year old man

PET/CT Image of the Year
Unusual primary neuroendocrine tumour sites: uterus (3 cases), prostate (3), ovary (1), kidney (1), breast (1), ear (1), paraganglioma (3) and lymphoma (1).

$^{68}$Ga-DOTA-NOC imaging affected the care of 12/14 patients.
Molecular Imaging From Head To Toe

PET/CT

SPECT/MRI

PITUITARY

LEFT EAR

LYMPH NODE

OSTEOMYELITIS
Noticeable better diagnosis of NET with $^{68}$Ga-DOTA-TATE PET

$^{18}$F-DOPA PET was false negative in half the patients

Uptake of $^{18}$F-DOPA tends to correlate with increased levels of serotonin

In case of absent somatostatin receptors and elevated levels of serotonin, $^{18}$F-DOPA PET should be considered as a possible alternative examination
How Did FDG Become “The Tracer Molecule of the 20th Century”? 

(1) FDG measures a key biochemical process (energy supply)  
(2) Clearly linked to surgical decision-making  
(3) Legislative support obtained funding via CMS  
(4) Early adoption and promotion by industry  
(5) Regional suppliers  
(6) Easily automated chemical synthesis  
(7) 110 minute half-life  
(8) PET/CT increased appeal by joining structure and biochemistry
Availability

In 1996, there were 10 regional FDG distribution sites in United States.

By 2008, there were 110 FDG distribution sites in United States.

There are now 10 production sites in Japan, supplying 50 hospitals.
CMS (Medicare and Medicaid) National Oncologic PET Registry

- 22,975 FDG studies (83.7% PET/CT) in one year from May 8, 2006.

- Results from 1,178 centers: Management changed in 37.2%.

March 20, 2008 J Clin Oncol.
• Representatives from the National Oncologic PET Registry have formally asked the U.S. Centers for Medicare and Medicaid Services (CMS) to expand federal reimbursement for the use of FDG-PET in all oncology applications.

• They ask for FDG-PET coverage for the diagnosis, staging, and restaging of all oncology applications.

• Decisions regarding use can be made by physicians ("self-regulation by personal acceptance of risk"). Is this the regulatory mechanism of the future for imaging procedures? Analogous to surgeons making decisions to operate.
“There is a limit to how much regulation can do. In the final analysis, you could write all the rules you want, but there has to be a philosophy of ethical behavior that comes from human beings operating in a professional way.”

William H. Donaldson
D-SPECT – A novel dedicated cardiac SPECT scanner

Brian Hutton¹, Kjell Erlandsson¹, Krzysztof Kacperski¹, Dean Van Gramberg¹, Nathaniel Roth²

Institute of Nuclear Medicine, University College London, UK
Spectrum Dynamics, Caesaria, Israel
• The high sensitivity and count-rate facilitate high quality dynamic acquisition

• The good energy resolution permits dual radionuclide imaging, including $^{99m}Tc$ / $^{123}I$
An Example

Simultaneous dual isotope myocardial perfusion imaging with D-SPECT

S Ben-Haim, BF Hutton, D Van Gramberg, WA Waddington, EM Prvulovich, JB Bomanji, AM Groves, K Kacperski, N Roth, PJ Ell

Institute of Nuclear Medicine, University College Hospital, London, UK and Spectrum-Dynamics, Caesarea, Israel

Accuracy and image quality of simultaneous DI MPI with D-SPECT are equal to conventional MPI with separate stress and rest acquisitions
Every hospital will have a cyclotron in 30 years (as I said 42 years ago in *Nucleonics*).
Ron Nutt, CTI and GSK

- The energy of the beam is 7.5 MeV and can produce 50 Millicuries of C-11 or F-18.
- N-13 or O-15 cannot be produced.
- To acquire the Biomarker Generator requires a “franchise fee” of $200,000.
- Then $100.00 per dose to the franchiser. A minimum of eight doses must be produced each day.
- Local production of PET tracers is analogous historically to the conversion from mainframe to personal computers.
### Potential F-18 Products That Could Be Provided In-House

<table>
<thead>
<tr>
<th>Product</th>
<th>Function</th>
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<tbody>
<tr>
<td>F-18 DOPA</td>
<td>Dopamine synthesis (neuroendocrine, melanoma, lung ca</td>
</tr>
<tr>
<td>F-18 fluorouracil</td>
<td>Pyrimidine analogue (colorectal liver mets)</td>
</tr>
<tr>
<td>F-18 fluoro-tyrosine</td>
<td>Large amino acid transport, not protein synthesis</td>
</tr>
<tr>
<td>F-18 FACBC</td>
<td>Amino acid transport (prostate cancer)</td>
</tr>
<tr>
<td>F-18 fluorocholine</td>
<td>&quot;</td>
</tr>
<tr>
<td>F-18 fluorothymidine*</td>
<td>DNA synthesis</td>
</tr>
<tr>
<td>F-18 fluorestradiol</td>
<td>Estrogen receptors</td>
</tr>
<tr>
<td>F-18 fluoroazomycin arabinoside (F-18 FAZA)</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>F-18 misonidazole (F-18 MISO)</td>
<td>&quot;</td>
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<tr>
<td>F-18 FRP-170</td>
<td>&quot;</td>
</tr>
<tr>
<td>F-18 FACT</td>
<td>Amyloid</td>
</tr>
</tbody>
</table>

Fluorination changes the biological properties so toxicity testing is needed.

Automation still needs expertise to monitor and fix problems.
Microfluidics with glass based “liquid PTFE*”

Ron Nutt, CTI and GSK

* polytetrafluorethylene
Glass Based Microchemistry
Fast, High Yield & Low Mass

98.3% FDG
100 Seconds
160°C
Increased Yields Resulting From Use of Micro-fluidics

[Chemical structures and descriptions]

Metabolically Activated Malignant Lesions
50% vs 10%
48 min vs 2 min

Detects Cell Proliferation
25% vs 94%
60 min vs 2 min

Detects Hypoxia
23% vs 34%
49 min vs 1 min

Prevents to Labeling Other Compounds
58% vs 92%
43 min vs 2 min

Detects and Quantifies Alzheimer's Disease in Living Patients
50% vs 68%
60 min vs 3 min

Reporter Gene Expression
6% vs 36%
60 min vs 1 min
Advantages of “In-house” Production of Radiotracers:

(1) Easier regulatory approval
(2) Ever-increasing numbers of tracers
(3) Ready availability
(4) Decreased cost of care per patient
Advances In Nuclear Cardiology
Screening For Coronary Artery Disease in Asymptomatic Persons

The ACCF/ASNC* appropriateness criteria predict outcomes in patients without known coronary artery disease

Mouaz Al-Mallah, MD
Marcelo Di Carli, MD
Advanced Cardiovascular Imaging
Brigham and Women’s Hospital

*American College of Cardiology Foundation
American Society of Nuclear Cardiology

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SPECT-MPI Appropriateness Study
Results
N=5943

- Appropriate: 75.3%
- Inappropriate: 11.6%
- Uncertain: 13.1%
The Continuum of Coronary Artery Disease by Quantitative PET-CT

Mehrbod S Javadi, Riikka Lautamäki, Jennifer Merrill, Corina Voicu, Frank M Bengel

Division of Nuclear Medicine
Department of Radiology
Johns Hopkins University
Preclinical Disease

Abnormal Vascular Reactivity (Endothelial Dysfunction)

Vascular Remodeling and Plaque

Clinical Disease

Stable Flow Limiting Coronary Stenosis

Occlusion

(1) Quantitative PET: Coronary Flow Reserve
(2) CT Angiography: Plaque Burden
(3) Qualitative PET: Relative Regional Ischemia/Infarction

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In patients with suspected CAD, assessing microvascular disease and coronary artery plaque burden plus measurement of coronary flow reserve (CFR) identifies those persons at risk for progression to clinically overt CAD.
Quantification of Myocardial Blood Flow with PET-CT and $^{82}$Rb – Validation in a Canine Model of Myocardial Ischemia


Cardiovascular Nuclear Medicine, The Johns Hopkins University, Baltimore, MD
Quantification of myocardial blood flow with $^{82}\text{Rb}$ improves the diagnostic and prognostic value of cardiac PET-CT studies in identification of balanced ischemia, monitoring of therapy or detection of endothelial dysfunction as a CAD precursor.
Carotid Intima-Media Thickness (US), Coronary Artery Calcification (EBT) and Coronary Vasomotion in Asymptomatic Type-2 Diabetic Patients

TH Schindler, J Goldin, GM Vincenti, R Nkoulou, O Ratib, HR Schelbert

David Geffen School of Medicine at UCLA
University of California at Los Angeles

Cardiovascular Center, Division of Cardiology, Department of Internal Medicine, Geneva
• 34-44% of type 2 diabetes mellitus patients examined with PET had coronary endothelial dysfunction, a functional precursor of CAD, without coronary artery calcification (CAC) or abnormal increases in carotid intima-media thickness (IMT), as determined by ultrasound and electron beam tomography.

• Thus, coronary endothelial dysfunction can be detected by PET before structural alterations of the arterial wall may be seen.
Multi-Tracer PET Characterization of Impaired Myocardial Sympathetic Innervation in the Viable Infarct Borderzone


Division of Nuclear Medicine, The Johns Hopkins University, Baltimore, MD
Sympathetic Innervation After Myocardial Infarction

- The viable infarct borderzone is arrhythmogenic.
- Nuclear imaging shows impaired innervation in this borderzone.
- Three $^{11}$C-tracers were combined to investigate different components of presynaptic nerve biology.

$[^{11}\text{C}]-\text{Epinephrine}$
- Normally stored in vesicles which protect from metabolism

$[^{11}\text{C}]-\text{Hydroxyephedrine}$
- Avidly taken up, no metabolism

$[^{11}\text{C}]-\text{Phenylephrine}$
- Not efficiently stored, leaks from vesicles and is degraded
There is impaired neuronal biochemistry without complete denervation, which contributes to arrhythmogenicity in the infarct borderzone. This state may be reversible. Neuronal imaging can guide novel antiarrhythmic therapies.
Beyond Calcium Score in Preventive Cardiology

The value of calcium score and myocardial perfusion SPECT in the prediction of severe cardiac events during long term follow-up in patients with known coronary artery disease

Uebleis C. ¹, Rominger A. ¹, Becker A. ², Becker C. ³, Bartenstein P. ¹, Hacker M. ¹

¹ Department of Nuclear Medicine, University of Munich, Germany
² Department of Cardiology, University of Munich, Germany
³ Department of Radiology, University of Munich, Germany
• n = 260 with known CAD

• Calcium score and myocardial perfusion scan within 90 days

• Follow-Up 5.3 ± 2.9 years (0.2 – 10 years)
• n = 23 severe cardiac events (cardiac death or myocardial infarction)

• Highest annual event rate was in patients with a calcium score > 400.

• Calcium score and coronary stenosis were strong and independent predictors of severe cardiac events.
Inflammation and vascular calcification represent different stages in the evolution of an atheromatous plaque.

Measurements of $^{18}$FDG uptake in the aortic arch are highly reproducible and correlate poorly with degree and location of calcification.
• Inflammation is important in both the pathogenesis and clinical outcome of atherosclerosis
• Atherosclerotic plaque rupture is a consequence of inflammatory cell activity within the plaque
• Plaques containing numerous inflammatory cells, in particular, macrophages, have a high risk of rupture
• Current widely-used imaging techniques provide anatomic data, but no indication of plaque inflammation
• By detecting regions of plaque instability through markers for inflammation, patients at risk can be treated to prevent future events
We need expertise in both structural and molecular imaging.

Clinically significant incidental findings on the CT portion of Rubidium-82 PET/CT myocardial perfusion imaging

McKee B, Dou Y, Raja S, Pinkus E, Flacke S

Lahey Clinic
Immediate additional workup  

$n = 7/75$ (9%)

- New pulmonary nodules $> 4$mm  
  $(n = 5)$
- Hepatic Metastases  
  $(n = 2)$

- Pulmonary nodules $> 4$mm  
  $(n = 8)$
- Pleural effusion  
  $(n = 5)$
- Hiatal hernia  
  $(n = 4)$
- Biliary dilatation  
  $(n = 3)$
- Pulmonary metastases  
  $(n = 3)$
- Aortic aneurysm  
  $(n = 2)$
- Bronchopleural fistula  
  $(n = 1)$
- Pneumobilia  
  $(n = 1)$
- Breast mass  
  $(n = 1)$
- Adrenal adenoma  
  $(n = 1)$
- Cirrhosis  
  $(n = 1)$
- LHIS  
  $(n = 1)$

Normal  

$n = 46/75$ (61%)

Film/Chart Review  

$n = 22/75$ (29%)
Outcomes in patients with abnormal myocardial perfusion imaging and normal coronary angiogram

T. Dresser, K. Delcour, A. Chockalingam, S. Kuppuswamy, A. Khaja

Harry S Truman Memorial Veterans Hospital
University of Missouri-Columbia, School of Medicine
808 patients had myocardial perfusion imaging and coronary angiogram

48 patients had abnormal MPI and normal coronaries

16 of 48 patients had cardiovascular events during the next 2-10 years

   Cardiac events: 7
   Cerebrovascular events: 6
   Peripheral revascularization: 3
Screening of stress-induced perfusion myocardial ischemia in a large cohort of diabetic patients

Nuclear Medicine Division and Cardiology Division, University Hospital of Geneva
Screening of 386 DM patients for myocardial ischemia with 201-Tl SPECT

Prevalence of a perfusion abnormality in diabetic patients (%)

- Symptomatic Pts: 44% (Normal MP: 56%, Abnormal MP: 42%)
- Asymptomatic Pts: 42% (Normal MP: 58%, Abnormal MP: 42%)

p=ns
The prognostic value of rest myocardial perfusion imaging in diabetic patients

Zhifang-Wu, Sijin-Li, JZ-Liu, XF-Li, G-Hu,
J-Wang, Y-Cheng, HY-Liu

The First Hospital of Shanxi Medical university,
Taiyuan, Shanxi, China
1047 pts

- 172 diabetic pts.
- Mean interval of following up was 33.25 ± 14.95 (1~56) months.
Follow-up (months)

Diabetic

Non diabetic

CADIAC EVENT FREE RATE (%)
SPECT Screening in Diabetic Patients

A normal SPECT cardiac study has a high negative predictive value for future cardiac events, but diabetic pts still had a significantly higher cardiac event rate compared with non-diabetic pts, whether or not the myocardial perfusion image (MPI) is normal or abnormal.
The economic value of molecular imaging

dV/dt = fK*

where V = Value
K = Knowledge

• Correct decision-making depends on knowledge.

• Increasing knowledge by molecular imaging is expensive, but making correct decisions decreases the cost of caring for each patient. It may increase overall institutional costs because increasing productivity will increase demand for the procedures. This is a key point.
Assessing the value of a procedure

- Time in days from detection of disease to beginning of treatment \((t_1)\).
- Time from beginning treatment to beginning of improvement of patient \((t_2)\).
- Length of stay in hospital \((t_3)\)
- Time to return to normal activities \((t_4)\)
- Time from beginning of treatment to time of death \((t_5)\).
- All times in days are assigned economic values.

Value of the procedure:

\[
V = \frac{f(t_5)}{f(t_1) + f(t_2) + f(t_3) + f(t_4)}
\]