New Concepts in *cardiac imaging 1987*

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Contributors

Stephen L. Bacharach, Ph.D.
Department of Nuclear Medicine
Clinical Center
National Institutes of Health
Bethesda, Maryland

Robert O. Bonow, M.D.
Senior Investigator
Chief, Nuclear Cardiology Section
Cardiology Branch
National Heart, Lung, and Blood Institute
Bethesda, Maryland

Thomas F. Budinger, M.D.
Donner Laboratory
Department of Electrical Engineering and Computer Sciences
University of California at Berkeley
Berkeley, California
Department of Radiology
University of California, San Francisco
San Francisco, California

Robert C. Canby, M.E.E.
Fellow, Stanley J. Sarnoff Society for Research in Cardiovascular Science
Cardiac NMR Laboratory
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Jay Clarke, Ph.D.
MRC Cyclotron Unit
Hammersmith Hospital
Royal Postgraduate Medical School
London, England

Terrence L. Cogswell, M.D.
Instructor in Medicine
Cardiology Division
Department of Medicine
Medical College of Wisconsin
Zablocki VA Medical Center
Milwaukee, Wisconsin

John E. Deanfield, M.B.
MRC Training Fellow
MRC Cyclotron Unit
Hammersmith Hospital
Royal Postgraduate Medical School
London, England

Christian deLandsheere, M.B.
NATO Fellow
MRC Cyclotron Unit
Hammersmith Hospital
Royal Postgraduate Medical School
London, England

Robert E. Dinsmore, M.D.
Director, Cardiac Radiology
Massachusetts General Hospital
Boston, Massachusetts

W. Jay Eldredge, M.D.
Director, Section of Cardiac Imaging
Deborah Heart and Lung Center
Associate Clinical Professor of Pediatrics
University of Medicine and Dentistry of New Jersey
Rutgers Medical School
Browns Mills, New Jersey

Gabriel A. Elgavish, Ph.D.
Assistant Professor of Biochemistry and Medicine
Cardiac NMR Laboratory
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Stephanie Flicker, M.D.
Chairman, Department of Radiology
Deborah Heart and Lung Center
Browns Mills, New Jersey

Walter L. Henry, M.D.
Professor, Division of Cardiology
University of California at Irvine
Irvine, California

Terry Jones, Ph.D.
Medical Research Council
Cyclotron Unit
Hammersmith Hospital
London, England

Peter Mansfield, Ph.D.
Professor of Physics
Department of Physics
University of Nottingham
Nottingham, England

Richard S. Meltzer, M.D., Ph.D.
Associate Professor of Medicine and Radiology
Director of Echocardiography (Cardiology)
Director of the Contrast Echocardiography Research Laboratory
University of Rochester
Rochester, New York

Joel Morganroth, M.D.
Professor of Medicine and Pharmacology
Director, Sudden Death Prevention Program
Likoff Cardiovascular Institute
Hahnemann University Hospital
Philadelphia, Pennsylvania

Orhan Nalcioglu, Ph.D.
Professor, Department of Radiological Sciences
University of California at Irvine
Irvine, California

Harold A. O'Brien, Ph.D.
Cardiology Division
Brigham and Women's Hospital
Boston, Massachusetts

Ioannis P. Panidis, M.D.
Assistant Professor of Medicine
Co-Director, Cardiac Ultrasound Laboratory
Likoff Cardiovascular Institute
Hahnemann University Hospital
Philadelphia, Pennsylvania

James L. Ritchie, M.D.
Professor of Medicine
Division of Cardiology
University of Washington
Veterans Administration Medical Center
Seattle, Washington

Kiran B. Sagar, M.D.
Associate Professor of Medicine
Cardiology Division
Department of Medicine
Medical College of Wisconsin
Zablocki VA Medical Center
Milwaukee, Wisconsin

David A. Sato, M.D.
Clinical Instructor
Division of Cardiology
University of California at Irvine
Irvine, California

Heinrich R. Schelbert, M.D.
Division of Nuclear Medicine and Biophysics
Department of Radiological Sciences
UCLA School of Medicine
Laboratory of Nuclear Medicine
Laboratory of Biomedical and Environmental Sciences
University of California, Los Angeles
Los Angeles, California

Andrew P. Selwyn, M.D.
Director, Cardiac Catheterization Laboratories
Department of Medicine
Brigham and Women's Hospital
Associate Professor of Medicine
Boston, Massachusetts

Michael Shea, M.D.
Clinician-Scientist Awardee of the American Heart Association
MRC Cyclotron Unit
Hammersmith Hospital
Royal Postgraduate Medical School
London, England

Robert M. Steiner, M.D.
Professor of Radiology
Thomas Jefferson University
Philadelphia, Pennsylvania

John R. Stratton, M.D.
Associate Professor of Medicine
Division of Cardiology
University of Washington
Veterans Administration Medical Center
Seattle, Washington

Jonathan Tobis, M.D.
Associate Professor
Division of Cardiology
University of California at Irvine
Irvine, California

L. Samuel Wann, M.D.
Associate Professor of Medicine
Cardiology Division
Department of Medicine
Medical College of Wisconsin
Zablocki VA Medical Center
Milwaukee, Wisconsin

Richard Wilson, M.D.
British American Heart Research Fellow of the American Heart Association
Fulbright Scholar
MRC Cyclotron Unit
Hammersmith Hospital
Royal Postgraduate Medical School
London, England

Preface

NEW CONCEPTS IN CARDIAC IMAGING 1987 (NCCI) extends the philosophy of the first two volumes in this annual series by providing critical reviews of selected but timely topics thematically related to clinical cardiac imaging. Reviews cover the four types of cardiac imaging modalities: ultrasound, radionuclide, x-ray, and magnetic. Written by acknowledged experts, these reviews are designed to explain clearly and critically selected aspects of the science and advances in the technology.

The lead article for this year's volume is "The Practicality and Operation of PET" by Terry Jones. This contribution places PET technology in practical perspective and speculates on the future. While enormous potential for PET exists, its widespread applications are limited by cost and other resources (space, personnel, etc.). Nevertheless, major industrial organizations are now becoming involved and a wide variety of clinical applications for PET are being established in the cardiology literature. It appears that within the next decade PET imaging will be widely available. Dr. Jones' analysis is truly worth reading since it is an exposé of things to come.

Each of the four sections of this NCCI volume opens with an overview containing editorial perspectives about the articles. The topics covered in Part 1, Ultrasound Methods, include evaluation of heart function during exercise, contrast echocardiography, and detection of cardiac masses. Part 2 presents reviews of radionuclide methods and utility of measurements to assess left ventricular diastolic function, platelet imaging, PET for assessment of myocardial perfusion, and PET relative to other methods to detect myocardial ischemia. Articles in the section on x-ray imaging techniques address the diagnostic role of digital subtraction angiography and cine-CT (in congenital heart disease). This year's section on magnetic methods includes the following issues: high speed NMR imaging, NMR contrast agents, application of NMR imaging to evaluation of left ventricular function, and the potential hazards of NMR methods.

There is little doubt that great strides continue in cardiac imaging, and NCCI is intended to help you keep abreast of these developments. For example, the trend toward an entirely noninvasive diagnostic examination, ultimately reserving cardiac catheterization for therapy, will be addressed specifically in the 1988 volume with a special section on noninvasive angiography.

The Editorial Board hopes that you will enjoy and learn from the NEW CONCEPTS IN CARDIAC IMAGING series of critical reviews. We welcome your comments and suggestions.

GERALD M. POHOST, M.D.
EDITOR-IN-CHIEF

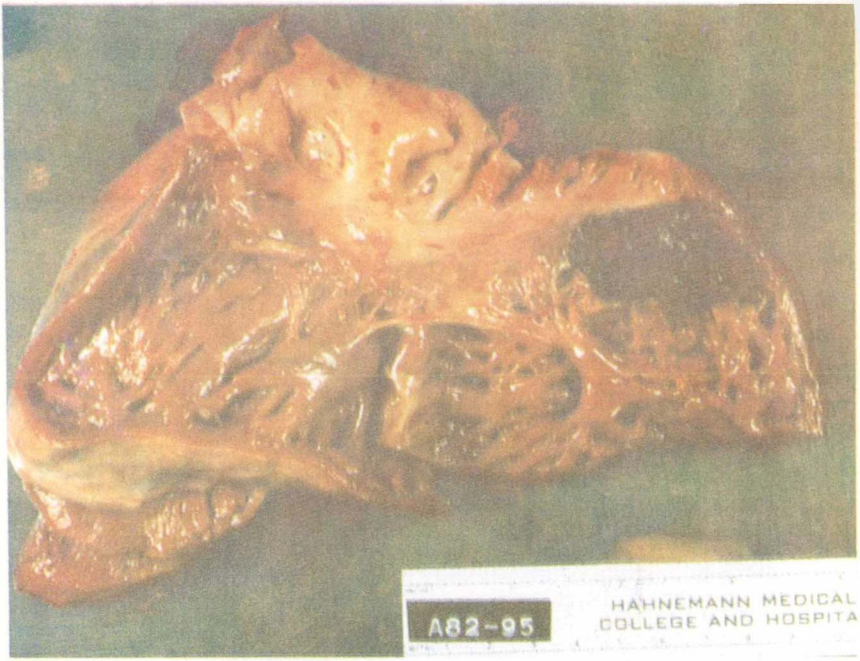

PLATE 1 (Fig 12, C, Panidis Chapter).—Autopsy specimen showing a thrombosed vegetation involving the septal leaflet of the tricuspid valve.

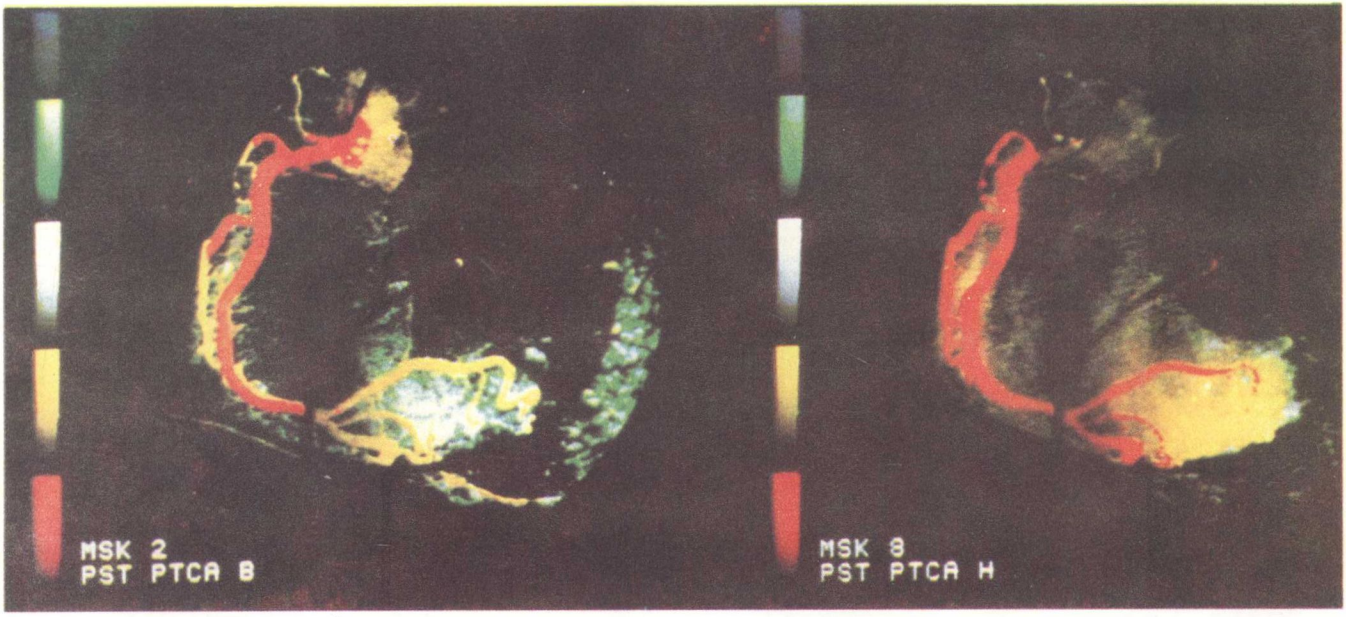

PLATE 2 (Fig 4, Sato Chapter).—Color-coded contrast medium appearance picture (CMAP) generated from LAO digital subtraction angiograms post *(PST)* right coronary artery angioplasty *(PTCA)*. Five successive diastolic images following contrast injection are selected and color coded. Red is assigned to pixels with contrast density exceeding 8% above baseline density in the first postinjection cycle, yellow for the second, white for the third, green for the fourth, and blue for the fifth cycle. The frame on the *left* represents flow at baseline postangioplasty. The frame on the *right* demonstrates increased flow following a hyperemic stimulus which represents a normal response and implies a hemodynamically successful angioplasty. (*Photo* courtesy of Robert A. Vogel, M.D.).

Contents

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The Practicality and Operation of PET

TERRY JONES, Ph.D.

Medical Research Council, Cyclotron Unit, Hammersmith Hospital, London

POSITRON EMISSION TOMOGRAPHY (PET) represents the most advanced means for noninvasively investigating regional tissue function. The tomographs themselves can provide quantitative data on the uptake and transit of tracers within tissues.[18] Short-lived, positron-emitting radioisotopes, such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F, offer suitable labels for biologic molecules. Efficient chemical synthetic methods have been developed to label a range of chemical compounds so that usable amounts of tracer material can be made despite the rapid decay of the radionuclides.[12] Positron emission tomography represents two components of accuracy for in vivo tracer studies. Natural biologic molecules can be labeled and their regional tissue concentrations measured. This enables tracer kinetic models to be defined, based on the known tissue compartmentation of biochemical compounds. The recorded quantitative scan data can then be processed through these models to obtain values for the biochemical, physiologic, or pharmacologic function of the tissue being traced.

In cardiologic conditions, disturbances in regional tissue function occur both in the myocardium itself and in other vital and peripheral areas of the body. In view of the difficulty of investigating these tissue function disturbances, and the degree of pathophysiologic ignorance that exists, PET offers a relevant tool for investigative cardiology. However, to date, comparatively few groups have explored the use of PET in cardiology or, for that matter, in other areas of medicine. The proponents of this advanced methodology are motivated by the potential contribution it can make to furthering knowledge of focal human disease and its treatment. This motivation, on occasion, is blunted by the less-than-enthusiastic response and,

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indeed, lack of interest exhibited by the medical community at large. Why is there a "turn off" from PET, and could there be a "turn on"? Is it that clinicians do not think in terms of regional tissue function, despite the educational grounding most have in scientific subjects? Or is it that the technical and logistic aspects of this speciality are barriers to acceptance and interest? This chapter places these technical aspects in their practical perspective. My aim is to encourage clinical cardiologists to ask questions about PET methodology and to extend their currently modest involvement in this area of investigation.

THE PERCEPTION OF PET BY THE CLINICAL COMMUNITY

This journal is concerned with cardiac imaging. Let us then examine what image the cardiologist and the medical community at large have of PET and its application. It is seen as a logistically complex and expensive methodology whose use is confined to a few centers, which, through the drive of some individuals, have gathered funds to explore the application of PET. The need for a cyclotron, radiochemistry skills and laboratories, expensive PET scanners, in addition to the expertise required to interpret the recorded data, tend to extinguish sparks of clinical interest. Also, the spatial definition of PET images, although representative of tissue function, are not like the crisp anatomical scans offered by x-ray, computed tomography, and nuclear magnetic resonance imaging. This superficial inspection of PET and the "complexity shock" are barriers to the recognition that functional resolution is being offered. The fact that a PET scan could represent the state of the tissue's well being and response to treatment is often not reflected upon. Up until now, it has been inappropriate for clinicians to order a PET scan, since applications have required a close involvement with the process of data collection and analysis. It is this commitment that is the key to advancing the field and leveling the barriers before it.

At present, the actual number of cardiac PET studies being undertaken is very small, and some are analyzed and assessed outside of mainstream cardiology. The PET enthusiasts are dispersed internationally, and the "critical mass" of investigators needed to advance areas of application has yet to be created. Nevertheless, the investigative tools now exist, and so

do the clinical cardiologic questions. Additionally, medical doctors, having a better-than-ever grounding in basic sciences, should, in principle, be appreciative of what PET has to offer. From the outset, the question is not, "*will* this area ever be accepted?" but "when?" Let us then look at the "turn offs" that are associated with this specialty.

LOGISTIC HURDLES IN PET

The principal indigestible aspect is the technology necessary to implement PET scanning. On closer examination, it is seen that much of this technology is rapidly becoming streamlined. A cyclotron, that is, a charged particle accelerator, is needed to produce the short-lived positron-emitting tracers. General medical use of such equipment may seem impractical. However, linear accelerators of electrons (Linacs) are used extensively for supervoltage radiotherapy of human cancers. These sources of intense radiation, like cyclotrons, also have to be shielded. There is currently a move to provide cyclotrons suitable for hospitals which are as practical as therapy Linacs. There are now six commercial manufacturers (three in Japan) of baby cyclotrons, tailored for hospital PET studies. The labeling of tracer compounds with the short-lived isotopes is also seen as being formidable. Shielded hot cells are needed, and so are remotely controlled, novel radiosynthetic processes and efficient quality control procedures. This challenge has been taken up, and specific routes for synthesis have been identified that offer a whole range of labeled compounds.[12] For example, the method based on the use of $^{11}CH_3I$ is able, in principle, to label some 15% of the drugs in the pharmacopoeia with ^{11}C within a synthetic time of 40–60 minutes. By adopting standard methods, labeling with short-lived isotopes could become more widespread than at present.

The PET scanners themselves are expensive. This is due not least to the limited commercial market and because the underlying technology is still being improved upon and hence has required developmental capital. Nevertheless, much effort from industry and the universities is being channeled into perfecting the spatial resolution, sensitivity, and cost effectiveness of PET scanners. There are currently at least six companies manufacturing PET scanners together with computer packages for image processing. It is predicted that, within a few years,

machines with the theoretical limit of 2–3-mm resolution will be commercially available. At present, 5–6-mm machines are in use, and already they are making convincing impressions on those who thought, because of their experience with the earlier generation of scanners, that PET meant blurred images. Also, the first PET scanners recorded just one transaxial plane of data at a time so that complete surveys of the myocardium were achieved with difficulty. The current multiplane scanners overcome this problem and provide the overall functional landscape of the organs.

The full scope of PET as a means for studying a wide range of tracers has yet to fully express itself. At present, few PET tracer procedures are sufficiently perfected to provide quantitative measurement of a specific entity of tissue function. Established measurements include blood flow, oxygen, glucose, and fatty acid utilization, amino acid transport, and some receptor binding studies. The study of receptor binding is attracting much interest, since the inherent sensitivity of PET is unrivaled for such in vivo measurements. Methods have also been established for measuring certain components of tissue function—in particular, energy supply and metabolism. The chief growth of the PET methodology lies in the creation of new, accurate procedures. To implement the existing techniques, care is needed in the recording and analysis of data, but an investigative clinical laboratory is well able to do this. A cost analysis of PET for clinical use has been reported.[11]

CARDIOLOGIC EXPERIENCE OF PET

Seven or eight of the current PET groups have undertaken cardiologic studies. While not all of the same depth, the practicality of these studies has been illustrated. Interest has centered on the use of ^{82}Rb to study transit changes in myocardial perfusion.[5, 6, 23, 24] Tissue energy metabolism methods, involving glucose and fatty acid utilization, have been introduced. Interesting and new information has been obtained about patients with angina, myocardial infarction, and cardiomyopathies. It is not one of the aims of this paper to discuss the significance of these findings. (Recommended reviews,[30, 31, 33, 34, 36] clinical papers,[2, 3, 8–10, 14, 15, 21, 22, 25–29, 35] and reports[1, 7, 17, 32] covering these studies are named in the chapter references.) Parallel PET pulmonary studies have also

been reported, including the measurement of regional extravascular lung water in cardiac patients.[20, 38, 40–42]

THE FUTURE SCOPE FOR PET CARDIOLOGY STUDIES

Most of the PET cardiology work to date has centered on energy supply and utilization within the myocardium. Nevertheless, study of the functional state of other organs will be needed in order to assess how this relates overall to the cardiac conditions. It is clear, for example, that renal perfusion is often central to cardiac work and output in hypertensive states. Also, PET receptor ligand studies of the myocardium will become of interest. Methods have already been reported for muscarinic receptor measurements.[37] The interest in examining β-adrenergic receptors is focused on the fact that their density is reduced in the failing heart.[4, 13, 19, 39] Investigation of dopamine-receptor function in organs such as the kidney bear direct relevance to a treatment aimed at improving cardiac function.[16] The extensive amount of cardiac bypass surgery currently being undertaken stimulates the need to study the functional consequences of these procedures on organs other than the heart.

CONCLUSION

The introduction of positron emission tomography into cardiology is occurring slowly, but surely. The lack of expected enthusiasm from cardiologists stems mainly from what they perceive as being unsurmountable logistic difficulties. As this speciality matures, it is clear that the logistics can now be circumvented, and the new generation of PET scanners offer not only functional information on tissue function but spatial information that is comparable with other imaging modalities. This investigative tool needs to be explored, to add to man's knowledge of cardiac diseases and their treatments. It would be appropriate for more academic departments of cardiology to ask questions about cardiac disease using PET methodology. This would certainly place the results into the context of advanced clinical practice. There continues to be a search for an objective and direct means of assessing clinical treatment. Positron emission tomography offers this, but to exploit the opportunity, clin-

ical investigators will need to orientate their thinking in terms of focal tissue biochemistry, physiology, and pharmacology.

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