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NMR Clinical Imaging and Spectroscopy: Its Impact on Nuclear Medicine

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What Does NMR Offer That Nuclear Medicine Does Not?

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Nuclear Magnetic Resonance or Magnetic Resonance Imaging, as it is now commonly called, began as an analytical tool for chemists. It was later used by biochemists to explore the structure of more complex biological molecules. Beginning in the early 1970's scientists realized that images could be created by sampling the object in a "raster like" manner. More sophisticated techniques were applied using gradient amplifiers and pulsed Fourier techniques. From images of a piece of fruit the system expanded to encompass the whole body. By the late 1970's clinical images were being obtained. In the early 1980's medical specialities separated into camps all trying to claim ownership for this new clinical tool. The radiologists claiming ownership since it was an imaging tool, the nuclear physicians claiming ownership because if its ability to no only create images but to also explore the chemistry and physiology of tissues. Besides, it did deal with the "nuclear" structure of the atom, the domain of "nuclear medicine".

As the dust cleared the "nuclear" was dropped from Nuclear Magnetic Resonance and the Radiologists had control of the imaging. It is interesting to look at Spectroscopy though. Radiologists are comfortable with anatomic images but most are uncomfortable with the biochemistry and "non-imaging" data. The nuclear medicine community has maintained an interest in NMR Spectroscopy as evident by the NMR Council of the Society of Nuclear Medicine and the presence of NMR sessions at the annual meeting.

In the early 1980's there were cries about the demise of nuclear medicine due to the almost "omnipotent" power of Computed Tomography and NMR/MRI. This was triggered by the precipitous decline in the number of brain scans coupled with the early decline of liver spleen scans looking for metastatic disease.

The topic of this symposium was chosen to discuss just those fears. It is the responsibility of the speakers to discuss the impact of NMR/MRI on the field of

Nuclear Medicine. The topics of discussion we chosen for different reasons. Each is a major clinical area within Nuclear Medicine and each is felt to be a target by competing modalities. Oncological imaging will be discussed because there is rapid change, the loss of some examinations (i.e. liver) and the near clinical application of new agents (i.e. monoclonal antibodies). NMR Spectroscopy was chosen because we are now a decade following its initial proposal regarding it's "imminent" clinical future. Cardiology because of its current dominant role in Nuclear Medicine and the new developments in cardiac MRI/MRS which may impact the future of Nuclear Cardiology. Lastly, we must look to the future and answer the question, "is Nuclear Medicine dying?"

Oncological Imaging:
Now, Future and Impact

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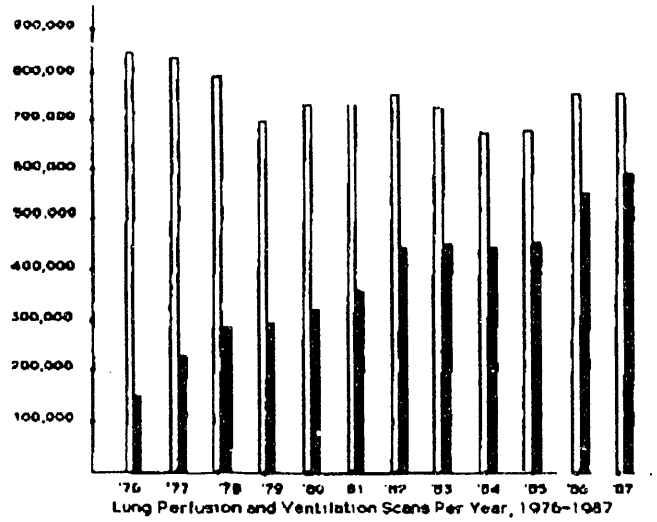
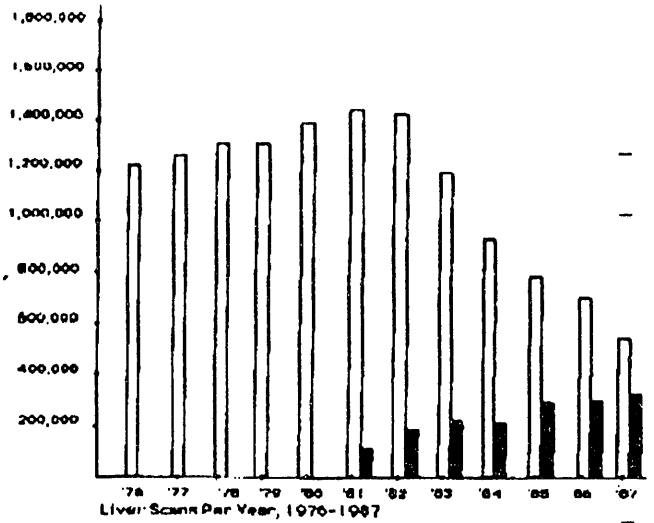
OVERVIEW

An interesting "NEWSLINE" appeared in the June 1988 Journal of Nuclear Medicine presenting the results of a survey performed by Market Measures, Inc. of West Orange, New Jersey (see included graphs). Although this survey only included *in vivo* procedures performed in hospitals many believe that it still reflects overall trends in Nuclear Medicine. The decline of brain scans from a high of 2.1 million in 1976 to approximately 100,000 thousand in 1987 was attributed to MRI and CT. If one looks back the impact was from CT not MRI. Clinical MRI did not reach its full neuroradiological impact until the late 1980's. Also, if one looks at other countries where MRI is less prevalent (i.e. Canada), identical trends have occurred. Those practicing CT and MRI realize that, in fact, the late 1980's brings forth MRI examinations beginning to replace neuro CT procedures much like the decline of nuclear medicine brain scans being replaced by CT scans in the late 1970's.

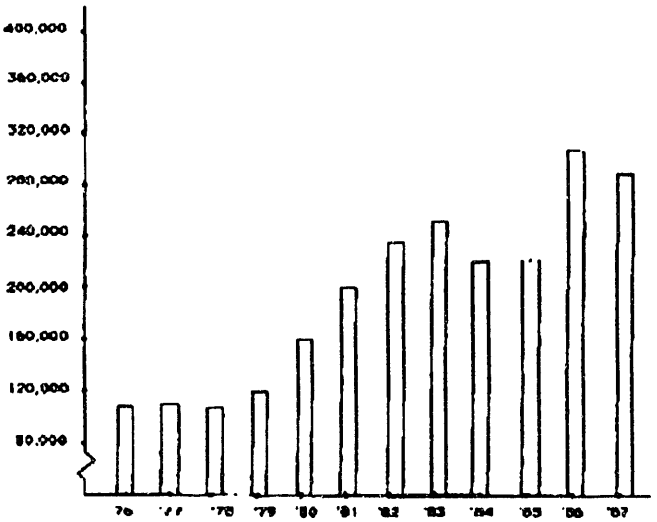
Another nuclear procedure that has declined over the last ten years is the liver-spleen scan. In 1981 it reached a peak of over 1.4 million scans while in 1987 the numbers have declined to about 500,000 scans. As one critically reviews these two procedures they have several characteristics in common; they were targeted at specific organs looking primarily for anatomic abnormalities and they need high anatomic resolution, something that Nuclear Medicine has never offered.



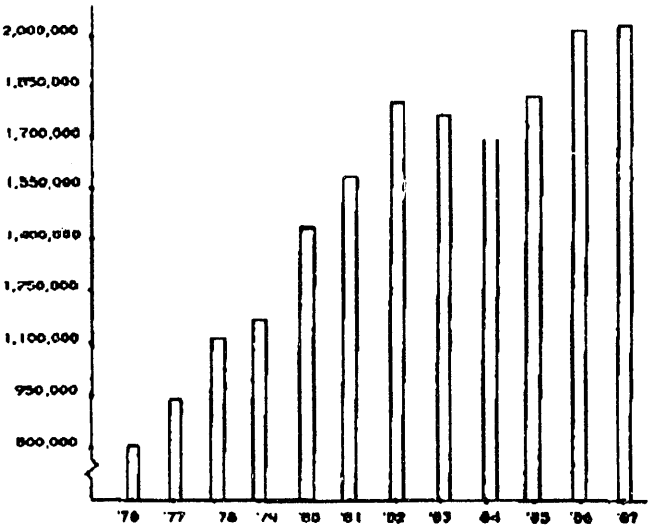
Lung Perfusion and Ventilation Scans Per Year, 1976-1987



Liver Scans Per Year, 1976-1987



Kidney Scans per year, 1976-1987



Bone Scans Per Year, 1976-1987

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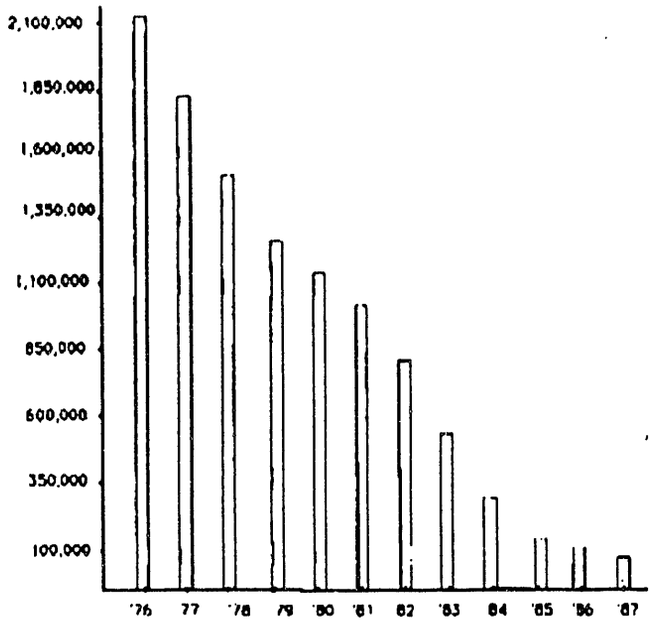
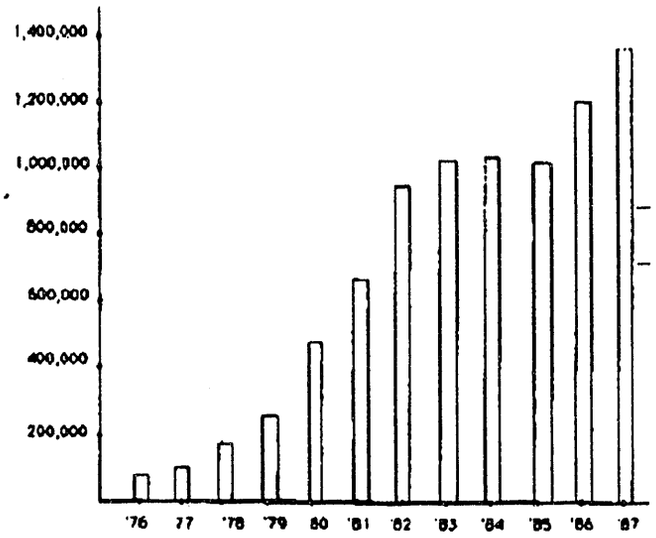
What is striking about the decline of liver scans is the concomitant growth in hepato-biliary studies. From about zero in 1980 to over 300,000 in 1987. Hepato-biliary studies are "functional or physiological" and not "anatomic". Reviewing the other graphs one sees that "physiological" studies have increased (renal, cardiac and V/Q scans). The one procedure that is not purely physiological / functional is bone scans. From 1976 until 1987 there has been almost a 300%

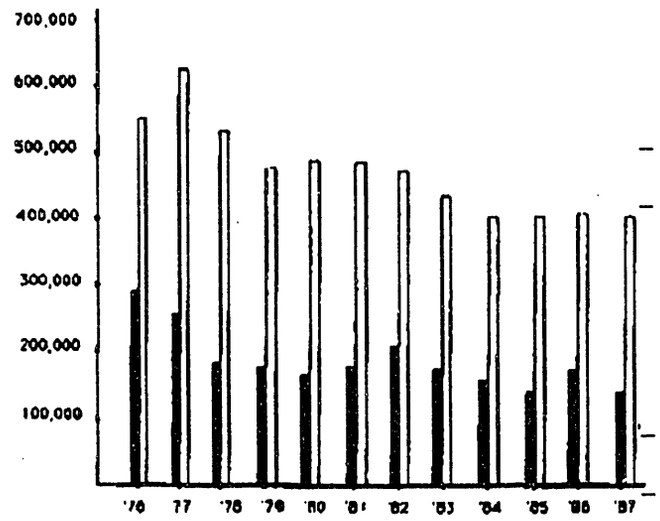
#Note: These graphs were taken from NEWSLINE of the Journal of Nuclear Medicine, Vol 29:6, pages 1009-1010, 1988.



Brain Scans Per Year, 1976-1987



Heart Scans Per Year, All Types, 1976-1987



Thyroid Scans Per Year, 1976-1987

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increase in numbers, from 800,000 to over 2 million. Bone scans are the single highest performed *in vivo* examination in Nuclear Medicine. Is the bone scan the brain scan of 1987? Bone scans account for about 25% of all nuclear medicine procedures. If bone scans were to suffer the same decline as brain scans then the economics of NM would be considerably different.

$Note: These graphs were taken from NEWSLINE of the Journal of Nuclear Medicine, Vol 29:6, pages 1009-1010, 1988.

NMR/MRI ONCOLOGICAL APPLICATIONS

Present day MRI is an anatomic tool following the development pathway of Computed Tomography. Even though the information content of the MR image is much richer then CT and new pulse sequences can extract more and different information from the object, MRI is still primarily an anatomic imaging tool. By volume of procedures alone the most common examination is the central nervous system, brain and spine. When MRI availability was limited it was used primarily to look for tumors, demyelination and evaluating patients who had neurological findings and normal CT scans. In Canada where there are less than two dozen scanners for the whole country, MRI is still primarily used for evaluation of the central nervous system for tumors. In the U.S., as the number of units have increased the areas of clinical application have grown. For example, now there are centers who perform purely orthopedic MRI. Excess "magnet capacity" promotes exploring existing "procedural markets." Of late a number of manuscripts have come across my desk where the investigators have looked at the sensitivity and specificity of MRI versus Bone Scans for detecting bony metastasis. The results are impressive and not surprising, MRI has greater sensitivity and specificity then bone scans. Some cry bone scans are better since they can screen the whole body! Because of the fat signal seen on T1 sequences (short TR's), scanning large areas of the body are not difficult or time consuming. Newer developments in MRI which allows for imaging in seconds (soon sub-second) will allow for screening the trunk and main appendicular skeleton in the same amount of time as a bone scan.

FUTURE

Futurist seem both interesting and amusing. Usually more amusing! There are certain present day facts that seem to hint of the future, or at least the near future. Monoclonal antibodies, the "magic bullet" seemed so close just a few years ago but today they seem far into the future. Although scientists still take monoclonal research seriously, some drug companies seems to be retreating. It appears that two major radio-pharmaceutical manufacturers have either closed or nearly closed they monoclonal efforts. Some say that today there is not one routine clinical antibody [I know that there are some who will debate this]. The FDA seems concerned about monoclonals and approval on a large scale may take many years. PET scanning clearly dominated the most recent Society of Nuclear Medicine meeting but the U.S. federal government has made it clear that the economics of PET make it unattractive

as a routine clinical tool even though they want to continue to support research centers.

In a recent conversation with a pharmaceutical manufacturer they made it clear that the volume of potential oncological procedures compared to cardiovascular and neurological procedures makes developing tracers for oncology a less attractive market. The door was not slammed shut, they did say that as agents for the big two are developed then oncology will become attractive again.

CONCLUSION

As this topic is reviewed one must never loose sight of the fact that clinical volume, profits, growth, etc. are business terms and not scientific or academic The field of nuclear medicine is richer in scientific and pathophysiological principles than ever and the field still needs curious minds to explore new physiology. As Paracelsus said almost 500 years ago, "the body is a conglomeration of chemical reactions. When these are deranged only chemical medicines can correct them." To quote Henry Wagner, M.D., "imaging in vivo chemistry remains the most fundamental principle of nuclear medicine."

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Magnetic Resonance Spectroscopy/Spectroscopic Imaging and Nuclear Medicine: Past, Present and Future

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OVERVIEW

Magnetic Resonance Spectroscopy has proven one of the most valuable tools for non-destructive analysis of molecular structure for the chemist and biochemist. More recently the application of spectroscopy to *in vivo* analysis of biochemical and physiological problems has provided a unique non-invasive window to metabolism. The questions of spectroscopy past were of a general nature, such as, what can we do with *in vivo* spectroscopic information. The problems of spectroscopy present are often of a technical nature with issues of localization, patient compliance, data analysis and presentation, as well as quantization among some of the current topics. Spectroscopy future presents the questions of practicality in the clinical environment, economics of diagnostic imaging, and the role of functional imaging, especially MRS, in clinical medicine. Solutions to most of the technical problems now exist and many are implemented in commercial equipment. Others, such as data presentation for clinical utilization, remain a topic of debate with a clear trend toward image related presentation. The future of spectroscopy and its relation to functional imaging will depend to a great extent on the proliferation of the technology and availability of trained personnel to interpret the data.

SPECTROSCOPY PAST: Capabilities and Questions

<u>What problems can magnetic resonance spectroscopy solve?</u>

In vivo spectroscopy provides a window to intermediary metabolism. Energetics as well as tissue status can be probed using phosphorus spectroscopy. Hydrogen spectroscopy can be used to evaluate buildup of lactate and changes in other metabolites such as N-acetylaspartate or carnitine. Fluorine spectroscopy can be

used to track the degradation of extrinsic agents such as anesthetics and chemotherapeutic agents. Carbon spectroscopy can be used to evaluate glycogen and fat status and in special cases labeled metabolites. In all cases it is important to remember that MR is basically limited to millimolar concentrations in detection sensitivity and thus is not optimal for tracer studies. However, many intermediate metabolic substrates are of sufficient concentration for attack by *in vivo* spectroscopy/spectroscopic imaging.

Where does the spectrum come from?

Localization Methodology:

After signal to noise and magnetic field homogeneity, localization methodology has been the major problem in spectroscopy. In the past few years, however, a trend toward imaging as a basis for localization has emerged with the application of chemical shift imaging and image selected single voxel techniques overshadowing simple surface coil localization. This has been aided by improvements in RF and gradient hardware including shielded gradient coils which allow rapid phase encoding with minimal eddy currents. The development of high sensitivity volume and conformable coils has provided a new impetus for metabolic imaging in the brain and other organs. In general, although there are some occasional disagreements over the "optimum" technique, the problem of localization for MRS has been solved.

Hydrogen mapping for metabolic images:

Related to the problem of localization is the issue of mapping the low spatial resolution spectroscopic information to the high resolution hydrogen image. Most of the localization techniques (CSI, ISIS, PRESS, STEAM, etc.) deal adequately with the problem although the question of multiple voxels is addressed most efficiently by CSI. Again, this problem like its twin localization has been solved.

What nucleus should I use?

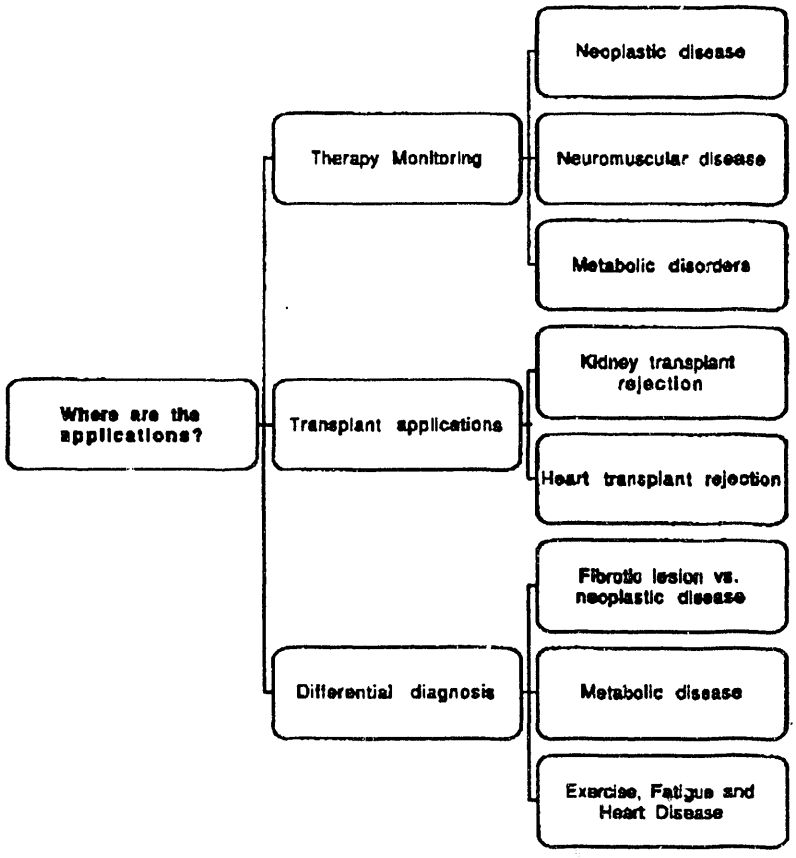
Clearly more work has been accomplished with phosphorus and more models have been studied with this nucleus but hydrogen studies are improving with the use of STEAM, PRESS and CSI for localization and some work with other nuclei such as carbon, fluorine, and sodium is moving ahead. Currently phosphorus and hydrogen

occupy the # 1 and #2 positions with all others quite far behind. This is primarily due to the poorer sensitivity and/or concentration of the latter nuclei.

SPECTROSCOPY PRESENT: Clinical Research and Experience

Where are the applications?

Preliminary work at a number of sites has shown the diseases in the following outline to be the major thrust of spectroscopic clinical development. Localization methodology has played a major role in the transition of spectroscopy from a "diffuse" disease technology to a "focal" disease technology. The following "tree" indicates some of the areas where spectroscopy will likely play a clinical role.



SPECTROSCOPY FUTURE: Dissemination, Training, Research, and Clinical Integration

The dissemination of MRS technology has already started with research accessories offered by the major MR manufacturers and research is underway in various sites throughout the world. Some sites are focussed on basic biomedical research while others are including early clinical research in their focus. The results look promising in some areas and short training programs are beginning to appear for MRS in addition to the already wide selection available for MRI.

The Role of the Spectroscopist in Clinical Spectroscopy

Currently, there is a need for a specialist in performing and analyzing spectroscopic data but with advances in software and hardware, data acquisition can be handled by trained technologists and evaluated by trained clinicians. For clinical integration of MRS with other functional imaging the specialist must begin the process of training clinical practitioners. Hopefully, there will still be a market for *in vivo* spectroscopists in MR flow imaging.

MR Cardiology: Now, Future and Impact

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OVERVIEW

Magnetic resonance techniques have specific advantages when applied to diagnosis of cardiovascular diseases. The non-invasive nature coupled with the high soft tissue contrast and sensitivity to blood flow make magnetic resonance techniques extremely useful for improving the sensitivity and specificity of cardiovascular diagnosis.

The trade-offs between temporal, spacial, and contrast resolution define the overall clinical usefulness currently available in modern diagnostic MR instrumentation. Gains in spacial resolution can be obtained at a loss of signal to noise and, therefore, to a minimal degree compensating for increased scan times. However, this increase in scan time at some point becomes prohibitive and limits the overall spacial resolution. Contrast resolution although effected both by temporal and spacial factors is largely dependent on the choice of pulse sequence parameters and implementation. In evaluation of cardiovascular diseases where temporal resolution or the evaluation of abnormalities is of paramount importance and spacial resolutions of one to two millimeters are more than adequate, MR becomes a very useful non-invasive diagnostic test. Additionally, the trade-offs in special resolution and time are important factors in considering MR spectroscopic applications for cardiac abnormalities.

CLINICAL

Current clinical applications bridge virtually all areas of cardiovascular diseases. Early work had demonstrated MR to be an extremely sensitive method for the evaluation of acute myocardial infarction. The excellent contrast generated because of T2 of acute myocardial infarction can be visualized as early as 1 hour and accurately represents the size of an acute infarction. Although this is accurate, simple and non-invasive this technique has not been widely utilized for evaluation of acute infarction. MR spectroscopic techniques can identify infarcted tissue, however, the

temporal resolution and spacial resolution trade-offs made it of limited value in acute myocardial ischemia. The development of fast imaging techniques included cine gradient recalled imaging of the heart have opened new areas for function evaluation of cardiovascular structures. Cine MRI techniques, because of their sensitivity to flow and turbulence make excellent representations of valvular abnormalities. Both qualitative and quantitative assessments of the severity of disease can be obtained by cine MR techniques of valvular disease. The excellent sensitivity to blood flow, and relatively high contrast resolution obtained both with spin echo imaging and cine MRI have allowed a wide application to the evaluation of children with complex congenital heart disease. The identification of great vessel abnormalities and surgically placed shunts is far superior to other existing non-invasive techniques such as echo cardiography.

FUTURE

The future applications of MR techniques will include an expansion of the role of MR spectroscopy. Because of the limitations of both temporal and spacial resolution this role may be somewhat limited to diffuse myocardial diseases. Current applications suggest that phosphorous spectroscopy may be an excellent method for the evaluation of cardiac transplant rejection. The development of new fast imaging techniques based on the existing cine MRI techniques adds a tremendous dimension to the potential impact of MR in the heart. SAT cine techniques which allow the direct tagging of myocardium and assessment of the direction and magnitude of motion of individual portions of the myocardium allow for the first time in non-invasive evaluation of myocardial motion. In past this evaluation was only available through implanted crystals or tantalum tags. Velocity and coded cine (VINNE) allows the direct measurement of velocities at the size of an individual pixel. By demonstrating both the direction and magnitude and flow within vascular structures non-invasive diagnosis of major vascular abnormalities has been greatly enhanced. In the future it is felt that these methods as they improve will allow the direct measurement of flow within smaller structures such as coronary arteries or coronary artery bypass grafts. One of the most rapidly advancing areas is the applications of MR angiography not only to great vessels but to the coronary arteries themselves. Again these techniques are dependent upon improvements on imaging time and signal to noise. Both software and hardware advances will have a strong impact on the ultimate spacial resolution obtained from these MR angiographic techniques when applied to the coronary arteries.

IMPACT

The impact of the existing and developing techniques on clinical care depends largely on their implementation. The current state of the art in most areas allows for more accurate quantitative measurements of multiple parameters such as myocardial mass, volumes and vascular dimensions. The impact, however, of this "improved" information is still largely to be determined. The long term effect must be an enhancement of diagnostic capabilities and an overall reduction in patient care costs by eliminating either unnecessary procedures or reducing the patient's hospital stay. An effective collaboration between MR imagers, surgeons, and cardiologists is required for the overall useful utilization of these techniques.

New Frontiers of NMR and Nuclear Medicine Research

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A prediction of the future expectations for NMR and nuclear medicine is based on an evaluation of the respective unique capabilities of these two modes for both invasive and non-invasive studies of human biochemistry and physiology in normal and abnormal states. The most general unique capability of NMR is the ability to detect chemical composition; whereas, the unique ability of radioactive tracer techniques is the superior sensitivity for detection of temporal and spatial distribution of ligands. when we couple these distinctive capabilities with the physical and safety limitations of both NMR and nuclear medicine techniques, we can make predictions regarding future opportunities. Under the topics below technical potentials and limitations will be presented along with medical science examples.

HIGH RESOLUTION NMR IMAGING

Whereas NMR can reveal an anatomical image based on the abundance (90 Molar) and behavior of protons in tissues, the intricate changes in the architecture of organs such as the brain and kidneys, which accompany disease states, cannot be easily measured with present technology because such measurements require 3-dimensional descriptions with resolution of less than 1mm in all 3 dimensions. This limitation is expected to be overcome by the marriage of new computer architectures and high-field magnets (e.g.,4T). Thus, hypotheses regarding neuroarchitectural patterns associated with human behavioral disorders can be tested, and this area of imaging might be fruitful for practical differential diagnostic work.

FAST IMAGING

The capabilities of acquiring stop-action images of moving organs such as the hear, gut, etc. depends on our ability to rapidly switch the magnetic gradients. Major advances have been made in the gradient technologies and NMR pulse sequence developments such that very rapid imaging is now available. However, the combination of fast imaging and high resolution seems to be a major limitation because the rate of field change necessary for acceptable images is near or in fact beyond the threshold of neuromuscular stimulation by the induced currents. The limitation here is not only patient discomfort but the potential of cardiac fibrillation. Data on the threshold near 40 T/sec will be presented.

SPECTROSCOPIC STUDIES

A definite future expectation for NMR is in spectroscopic studies leading to the determination of chemical composition and metabolic pathways in normal and diseased states using ^{13}C. With high-field NMR (e.g., 4T to 10T), it is possible to evaluate the particular chemical patterns of fatty acids, carbohydrates and amino acids dynamically using ^{13}C NMR with endogenous and exogenous ligands. For example, it is now possible to evaluate the ratio of saturated to unsaturated fatty acids in the adipose tissue of patients. In the future it should be possible to demonstrate differences in carbohydrate metabolism by ^{13}C NMR of the liver in patients.

Phosphorus NMR has been disappointing because of the nonspecificity of changes in ATP and creatine phosphate. However, with increased fields (e.g., greater than 2T) and new selective region techniques, the study of phosphoesters and other components associated with both lipid and carbohydrate metabolism, *in vivo* phosphorus spectroscopy has a potential for practical clinical studies. For example, the recent demonstration of abnormal metabolic carbohydrate pathways in the diabetic lens has opened a new frontier for studies of subtle metabolic aberorrations associated with the morbid sequellae of diseases. An hypothesis regarding protein cross-linking, atherosclerosis, diabetic changes, and generalized aging will be presented as a future application for high-field NMR studies.

NUCLEAR MEDICINE EMISSION TOMOGRAPHY

The general application of tomography in nuclear medicine has followed the pattern of PET research to SPECT clinical studies. This same pattern is expected in the future; however, because of the superior resolution capabilities of PET studies at the level of sub-cortical structures will remain the domain of PET in the foreseeable future. Specificity studies of the relative amounts of dopamine receptors between layers of the cortical ribbon and central gray matter will not be easily obtained in a reliable fashion until major advances are made in PET detectors. PET resolution of the futures is expected to be 2mm in plane and this resolution coupled with more specific ligands for neuroreceptors have the potential of major breakthroughs in the understanding of mental disorders -- indeed, mental behavior in general. Examples of our inability to evaluate balances of neuroceptors in the brain until we obtain higher resolution instrumentation will be given.

NEW FRONTIERS IN RADIONUCLIDE IN VITRO STUDIES

The capabilities of measuring enzyme activities along metabolic pathways have not generally been pursued because of the radiation hazards associated with 14C. With the new development of a practical mass spectrometer, it is now possible to carry on studies of the metabolism of amino acids, fatty acids, carbohydrates, and other ligands with the sensitivity over 1 million times better than conventional scintillation counting. Advances in this field are dependent on technological improvements in sample preparation and some rather simple small accelerator developments. For example, it is now feasible to study specific amino acid metabolism kinetics *in vitro* by evaluation of sequential blood samples after injection of acceptable levels of ^{14}C labeled precursors.

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