In this issue

Since its discovery in mid 1940s, Nuclear Magnetic Resonance (NMR) has played an important role in many branches of science. In recent years, NMR is a widely used noninvasive technique for obtaining diagnostic radiological images as well as for studying tissue metabolism *in vivo*. The imaging applications of NMR evolved more or less independently of the metabolic applications and it became necessary to introduce the two acronyms: MRI (magnetic resonance imaging), based primarily on the detection of hydrogen (proton) signals from water, and MRS (*magnetic resonance spectroscopy*), used for the detection of metabolites. Many features are common to these techniques and are really variants, or extension, of the more traditional NMR.

In vivo MRS of cells, organs and tissues in humans and animals are an extension of high-resolution NMR techniques but applied to more complex systems. It can be used to observe different metabolites present in a particular region and determination of the concentration and relative levels of these metabolites provide information on normal and abnormal states of tissues and organs and their response to various therapeutic modalities. In short, *in vivo* MRS can be used as a unique means for probing the biochemistry of living systems. MRI, on the other hand, is a new, state-of-the-art, noninvasive imaging modality in diagnostic radiology. It produces a spatial display of the distribution of nuclei (such as hydrogen) and provides a high-resolution morphological picture (anatomical information) with superior contrast resolution compared to CT scanning. Even though MRI and MRS have evolved more or less independently for a number of reasons, *in vivo* localized MRS in humans and other living systems is mainly guided through MR images acquired earlier. Thus, the success of MRI has led to considerable interest in MRS as a noninvasive probe for monitoring the biochemistry of living systems.

The special section in this issue presents a collection of papers in the area of 'MRI and *in vivo* NMR', which will provide a glimpse of the recent status of the technique. During the past two decades the evolution of MRI has witnessed tremendous progress. In addition to its use as a premier modality for delineation of structural anatomy with high spatial resolution and exquisite soft tissue contrast, functional characteristics such as magnetic resonance angiography (MRA), tissue perfusion, diffusion contrast, and magnetization transfer contrast are possible. However, the most fascinating development is the discovery of the functional MRI techniques which allow us to map human brain functions, i.e. to visualize different cognitive processes. The technique is noninvasive and offers repeated studies of individual subjects at unsurpassed spatiotemporal resolution and with a high degree of flexibility in the design of cognitive paradigms. Despite its tremendous potential in cognitive neuroscience, ongoing methodologic developments pose significant challenges as has been discussed by Frahm (**page 735**). The article describes some of the crucial elements necessary to transform a paradigm-related change in brain activity into a corresponding MR activation map. In addition to its enormous application potential in the area of neurosciences for assessing individual pathophysiology and for characterization of several brain functions related to language, memory, etc., it also has important applications in neurosurgery. Identification of the anatomical relationship of a functional area to a tumour (which often distorts and displaces normal anatomy) is of great help to the neurosurgeon while planning the surgical approach and to preserve these primary areas during therapeutic operations.

The individual tumour physiology is one of the important determinants in the outcome of non-surgical treatments. Parameters such as tumour blood flow, tissue oxygenation and nutrient supply, pH distribution, and bioenergetic status significantly influence tumour response to irradiation, hyperthermia, chemotherapy and combination of these modalities. To improve the treatment efficacy, several agents that modify blood flow in tumours are currently under intense investigation. A noninvasive technique to study the effects of these agents on tumour blood flow and oxygenation would be of great use. Muruganandham and Jain (**page 744**) have reviewed the recent advances of MRI methodology namely, the dynamic Gd-DTPA and BOLD (*blood oxygenation* level dependent) contrast MRI techniques to monitor the changes in tumour blood flow and oxygenation. The usefulness of such measurements in tumour radiotherapy is illustrated by studies on the effects induced by diltiazem, a calcium channel blocker, on a murine tumour model.

Another interesting aspect of solid tumours which are heterogeneous, is that the hypoxia of tumour cells caused by abnormal and/or poorly developed vasculature, protects against the effects of radiotherapy. This hypoxia is partly due to rapid growth of the cells, which leads to inadequate and chaotic blood vessel development and thus to heterogeneity in the delivery of O_2 (and also other nutrients) to cells within the tumour. This has considerable significance for the efficacy of radiotherapy. McIntyre *et al.* (**page 753**) have outlined a noninvasive method of measuring tissue oxygenation using ^{19}F MRI from perfluorocarbons (injected intravenously) which are sensitive to oxygen concentration in RIF-1 fibrosarcoma and SaF sarcoma in mice. Perfluorocarbons (PFC) are organic molecules in which the hydrogen atoms have all been replaced by fluorine atoms, and hence give a strong ^{19}F NMR signal. Since ^{19}F atoms are entirely absent in the human body, they act as a perfect tracer for NMR studies. PFCs have a greater affinity for oxygen, dissolving a similar amount per unit volume as blood, and hence have been used both as a blood substitute and to supply oxygen directly to the lungs. Additionally, they are biologically inert, non-toxic and easily available commercially. Recently PFCs have been developed for MR use and when administered intravenously (i.v.) as a lipid emulsion, they are sequestered over a period of several hours into the reticuloendothelial system, particularly in tissues with high levels of macrophages, simplifying the task of imaging. The article by McIntyre *et al.* describes the details of ^{19}F MRI work carried out in mice models.

Quantitative tissue volumetry, especially normal tissues, can provide important information about the development and function of a normal human brain and can yield important clues regarding the underlying pathology in patients. For example, valuable information has been gained about the pathological processes in epilepsy and Alzheimer's disease from the volume measurements of various structures in the brain. The process of identifying and isolating a given tissue (in MR images) is generally referred to as segmentation. This is the most critical step in quantitating tissue volumes and depends on the contrast-to-noise ratio of the image. MRI gives a superb soft tissue contrast and can easily distinguish the brain gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Since MRI is a multi-parametric modality, the tissue contrast can be altered by simply changing the scan parameters or pulse sequences and this plays a crucial role in image segmentation. The focus of the review by Narayana *et al.* (**page 763**) is on the quantitation of MS (multiple sclerosis) lesion in the

brain, which is the most common demyelinating disease in humans. The authors have described novel pulse sequences employed for generating images with superior lesion-to-tissue contrast and also the methods employed for automatic lesion quantitation.

In vivo MRS is a powerful tool in the study of tumours and cancers. Biochemical information obtained through MRS indicates how the metabolism of the tumour differs from that of the normal tissue; it provides diagnostic information on the tumour type and grading, and may be used to monitor the efficacy of anticancer treatments. ^{31}P and ^{1}H are the most widely used nuclei in clinical MRS studies of cancer, giving complementary biochemical information. Doyle *et al.* (**page 772**) describe the recent research and the wealth of information that can be obtained noninvasively using this technique in human cancer.

Breast cancer is the leading cancer among females in developed countries, and is the second commonest cancer in developing countries, constituting a major health problem. Diagnostic techniques are becoming mandatory for early diagnosis, treatment, and improved survival. Several screening procedures available such as physical breast examination, ultrasound, and mammography are often limited in sensitivity and specificity. With the advent of clinical MRI methodology, a valuable new tool has been added to perform diagnostic mammography and combined with *in vivo* MRS it offers an attractive alternative to monitor tissue biochemical/metabolic changes. Jagannathan *et al.* (**page 777**) discuss in their article, the potential of noninvasively monitoring and assessing the response of human breast cancer to neoadjuvant chemotherapy using *in vivo* volume localized proton MRS method.

Gupta and Raja Roy (**page 783**) summarize nicely the application of MRI and MRS in tissue characterization of intracranial tuberculomas. The incidence of intracranial tuberculomas is on the rise both in the developed and developing countries. Differentiation of tuberculomas from other neoplastic and non-neoplastic lesions is essential as these can be managed conservatively with antituberculous drugs and unnecessary surgical intervention can be avoided. Gupta and Raja Roy point out how better tissue characterization of intracranial tuberculomas can be achieved using MRI, *in vivo*, *ex vivo* and *in vitro* NMR studies.

In addition to its widespread clinical use, MRI also has important applications in pharmaceutical research and development since it provides long term noninvasive monitoring of disease processes and assessment of pharmacological intervention. Since NMR is sensitive to structure and dynamics at the molecular level, MRI in combination with *in vivo* MRS permits simultaneous monitoring of the drug and its methods in pharmacokinetic studies. In principle, the drug concentration can be measured at different locations in the body or organ. Because MRS is performed on one magnetically active isotope (e.g. ^{7}Li, ^{19}F) at a time, there is no interference from background signals if the drug contains a label not normally found at significant levels in the body. Komoroski (**page 789**) in his review focuses the utility of the less commonly used nuclei such as ^{7}Li and ^{19}F in *in vivo* MRS to monitor psychoactive drugs and their metabolites directly, particularly in the human brain. Such measurement of drug levels in human brain may provide a measure of therapeutic or toxic effects, as well as insight into drug metabolism and mechanism of action.

Hyperthermic oncology is another interesting area which deals with selective tumour cell killing by induced local or general heating to temperatures between 41 and 45°C. The article by Rama Jayasundar *et al.* (**page 794**) demonstrates the feasibility of combining the fields of *in vivo* MRS and hyperthermic oncology successfully and presents the results obtained from tumour-bearing mice. It is believed that such a study would bring about greater understanding of what hyperthermia might accomplish clinically.

Schuff *et al.* discuss in their article (**page 800**), the recent technique of proton MR spectroscopic imaging (MRSI), sometimes referred as chemical shift imaging (CSI), in which one measures the regional distribution of important metabolites, although at much coarser spatial resolution than MRI for sensitivity reasons. In addition to mapping the distribution of a particular metabolite (for example, the amino acid *N*-acetyl aspartate (NAA) in human brain, which is exclusively found in neurons in high concentration), this technique, also called as multi-voxel MRS, provides the MR spectral data, simultaneously from a number of voxels in a pre-defined larger volume of interest. A distinct advantage of CSI over single-voxel techniques is its ability to give a better definition of the regions where the spectra are being measured. Schuff *et al.* have utilized this methodology to investigate changes in brain metabolites in Alzheimer's disease, epilepsy, and amyotrophic lateral sclerosis.

The latest MRI technique introduced into the clinical arsenal, is the echo planar imaging (EPI), which was proposed by Peter Mansfield in 1977. EPI is a unique MRI method because it can collect an MR image, from a single free induction decay signal (FID) in about 100 msec or less. It has many advantages such as improved efficiency, highest signal-to-noise (S/N) and contrast-to-noise ratio per imaging time, and helps to reduce motion artifacts in addition to reducing the scanning time drastically with higher patient throughput. EPI is the method of choice in the dynamic study of brain activity related to blood volume changes (BOLD) as outlined earlier by Frahm. EPI is a technically demanding experiment and is prone to severe artifacts related to hardware, experiment, etc. especially if it has to be applied to microimaging systems. Subramaniam Sukumar in his article (**page 808**) discusses the nature of these artifacts and various experimental methods to minimize these, are also presented.

MRI despite its relatively short history, has become a major diagnostic tool. Due to its multiplanar capabilities, high spatial resolution, excellent soft tissue contrast, and the absence of ionizing radiation, MRI has also developed as a powerful tool to guide interventional procedures, which is not covered in this special section. New designs of open magnet system allow improved patient access for MR-guided interventional procedures with the use of MR-compatible needles and catheters. Studies of interventional MR applications currently underway include aspiration cytology, chemoablation, cryoblation, etc. As MR technology matures, the technological limits on the achievable scanning speed and pixel resolution are rapidly approaching the limits imposed by the laws of physics, while the methodological limits of the technique are set by physiological safety considerations.

Regarding the role of *in vivo* MRS in clinical diagnosis, the growth has been somewhat slow due to several methodological complexities. Unlike MRI, which expanded very rapidly as a diagnostic tool thanks to prior radiological insights already gained from clinical X-ray, CT, etc. *in vivo* MRS explores a relatively vast and less well-chartered territory and cannot use prior knowledge to define which spectroscopic fingerprints are relevant to the expression or definition of a disease. However, the results obtained to date have provided a better insight into the molecular level understanding of various tissue pathologies, their progression, regression, and treatment. It is believed that the future advances in *in vivo* MR technology will facilitate the full integration of anatomical and functional MRI with metabolic and functional MRS.

N. R. Jagannathan