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THE SILVER ANNIVERSARY OF THE AMERICAN JOURNAL OF NEURORADIOLOGY: Twenty-Five Years of Documenting Advances in Neuroradiology

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THE SILVER ANNIVERSARY OF THE AMERICAN JOURNAL OF NEURORADIOLOGY: Twenty-Five Years of Documenting Advances in Neuroradiology

This issue of the *American Journal of Neuroradiology* marks our 25th anniversary. The silver border on the journal's cover and Reed Murtagh's clever cartoon help celebrate this important milestone in our history.

The *AJNR* has evolved from what many newly trained radiologists would now consider a "primordial neuroradiological ooze" in 1980 to the publication of the most recent advances in neuroimaging and neurointervention. These scientific advances have been mirrored by simultaneous improvements in the formatting and publication of the journal; the ownership of the journal by the ASNR in 1986, self-publication in 1992, and on-line publication in 2000 are just three of the more notable events of the past 25 years. The cover illustrates the steps in "evolution" to a more advanced form of existence, a process that has been guided by the editors of the journal and supported by the Executive Committee of the ASNR.

While it seems obvious today that American neuroradiology should have a journal published under the sponsorship of the ASNR, that opinion was not uniformly shared 26 years ago. There were some who, for a number of reasons, felt that neuroradiology ought to remain under the umbrella of the larger diagnostic radiology journals. Time and experience has shown that the vision of those who advocated a separate specialty journal was correct. Large societies such as the ASNR flourish when they have their own dedicated vehicle for publishing scientific material, a concept which is further strengthened when associated societies contribute their efforts and material to a single widely read journal. This in particular pertains to those societies that call the AJNR their home for scientific publications: the American Society of Head and Neck Radiology (ASHNR); the American Society of Interventional and Therapeutic Neuroradiology (ASITN); the American Society of Pediatric Neuroradiology (ASPNR); the American Society of Spine Radiology (ASSR); and the most recently formed society, the American Society of Functional Neuroradiology (ASFNR). Editorial remarks by John Ulmer and Anderi Holodny, the first President of the ASFNR, appear in this issue of the journal.

From the initial editorial leadership of Juan Taveras to the subsequent innovations by Mike Huckman, the second editor of the journal, the AJNR has become a premier site for the publication of research in clinical neuroradiology. Volume 25 of the Journal is nearly quadruple the size of volume 1, attesting not only to the growth of our field but also to the value placed in having an article published in the AJNR. The volume of submissions has risen dramatically over the past 7 years, from 610 in 1998 to well over 1000 in 2004. Concomitantly, the percentage of submissions from outside North America has increased even more abruptly so that these submissions now represent over two-thirds of all papers sent to the journal. Editorials now enliven the journal, color is more liberally used, and information is rapidly accessed through the journal's website. But in the end what really matters most, and what the journal should be judged by, are the advances in imaging and intervention found in its pages and the new, clinically useful information that the journal imparts to its readers. Over the years it can be said that the AJNR has succeeded remarkably well in this regard.

Radiology has been at the forefront of medical advances for the past quarter century and nowhere have those advances been more obvious than in neuroradiology. Look at volume 1 of the AJNR: the CT images are, by today's expectations, unacceptable. Interventional neuroradiology had not become the force it is now in the treatment of vascular diseases and vascular abnormalities. MR imaging was nonexistent, and to mention just a few of the now discarded techniques that were published in that first volume of the journal, there were articles highlighting the injection of air into the subarachnoid space, a technique that then was combined with CT to outline small cerebellopontine angle masses. At that time, linear and complex motion bony tomography was used to evaluate the temporal bone and skull base, and arteriography of the neck vessels was obtained by a video subtraction technique following intravenous injection of iodinated contrast material. In fact, the first appearance of MR imaging (then called NMR) in the AJNR was in 1982 in an article by Graeme Bydder et al, which was broadly entitled *Clinical NMR Imaging of the Brain*. Those with access to early issues of the AJNR will find it edifying to thumb through articles from the first few volumes of the AJNR to appreciate how far our field has advanced in a relatively short period of time.

MR imaging changed the radiologist's approach to many neurologic diseases, which previously had been invisible to imaging analysis. But even up to the time that the journal became self-published in 1992, many of the imaging procedures we now take for granted as virtually routine (fluid attenuated inversion recovery, diffusion-weighted imaging, short inversion time inversion recovery, single voxel MR spectroscopy) were either not available or were not routinely implemented. Even more recently, from the time the AJNR went online in 2000, there has been an increased use of parameters related to diffusion-weighted imaging such as fractional anisotropy and mean diffusivity,

perfusion imaging with either MR or CT, multi voxel MR spectroscopy, and new coil and stent technology for interventional procedures. Such advances continue at a geometrically progressive rate.

In 2030, when the golden anniversary issue of the AJNR is published, readers of the AJNR may look back at the January 2005 issue, and wonder how we ever practiced effective neuroradiology with the "limited" imaging tools at our disposal. But for now, neuroradiologists can be satisfied with the advances in neuroimaging and neurointervention and we all can point to the fact that the AJNR has been a repository for a major portion of that information.

ROBERT M. QUENCER
Editor-in-Chief

Functional Neuroradiology: A Call to Action

The American Society of Functional Neuroradiology (ASFNR) became a reality at the 42nd annual meeting of the ASNR at Seattle, in June 2004. The mission of the ASFNR is primarily to facilitate the translation of functional neuroradiology into clinical neuroradiologic practice. The precise definition of the subspecialty, however, remains in the eye of the beholder. Although some will consider functional neuroradiology to be the clinical application of blood oxygenation level dependent functional MR imaging (fMRI), we have seldom witnessed single new imaging techniques that have replaced or revolutionized existing imaging or clinical strategies. Typically, new techniques enhance clinical neuroimaging capabilities incrementally as they are integrated into existing practice. From that perspective, basing a subspecialty on a single technique would appear short sighted. One may take a broader view, suggesting that a functional neuroradiologist is one who studies and implements functional MR imaging techniques of any type, including fMRI, magnetoencephalography (MEG), diffusion-tensor imaging (DTI), and perhaps even perfusion, blood volume, and molecular MR imaging and MR spectroscopy. Others, however, may take a more expansive position and suggest that it is the study of both MR and non-MR physiologic brain imaging, including CT positron emission tomography and other non-MR imaging techniques of the future.

At the same time, it is neither the mission of the society nor is it practical to absorb all that exists in the clinical neurosciences or even in neuroimaging research. This can lead us down the same impractical pathways that have hindered the implementation of basic neuroimaging developments into clinical practice in the past. The clinical translation of even 10% of the published functional neuroimaging research would be an optimistic goal. A targeted translation of new techniques is the most judicious approach to define functional neuroradiology. This will require the devising of practical and cost-effective applications that impact treatment algorithms. Our proficiency in this arena has been based on three primary skills: 1) understanding of the technical and physical principals underlying our specialty, 2) a broad understanding of pathophysiologic mechanisms, and 3) an ability to integrate imaging data from multiple techniques and modalities and to communicate vital information to our clinical colleagues. All the while, we should remain capable of rapidly upgrading our integrative strategies as new developments arise.

It seems most reasonable then to define functional neuroradiology by its role in clinical imaging scenarios and the role of a functional neuroradiologist by the clinical impact he or she can bring to bear on a clinical problem. Such an approach is more intuitive and is preferable to technique or technique-specific definitions. Concomitantly, isolating image-based functional information from disease-induced alterations of brain physiology or neurotransmission fails to capitalize on our clinical understanding of disease processes. It is the integration of multiple functional techniques that will empower functional neuroradiology in the clinic. A functional neuroradiologist should be one who is accomplished in both anatomic and physiologic brain imaging, irrespective of technique or sequence design. Functional neuroradiology should incorporate a thorough understanding of the functional and physiologic basis of brain abnormalities with our existing diagnostic arsenals and will require an understanding of functional brain anatomy, the effects of lesions on cortical and white matter function, and the physiologic and biologic determinants of brain diseases. Only through this perspective can new imaging technologies be optimized and incorporated into the clinical setting. Having said this, it is fMRI that has led us into a new era of clinical neuroimaging that emphasizes the value of image-based physiologic information in addition to our standard anatomic and morphologic approach.

So, the question remains: how will the ASFNR achieve its goals? First, the society will seek to develop and support standards for the practice of functional neuroradiology. Physiologic imaging techniques often require the acquisition of low signal-to-noise data as well as mapping strategies to reveal anatomic relationships. Consequently, the acquisition parameters and postprocessing strategies are more complex, cumbersome, and vulnerable to critical errors. Standardization is the first step in gathering the information needed to optimize both acquisition and postprocessing strategies of a variety of new techniques. In addition, one of the key constraining factors in acquiring functional information by using fMRI is paradigm design. Fostering the standardization of practical and effective functional paradigms is essential to optimize the yield of useful functional

information. We must also draw on our understanding of basic physical and physiologic principals to define the limitations of functional and physiologic imaging techniques. Issues such as lesion-induced neurovascular uncoupling in fMRI and the inability to fully trace functionally distinct intersecting tracts by using DTI must be thoroughly addressed and appreciated by those in the field. Perfect functional or physiologic parameters are probably unattainable; nevertheless, quantifying the limitations of a technique in a given clinical imaging scenario is vital to the integrative approach of functional neuroradiology.

A second significant role of the ASFNR will be to develop and support standards for the training of functional neuroradiologists. This will include standardized training in the physical and physiologic principals underlying new imaging techniques and may be achieved through courses at meetings, written material, and web-based training. Whereas existing clinical training in neuroradiology emphasizes neuropathology, we need to increase emphasis on functional neuroanatomy and the clinical neurosciences. An understanding functional neuroanatomy is not a great leap for most neuroradiologists, who are already proficient in the multiplanar analysis of gross anatomy, yet it is the basis for translating functional imaging into clinical practice. As one begins to delve into the nuances of functional anatomy, it quickly becomes apparent that functional anatomy cannot be viewed in isolation from neurotransmission or neurophysiology. An understanding of how the brain works in total enables neuroradiologists to expand their capabilities beyond physiologic imaging. Such an understanding can be drawn upon in daily practice, is within easy reach of neuroradiologists and should be emphasized by ASFNR educational endeavors. A basic knowledge of functional neuroradiology, neurotransmission, and neurophysiology provides the basis for understanding the clinical neurosciences and the treatment strategies devised to counter neurologic diseases. Understanding the effects of treatment strategies will likewise shape the role of functional and physiologic imaging in clinical practice. Thus, a positive translational feedback will result from such educational pursuits.

A third important goal of the ASFNR will be to foster research in functional neuroradiology and, in the process, promote a close fellowship and exchange of ideas between neuroradiologists and colleagues in related fields, including basic science researchers. To translate new techniques into clinical practice, two key areas of research should be emphasized: 1) technological validation and 2) clinical validation. Technological validation is something neuroradiologists are quite comfortable with, although the challenge is made more significant by unique acquisition and postprocessing vulnerabilities of functional and physiologic imaging. Clinical validation, on the other hand, is relatively foreign to our field. There currently exists little level I or II evidence supporting the use of most neuroimaging techniques used in today's clinical practice, despite the obvious benefits of such techniques to patients. In this new era, third-party payers and imaging vendors will require a higher level of clinical evidence to embrace new neuroimaging techniques as viable clinical tools. To this end, the ASFNR should facilitate multicenter, prospective studies by using appropriate reference standards. A fourth major goal of the ASFNR will be to establish channels for publication of scientific reports in the field of functional neuroradiology. The society will also seek to enhance its academic visibility by providing meetings for the reading and discussion of papers and the dissemination of knowledge regarding functional neuroradiology as part of the annual meeting of the ASNR or independent of that meeting. Through these and other efforts, the ASFNR hopes to promote the understanding of functional neuroradiology among patients, other health professionals, and public agencies and to enhance communications with these groups.

JOHN ULMER
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What Is Right about MRI Permeability Studies

The pathophysiology of the blood-brain barrier (BBB) has been described as an important factor in central nervous system disease and continues to be a topic of great interest to many researchers from a wide range of disciplines. The award of three Nobel prizes, those in medicine (MR imaging), chemistry (aquaporins), and physics (superconductivity) highlights the relevance and timeliness of the present topic. Although the understanding of this barrier has significant implications for disease detection, it is also critical for the delivery of treatment to affected brain regions.

In the May issue of the *AJNR*, Law et al attempt to compare regional cerebral blood volume (rCBV) and vascular permeability (Ktrans) measurements obtained from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. According to that study, rCBV demonstrated a strong correlation with tumor grade, whereas Ktrans showed a weaker correlation. Some limitations existed in the study; for example, the method used to measure permeability may require further development and correlation with histopathologic findings. Only selected cases of glioma were used rather than a randomly

assigned group of tumors, thereby producing a better differentiation than expected, but compromising the usefulness and validity of the results. Although these results raise questions about the accuracy of the permeability measurements, this approach is of significant importance in evaluating tumors, since it may provide a noninvasive way to estimate leakage across the BBB and to assess the results of therapy.

Presently, the physiological mechanisms that control the brain environment are collectively known as the BBB. This barrier consists of a network of capillary endothelial cells that protect the brain tissue from toxins while supplying the brain with adequate nutrients. How circulating blood passes from arteries to veins was an absolute mystery until Marcello Malpighi explained it more than 300 years ago. But it was not until much later that Carl Ludwig and his pupil Christian Bohr evaluated the role of the capillaries in the transport of solutes between blood and tissues. In the early 1900s, Erlich and Goldman observed that dyes injected into the circulation did not stain the CSF, and this led to the idea of a *blood-brain barrier*, a name coined by Lewandowsky (bluthirnschranke). This concept was then expanded to include the blood-CSF barrier at the choroid plexus level. Further studies demonstrated that unique cerebral capillary endothelial cells with tight junctions comprised part of the BBB, and that these cells used specific carrier systems to transport substances required for cerebral metabolism.

MR imaging permeability studies attempt to measure the degree of disruption of the BBB by using an analysis of dynamic contrast-enhanced imaging. Tumors have a "leaky" BBB, since their endothelial cells have abnormal function and organization, with intercellular spaces and loose interconnections. But although changes in permeability affect the degree of leakiness across the BBB, other physiological parameters may also affect flow across the endothelium, including the regional hydrostatic and osmotic gradients, blood flow, and luminal surface area. The resulting flux is due to several mechanisms, including simple diffusion related to concentration gradients, diffusion facilitated by endocytosis, diffusion occurring through aqueous channels (aquaporins), and active transport by carrier protein molecules. Within tumors, the driving forces are affected by several factors, including the degree of edema and mass effect that create a "back pressure" and influence transmural pressure gradients. The interstitial fluid pressures may become elevated by leakage from adjacent blood vessels, decreased lymphatic clearance, and abnormal tissue biomechanical properties, all of which can lead to decreased hydrostatic gradients and to a greater relative role for diffusion. The region where extravasation occurs may be of a variable nature, possibly highly vascular, viable, or necrotic. The edema may be vasogenic or cytotoxic. Chemical mediators may also regulate the degree of permeability. Tumor vessels have irregular calibers and abnormal branching patterns, which create regional variations in leakage and make accurate blood flow measurements difficult.

Permeability maps thus reflect a complex interaction of a number of pathophysiological variables related to permeability and blood flow. But if the driving forces across the BBB are not known, how can algorithms based on flow measurements be sufficient to calculate the permeability of the BBB? Permeability maps may actually be more representative of leakage than leakiness, since they use flow parameters to infer the degree of permeability. This distinction may not significantly affect estimation of quantities such as inflow of administered agents, but could lead to decreased accuracy if the maps are used to predict tumor grade, which may be one of their most important clinical roles at present. Theoretically, modifications of permeability imaging techniques could be performed to account for additional factors such as the distribution and degree of regional edema, diffusion rates, etc. Increasing imaging resolution by using higher field strength magnets may also be useful to directly image the microvasculature.

What about the future? Consider this: a physician enters a "very special procedures room," ready to treat a patient with a brain tumor. First, he selects an agent that can open the blood-brain barrier reversibly without damaging it. As he administers this agent, an automated screen displays the actual opening of the BBB in real-time mode. He then injects a medication to treat the tumor and directly observes the changes in vascular leakiness and tumor blood flow. When the procedure is completed, he closes the BBB. The patient recovers without side effects. This may seem perhaps far-fetched; nevertheless, new approaches are presently being developed that could lead to such possibilities. Present measurements of permeability are difficult to perform sequentially or continuously, since the techniques involve a single bolus injection of contrast medium. However, new techniques based on labeled perfusion agents are being evaluated to monitor the status of the BBB continuously, as may be required during one or multiple interventions. New approaches to identify and target tumor vessels for more selective therapeutic interventions, and to open and close the BBB reversibly without causing tissue damage, are also being investigated.

With the continued development of newer and more effective therapeutic approaches, there is now an increasing need to improve the methods that we use to evaluate tumor blood flow and the BBB. Our advances in the imaging of tumor characteristics should also lead to a better understanding of the mechanisms that relate tumor growth with blood vessel and BBB abnormalities.

LUCIEN M. LEVY
Member, Editorial Board

Development of the C1–C2 Puncture in Neuroradiology: A Historical Note

From the time of Ayer in 1920, the accepted method of accessing CSF from the craniocervical junction was the cisternal puncture, in which the spinal needle is directed sagittally in a midline plane from a point just beneath the occiput. For this approach, the patient was placed in the lateral decubitus position or seated upright in a chair with his or her head flexed. An assistant maintained the patient's head in position. The needle was simply advanced until CSF was obtained, at which point the advance of the needle was stopped. The entire process was freehand. However, given the trajectory of the needle directed toward the vulnerable brainstem, the short distance between the dura and medulla, the possibility of head motion, and the absence of good monitoring technique, this method had marked limitations. It is not surprising that a number of complications occurred. Such complications included medullary injury, as evidenced by vomiting or cessation of breathing; venous or arterial perforation; and compromised vertebral blood flow. With these problems, there was obviously a need for a new route to the CSF in the high cervical region. Nonetheless, in the absence of a reliable alternative, cisternal punctures continued, at least until 1973 (1).

At that time, a number of compelling needs prompted the development of a procedure for high cervical puncture. From the 1940s through the early 1960s, pneumoencephalography and myelography were standard diagnostic tests. These required the needle tip to be solely in the subarachnoid space to allow the installation of air or contrast agent in that space rather than a mixed injection in which some of the injection went into the subdural space. While myelography was frequently successful with a limited mixed injection, an air study never was: The patient had to be discharged home and brought back for a repeat study after the subdural collection had disappeared. In a training program, this repetition happened fairly frequently. With new access to the subarachnoid space in the high cervical region, however, the study could go forward without delay.

Besides the need to avoid mixed injections, there were three other reasons for a high puncture. First was the need to access CSF at the skull base for bacterial culture in patients with meningitis and loculation or to obtain a sample of CSF near the brain to analyze for tumor cells. Second was a need to access CSF above a spinal block. Lumbar puncture below the block might well precipitate herniation of a spinal mass, leading to paraparesis because of the lowered CSF pressure in the lumbar region. Third was a need to allow the performance of painless gas myelography. While Pantopaque (Lafayette Pharmacal, IN) was a radioattenuated material widely used in the United States for myelography at the time, its use had many drawbacks, including arachnoiditis. In Scandinavia, the use of Pantopaque was avoided for decades, and gas myelography was preferred as a contrast study. Some used a lumbar spinal approach (2) in which the patient's head was tilted sharply laterally toward the shoulder to keep air out of the head to minimize the adverse effects of headache and nausea. However, this technique did not always work and was not adopted in the United States.

If we were to obtain similar gas myelograms in the United States, how would we do so? We had some ideas. If we had our patients lie on a tomographic table with their head lower than their feet when the air was injected, we could titrate the exchange of gas for CSF, filling the entire lumbar and thoracic subarachnoid space, and still keep air out of the head. The gas could completely replace the CSF, and tomography could then be used to provide elegant sagittal radiographs of the spinal cord. To accomplish this, we punctured the subarachnoid space in the neck, allowing an exchange of gas for the CSF to the level of C1–2 that replaced all of the CSF throughout the lumbar, thoracic, and cervical regions *without* allowing air to reach the cranial subarachnoid space.

We noted that Rosomoff (3), a neurosurgeon, and colleagues showed that they could perform percutaneous cordotomy at C1–2 to relieve pain. If the neurosurgeons could safely perform an invasive procedure such as percutaneous cutting of the long tracts of the spinal cord, then we could perform the much less invasive procedure of accessing the CSF at that level, supplanting a cisternal midline puncture with a lateral cervical approach.

After studying the bony and soft tissue anatomy, including the course of the vertebral artery, we found that the subarachnoid space (although it was small) tended to open up posteriorly. One could puncture the subarachnoid space in the posterior part of the spinal canal from the direct lateral direction. With the needle point in position, the needle shaft would be held in alignment by the muscles in the lateral neck, so that with tubing attached and with the gentle aspiration of fluid, an injection of air could take place. The C1–2 lateral puncture could then be used for the exchange of gas for fluid in gas myelography, creating the so-called painless gas myelographic study. This technique was used in 1969–1970 at Yale University and was reported at the annual meeting of the Radiological Society of North America (RSNA) in November 1970 and in *Radiology* in 1972 (4).

In addition to gas myelography, this new high cervical puncture could be used to salvage a pneumoencephalogram or myelogram, to aspirate CSF

for bacteriology, to detect malignant cells near the brain, or to perform a puncture to obtain CSF above a spinal block. The procedure has been used successfully throughout the neuroradiologic world.

Unknown to the author until years later, Dr David J. Kelly, Jr. and Dr. Eben Alexander, neurosurgeons at Bowman Gray Medical Center, Winston-Salem, NC, reported use of a lateral C1–2 approach to instill positive contrast material (Pantopaque), into the high cervical subarachnoid space in 1968 (5). However, the spread of knowledge about the C1–2 puncture to neuroradiologists was thought to occur primarily by means of the RSNA presentation, by the publication in *Radiology*, and by personal and phone conversations concerning the procedure with scores of neuroradiologists at the time.

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