About Santa Barbara Cottage Hospital and Cottage Health System

The not-for-profit Cottage Health System is the parent organization of Santa Barbara Cottage Hospital (and its associated Cottage Children’s Hospital and Cottage Rehabilitation Hospital), Santa Ynez Valley Cottage Hospital and Goleta Valley Cottage Hospital.

The Santa Barbara Neuroscience Institute at Cottage Health System is a physician-led initiative established to focus on medical conditions over the full cycle of care. The Institute aims to deliver the highest value to the patient by incorporating best practices, applying resources judiciously, and measuring and reporting outcomes relentlessly.

On the Cover: The illustration by Josh Emerson shows a right-sided cavernous carotid fusiform aneurysm before interventional neuroradiologic treatment. The accompanying article and case study begin on page 10.

Table of Contents

4  Saving the Brain: Fifth Annual Symposium Presented
   Current Findings in Neuroscience
6  Supporting Post Stroke Motor Recovery
8  Specialized Neuro-oncology Care
10 Treatment of Complex Cerebral Aneurysms:
    The Use of Flow-diverting Devices
Dear Colleagues,

Over the past year, among the most common phrases spoken by hospital administrators and their medical staffs, at least in California, has been “physician alignment.” Such a short phrase with such a complex and ambiguous meaning. It seems to me, more likely than not, that the legal entanglements of such hospital-physician collaboration will take years to work out. On a simplistic level, however, I think that most physicians would like to work with their community’s hospitals now to improve the quality of the medical care and, at the same time, help drive down the cost of care.

In Harvard Business Review’s “Fixing Healthcare from Inside and Out,” Jon Meliones, MD, as chief medical director of Duke Children’s Hospital (DCH), writes about how they turned their net margin of $11 million in the red to $4 million dollars in the black and cost per case from $14,889 to $10,500 in just three years. “They” refers to groups known as “clinical business units” consisting of individual service line invested clinicians working with equivalently subspecialized nurses, therapists, social workers and administrators.

They created this impressive clinical turnaround by borrowing from industry. The “balanced scorecard approach” was developed by Kaplan and Norton for Fortune 500 companies and divides attention among four equally important quadrants: 1) financial health; 2) consumer satisfaction; 3) internal business procedures; and 4) employee satisfaction. Meliones and his co-workers first looked at “best practices” and used those to develop clinical pathways and from there put in place teams called “clinical business units.” Within these units the head administrator and physician share responsibility which includes review of financial information as well as patient and staff satisfaction. To obtain traction, Meliones writes, “developing and implementing a balanced scorecard is labor-intensive because it is a consensus-driven methodology. To make ours work required nothing short of a pilot project, a top-down reorganization, development of a customized information system and systematic work redesign.”

One referenced example of a programmatic change began with the simple observation that babies recovering from heart surgery had feeding problems and that parents had to learn how to feed them. After the decision was made to move up the day parents were taught how to feed their infants from the last hospital day to the day following surgery, children were discharged earlier and attendant hospital costs were reduced 28 percent.

Dr. Meliones states that “overall, the results we’ve achieved at DCH…. were stunning.” By using multiple clinical pathways and improving communication with patient’s families and staff, he noted, customer satisfaction jumped 18 percent, length of stay dropped from 7.9 to 6.1 days over four years, readmission rates fell from 7 percent to 3 percent, and employees noted a 45 percent improvement in job satisfaction.

Whether we, as a medical staff and hospital, choose the “balanced scorecard approach” or some other iteration is probably not as important as recognizing the urgency of working in organized practice units with the goal of improving the care we are delivering and lowering the cost of such care.

Sincerely,

Thomas H. Jones, MD
Neurosurgeon and Medical Director
Santa Barbara Neuroscience Institute
The fifth annual Neuroscience Symposium presented by the Santa Barbara Neuroscience Institute at Cottage Health System took place this past October and presented an overview and update on the latest advances across a broad spectrum of neurologic topics.

**Featured Presentations**

The Fifth Annual 2012 Saving the Brain Neuroscience Symposium of the Central Coast hosted the following lectures:

- **Stem Cell Therapy for Stroke** by Gary Steinberg, MD, PhD
- **Modulating Memory: Deep Brain Stimulation for Alzheimer’s Disease** by Francisco Ponce, MD
- **Traumatic Brain Injury** by Rocco Armonda, MD
- **Neurocritical Care, Our Future** by Michael De Georgia, MD
- **Inside the Black Box: Brain Oxygen Monitoring and Neurologic Disorders** by Mary Kay Bader, MSN, RN
- **Intraoperative MRI—The Future Is Here** by Michael Chicoine, MD
- **Nanotechnologies in the Future of Biomedical Research and Medical Care** by Jamey Marth, PhD
- **Intracerebral Hemorrhage: Management, Trials and Future** by Alejandro Rabinstein, MD
- **Update on Stroke Prevention** by Neil Schwartz, MD, PhD
- **Transient Ischemic Attacks** by Philip Delio, MD
- **Development of a Regional Neurovascular Center** by Alois Zauner, MD
- **Neurointerventionalist’s Toolbox** by Matthew Tenser, MD
Traditionally, the speakers at the Symposium have been some of the top researchers, clinicians and scientists in their respective fields, and this year was no exception. Whether it is the Santa Barbara weather, the promise of a high-level educational program or the opportunity to speak to an engaged group of regional physicians, nurses and neuroscientists, it is rare for any of the invited speakers to decline the invitation. The result is a program of lectures from the best and brightest in the field of neuroscience, with invited speakers from the nation’s most comprehensive academic neuroscience centers and academic institutions.

While it is often difficult to choose a “theme” that unites the broad scope of lectures each year, the Fifth Symposium included updates on some of the more relevant topics in neurology and neurosurgery: acute interventional stroke treatment, stem cell therapy for stroke, neurocritical care issues in traumatic brain injury and implantable neurostimulators for the treatment of a dementia amongst others.

Speaking to a broad audience of almost 200 people that includes physicians, nurses and neuroscientists poses a challenge to the invited lecturers. Too much detail or focus on neurologic minutia may lose the interest of all but the most dedicated academicians, while too broad a topic will not engage the practicing neurologists and neurosurgeons who are looking for more that a simple review of neurologic topics. This year’s speakers did an outstanding job of presenting material that was engaging to all, and as a testament to the quality of the presentations, most of the speakers themselves attended the rest of the Symposium in its entirety.

The caliber and expertise of this year’s speakers resulted in a number of memorable presentations, not the least of which was that of Dr. Gary Steinberg, Chairman of Neurosurgery at Stanford University, and arguably one of the world’s foremost experts and pioneers in the use of fetal stem cells for recovery after acute ischemic stroke. His preliminary data showed the migration of primitive stem cells towards damaged stroke tissue in an effort to regenerate and repair damaged neurons. While still restricted to research protocols, the promise of such therapy in real world clinical practice holds tremendous promise for the treatment of what is currently the leading cause of disability in the United States.

With the close of this year’s Symposium, there was already talk of topics for next year, how to improve the program and how to attract as many participants as possible. Given the success of the Symposium to date, there is much anticipation for October of 2013. Special thanks go to Alois Zauner, MD, for organizing the Symposium from its origins five years ago, to Thomas Jones, MD, for wisely recognizing the role of the Santa Barbara Neuroscience Institute as a conduit for the event and, of course, to Cottage Health System for its continued support of such an important educational program for the Central Coast and our medical region.

For more information about Santa Barbara Neuroscience Institute at Cottage Health System, our conferences or to watch video excerpts from previous conferences, please visit our website at www.sbni.org.
The new training paradigms were sparked by animal studies in the 1990s, which demonstrated activity-induced cortical reorganization and provided promise for restorative strategies, as opposed to compensatory strategies, to address hemiparesis. Active interventions have included constraint-induced movement therapy (CIMT), massed practice and locomotor training (body-weight supported ambulation). Additionally, adjunctive therapies have developed to prime the brain with application of sensory stimulation or an electromagnetic field to the central nervous system (CNS) and peripheral nervous system (PNS). Clinical research to evaluate therapeutic effectiveness has been difficult to perform due to heterogeneous clinical profiles and lack of uniform interventions and outcome measures. In the last decade, however, multiple sites have coordinated efforts to produce a small number of sufficiently powered and randomized-controlled trials to study functional outcomes. Lastly, advanced neuroimaging studies on humans have offered insights into the experience-induced restructuring of residual neural tissue that confers motor learning. The sum of this research points towards the importance of repetitive, task-specific practice to remediate motor deficits following CNS damage.

Clinical trials to date overwhelmingly point to the importance of practice intensity to promote motor learning. The largest (multicenter) RCT of post-stroke ambulation, the Locomotor Experience Applied Post Stroke (LEAPS) trial, examined walking speed recovery after stroke. The gait speed of study participants receiving “usual” care at 6 months improved only half as much as those involved in an intensive structured activity of either locomotor training with body weight-supported treadmill training (BWSTT) or a home exercise program (.13 vs .025 m/s). Given that the study’s mobility entry criteria were modest, specifically the capacity to ambulate only 10 feet with no more than 1 person assisting, the generalizability of these findings are broad.

Most studies measure intensity of practice by duration of therapy, but level of exertion is another way to promote intensity. Dobkin, et al., showed that simply a daily verbal encouragement and knowledge of performance on a short walk trial can achieve that end. In this international, multicenter study, stroke patients in rehabilitation units were asked to increase their walking speed on beyond their comfortable walking speed but still within a speed that could be safely performed. At discharge, gait speed had doubled to 0.46m/s (exceeding the minimal clinically important change in gait speed of >0.16 m/s) and had exceeded that of the control group’s by 0.19 m/s. The functional implication, based on the well-accepted threshold of 0.4 m/s as predictive of a functional ambulation class (FAC) beyond household-level distances, is that the experimental group achieved the ability to ambulate short distances in the community whereas the control group did not.

Intensity of practice alone, however, appears insufficient for optimal motor learning; skill acquisition also requires task-specific practice. Body-weight supported treadmill training (BWSTT) and robotic-assisted step training (RAST), for example, are task-oriented therapies which were presumed to confer an advantage over over-ground training (OGT) by offering the opportunity for massed practice (for persons who could not otherwise support their own weight to walk). However, despite similar intensity of practice, lower limb advancement on a treadmill, facilitated by a robot or a therapist, has not yet proved superior to OGT. One reason that the anticipated benefits of intensive practice have not borne fruit is that errorless performance of an activity does not place the same demands on networks devoted to attention and/or motor planning. One might deduce, therefore, that performance errors—which demand changes in sequencing, timing and scaling of movements—are necessary to promote the encoding of information which confers motor learning.

Further evidence for the necessity of task-based practice comes from functional neuroimaging. In functional MRI (fMRI) studies of controlled limb movements, healthy controls show lateralized motor cortex activity, which results from the inter-hemispheric inhibition. However, following stroke, the damaged motor cortex can no longer
inhibit the contralateral motor cortex, and the patients show bilateral activation. Boyd, et al. (see Figure) demonstrated that on a post-training fMRI of a learned motor task, the general-use training showed no effect on the degree of bilateral activity, but that task-specific training (SP) was able to restore laterality to near that of the healthy brain. Moreover, the SP demonstrated greater improvement in reaction times as compared to GP therapy (p=.004).

While intense, task-specific practice is important to achieve motor recovery, capacity for improvement appears to be influenced by the initial severity of disability. In the LEAPS trial, for example, only half of study participants transitioned to a higher FAC (from household to limited community or from limited community to slow, unlimited community levels of ambulation) and these subjects were more likely to have started with a higher level of initial gait speed. Nevertheless, even if the effect size of therapeutic interventions for highly disabled individuals is modest, such a transition, especially the progression beyond household-level ambulation, is correlated with improved quality of life (QOL) measures (Schmid).

In summary, animal and clinical research has unmasked the essential ingredient of motor learning: intensive task-specific practice. Unfortunately, the allotted dose of therapy in acute and subacute rehabilitation settings does not appear to meet the anticipated sufficient dose required for optimal motor learning. Furthermore, observational data suggest that actual practice intensity is low and is frequently not task-specific (Lang). Feasibility studies on interventions such as accelerating the progression of tasks and reducing the number of rest breaks, as well as provision of recreational therapists to provide practice during non-scheduled therapy hours, deserve consideration. Additionally, since to date expensive robotic approaches have not conferred an advantage over comparable and less costly home-based therapies, wide implementation of practical, low-cost technologies should be a priority. For example, knowledge of performance provided by personalized–accelerometry devices or gaming software show promise as a pragmatic and effective means of achieving increased intensity and engagement in practice to achieve motor learning. Finding ways to continue to incentivize and harness the power of intense task-based specific practice is critical to improve functional outcomes and QOL through the continuum of recovery.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laterality Index Pre and Post Practice for the SP Group</strong></td>
<td><strong>Laterality Index Pre and Post Practice for the GP Group</strong></td>
</tr>
<tr>
<td><img src="image" alt="Graph A" /></td>
<td><img src="image" alt="Graph B" /></td>
</tr>
</tbody>
</table>

The Li is derived from fMRI data on the specified motor cortex. Sequence-specific motor skill learning significantly increases Li (p=0.034), which suggests restoration of ipsilesional hemispheric dominance.

### References


Jonathan Berkowitz, MD, PhD

We are fortunate to be a member of a research network with the UCLA Jonsson Comprehensive Cancer Center, through which we have opened a clinical trial that addresses this goal for women with breast cancer metastatic to the brain.

This year, the American Cancer Society estimates that more than 226,000 women will be diagnosed with invasive breast cancer and that more than 39,000 will die of this disease. In 25 percent of breast cancer cases, the human epidermal growth factor receptor 2 (HER-2) is overexpressed. Historically, this has been associated with a relatively poor prognosis. Over the last decade, the addition of trastuzumab, (Herceptin®, Roche), an antibody against HER-2, to chemotherapy has significantly improved survival of these patients, especially in those with localized disease.

While women with HER-2 positive metastatic breast cancer derive benefit from trastuzumab, this drug does not appear to have efficacy in the brain. This has become more important as breast cancer is the second most common cause of brain metastases. In one study, one third of women treated with trastuzumab for metastatic cancer developed brain metastases. In 50 percent of patients, the cause of death was progressive CNS disease. Another FDA-approved agent for treating HER2-positive metastatic breast cancer, lapatinib (Tykerb®, GlaxoSmithKline), showed a low response rate in patients with brain metastases after trastuzumab and radiation. Pertuzumab (Perjeta®, Roche) is the newest approved agent in this setting, but the study that led to its approval excluded patients with brain metastases.

Therefore, breast cancer with brain metastases represents a highly unmet medical need, for which novel targeted therapies are needed. This led to a study using afatinib, a small molecule, irreversible inhibitor of HER-2 as well as two other related proteins (HER-1 and HER-4); these may be important proteins to block to prevent resistance to HER-2 inhibition. In patients with HER2-positive metastatic breast cancer, who progressed after trastuzumab therapy, nearly half of the patients appeared to benefit from taking afatinib. In addition, in one lung cancer study with afatinib, a patient with brain metastases had a sustained response, and in another lung cancer study, those with or without brain metastases achieved comparable outcomes on afatinib.

The purpose of this study is to investigate whether afatinib alone or in combination with vinorelbine has any effect on HER2-positive breast cancer with brain metastases after failure of prior trastuzumab or lapatinib. In this study, patients will be randomized to receive afatinib, afatinib + vinorelbine chemotherapy; or investigator’s choice of medical treatment approved for metastatic breast cancer. This study is currently accepting new patients in our Santa Barbara and Solvang offices. We are also planning to have studies in the near future for patients with primary brain tumors, such as glioblastoma.

Please contact us with any questions at (805) 563-5800.
Case Report: Breast Cancer Metastatic to the Brain

The patient is a 42-year-old woman who was diagnosed with right-sided breast cancer in 2008. She had noted then that for the prior two months of breastfeeding, her daughter was not getting any milk from the right breast, where she had previously had mastitis. She was seen by her obstetrician, and a mass was felt in the right breast.

A mammogram showed an area of increased density encompassing a huge region of the upper outer quadrant of the right breast correlating to the hard mass. An ultrasound-guided biopsy of a 2.6cm mass in the right breast revealed invasive carcinoma with mixed ductal and lobular features. It was estrogen-receptor and progesterone-receptor positive, and HER2 was overexpressed.

An MRI of the breasts showed a 7.3cm x 4.3cm mass in the right breast primarily upper outer quadrant with extension to the nipple, sub-areolar region, anteriorly to the lower inner quadrant, with no contralateral disease, asymmetric lymph nodes more prominent on the right than the left. A PET scan demonstrated multifocal tumor in the right breast and multiple areas of abnormal nodal activity in the right axilla suggestive of metastatic disease, but negative for any other sites of disease.

The patient then underwent alternative medicine treatments and returned one year later, at which time she was found to have metastases to multiple skeletal regions and the lungs. She was then treated with docetaxel, carboplatin and trastuzumab for five of six planned cycles with an excellent response. She discontinued chemotherapy early because of toxicity.

She was maintained on trastuzumab and tamoxifen, which was well-tolerated. The patient was on these therapies for nearly two years until she complained of significant headaches with associated blurry vision and nausea. An MRI of the brain showed multiple lesions in the brainstem and both cerebral and cerebellar hemispheres, with significant edema.

The patient then received whole brain radiotherapy, and continued trastuzumab, with the addition of nanoparticle albumin-bound (nab) paclitaxel. After fifteen months of therapy, a brain MRI showed a right cerebellar nodule had grown from 4mm to 9mm. This was then treated with stereotactic radiosurgery, and lapatinib was added to her treatment regimen in January of this year.

Soon after, the nab-paclitaxel was discontinued and by June her brain metastases had progressed again. Lupron and tamoxifen were added at that time, but in November of this year her brain metastases had once again progressed. Fortunately, she is eligible for a clinical trial designed for patients with HER2 positive metastatic to the brain using a new agent called afatinib. She enrolled on the trial and was randomized to receive afatinib, and she has just recently started this medicine.
Treatment of Complex Cerebral Aneurysms: The Use of Flow-diverting Devices

by Alois Zauner, MD, Medical Director, Stroke and Neurovascular Center of Central California

The emergence of intracranial flow-diverting stents has sparked interest in a potential alternative for treating complex cerebral aneurysms.

Despite the tremendous evolution in endovascular therapy, some important limitations remain, particularly in the treatment of wide-necked, large and giant, or “nonsaccular” fusiform aneurysms.

To date, endovascular therapy has been almost exclusively focused on filling the aneurysm sac with embolic material, i.e., “endosaccular” treatment. This strategy is very effective for the treatment of smaller, narrow-necked aneurysms. However, these larger, more complex lesions can frequently be difficult to treat with coils, even when they are used with the commercially available self-expanding intracranial stents. Endovascular treatments of such lesions frequently fail to produce complete aneurysm occlusion. Even when complete or near-complete occlusion has been achieved after the initial embolization, these aneurysms remain prone to coil compaction and recanalization, and they frequently recur, requiring retreatment.

The Pipeline Embolization Device™ (PED) represents the first U.S. Food and Drug Administration-approved endovascular construct specifically engineered to function as a stand-alone device for the endovascular reconstruction of a segmentally diseased parent vessel. The PED is a self-expanding, micro-catheter-delivered, cylindrical mesh device composed of 48 individual cobalt chromium (75 percent) and platinum tungsten (25 percent) strands. The device has approximately 30 percent to 35 percent metal surface area coverage when fully deployed.

During the procedure, the PED is delivered through a microcatheter and deployed across the aneurysm neck. This device redirects the blood flow to its natural course and slows the
flow of blood into the aneurysm, which allows for the diseased vessel to heal and the aneurysm to eventually thrombose.

The PED was FDA-approved and launched in April 2011 and is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments.

Santa Barbara Cottage Hospital began using the device in November of 2011 and to date has performed more than 20 of these procedures.

Case Presentation

After a high-speed motor vehicle rollover accident, a 21-year-old female developed an arterial dissection and subsequent fusiform aneurysm and pseudo-aneurysm involving the cavernous segment of the left internal carotid artery (ICA).

The diagnostic cerebral angiogram demonstrated a 15 x 12 x 11mm lobulated and fusiform aneurysm arising from the dissected segment of the cavernous segment of the left ICA. A decision was made to place a flow-diverting stent after loading doses of clopidogrel (300mg) and aspirin (325mg) followed by maintenance doses of 75mg and 81mg. A 3.75 x 20mm flow-diverting stent was then placed across the distal left ICA proximal to the ophthalmic artery. A second flow-diverting stent measuring 4 x 18mm was telescoped into the first flow-diverting stent, reconstructing the cavernous segment of the distal left ICA. Post stent deployment angiogram demonstrated stagnant flow within the aneurysm.

Approximately 12 months after intervention, the patient returned for a follow-up diagnostic angiogram. Cerebral injection of the left ICA demonstrated normal contour of the reconstructed cavernous segment of the ICA and normal antegrade flow into the ipsilateral anterior and middle cerebral arteries.

Summary

The advent of flow-diverting stents, such as the PED, has generated much consideration and excitement in the neurointerventional community. These devices offer a treatment option for complex cases in which coil embolization is challenging or not feasible. The PED allows for reconstruction of the cerebrovasculature and has documented use in unfavorable aneurysm features, including wide neck, large size, fusiform morphology and post-treatment recanalization.

The PED allowed reconstruction of the cavernous segment of the ICA, and the telescoping of two devices supplemented coverage across the vascular defect, eliminating intra-aneurysmal flow. Follow-up angiogram performed 12 months later demonstrated normal flow dynamics and a completely thrombosed aneurysm.
What is the Cal-Neuro Network? The Cal-Neuro Network is a multi-hospital collaborative established by Santa Barbara Cottage Hospital (SBCH) for the care and advanced treatment of neurologic emergencies. As a Certified Stroke Center, SBCH has formed this network to offer its resources to patients and physicians in the surrounding communities and beyond.

Why have a network at all? While the significant investments in neuroscience technology and human resources are not feasible for all hospitals, every patient should have access to the highest levels of care possible.

When do I access the network? It is important to note that the network does not take the place of neuroscience resources in your local hospitals. The network is to be contacted only after consultation with your local on-call neurologist and/or local neurosurgeon.

How do I learn more? Please contact Gary Milgram, Service Line Director at gmilgram@sbch.org or call (805) 682-7111 x82008.

24-HOUR CONSULTATION
Ischemic Stroke, ICH, SAH, AVM, brain aneurysm and other neurovascular emergencies

Transfer Center: 1-888-MY-CAL-NEURO (1-888-692-2563)