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COVER ART: Original Drawing by Scott Rawlins
Scott Rawlins graduated from Earlham College with a degree in biology, and holds graduate degrees in museum education and medical & biological illustration from the George Washington University and the University of Michigan respectively. For many years Scott was a museum curator, working in this capacity at the Children’s Museum of Indianapolis, the Calvert Marine Museum and the Public Museum of Grand Rapids, MI. Since 1994 Scott has been a member of the art faculty at Arcadia University where he holds the position of Professor and teaches scientific illustration and design. He regularly exhibits his artwork nationally and has served on the boards of the American Society of Botanical Artists and the Guild of Natural Science Illustrators. He will assume the role of president of the Guild in July. His illustrations have appeared in the Society of Vertebrate Zoology, the Bulletin of the Museum of Comparative Zoology, Invertebrate Biology and Acta Zoologica, among others. Scott is presently acting as a research assistant in the paleontology department at the Academy of Natural Sciences in Philadelphia.
**Abstract:** The Capstone Project is the culminating endeavor of the undergraduate academic experience. It often involves the development of a discipline-specific thesis that reflects the student’s interests and cumulative knowledge, cultivated during the undergraduate years. In biological disciplines, the Capstone Project often requires the gathering of information from a significant number of resources, and the integration of that information to address a question of biological significance. Depending on the program and available resources, the Capstone Project in the biological sciences typically involves independent research of a specific biological question that may be addressed scholarly (through a critical review of the scientific literature) or practically (through work in the laboratory or field). In the current paper we describe the structure and implementation of the Senior Seminar in Biology course, a capstone experience for Biology majors at Arcadia University. In this course a student works one-on-one with a faculty mentor to produce a written thesis paper as well as a poster presentation, which he/she presents to a committee of faculty members and then to the general public. This course is designed not only to allow students to synthesize information and skills that they have learned throughout their tenure as biology majors, but also to aid them in developing written and oral communication skills.

**Introduction:** The undergraduate Capstone Project represents a scholar’s best work in critical thinking and demonstration of knowledge, coupled with the writing and presentation skills that have been acquired during his/her course of study. At Arcadia University, the Capstone Project for Biology majors is completed in the Senior Seminar in Biology course, which engages students to pursue, in depth, a line of inquiry that often reflects an intellectual curiosity about a biological process explored briefly in the classroom or through life experience. The line of inquiry may also be rooted in faculty-guided research in the laboratory or in the field, or may reflect a student’s career interest. Students are expected to formulate a distinct thesis question or hypothesis that can be addressed through a thorough understanding of the current literature or through direct testing using the scientific method or observational study. Those students who choose to work with a faculty member in the laboratory or field generally use their work as the basis for a laboratory- or field-based thesis, while those who are not involved with faculty-guided research will pursue a library-based thesis. Although students develop Capstone Projects as an independent endeavor, each student chooses or is assigned a faculty mentor, who provides expertise specific or related to the student’s chosen thesis topic. The thesis mentor plays an active role in the student’s progress throughout Senior Seminar. A mentor will typically 1) meet weekly with a thesis student to track the student’s progress, 2) provide detailed comments and feedback on drafts of the written thesis, 3) provide direction for poster design, and 4) assist in the preparation of the student’s thesis defense.

Preparation for the Capstone Project begins early in the student’s academic career at Arcadia. In the second year of study, a student majoring in Biology is required to take Biological Research Methods (BI242), a course that offers instruction on how to critically review the scientific literature and engage in scientific writing. This course also exposes the student to methodologies and statistical analyses employed in three sub-disciplines of Biology: Cell and Molecular Biology, Ecology and Animal Behavior. The scientific method, introduced in the first academic year, is reinforced in Biological Research Methods through direct experimentation in these sub-disciplines, as well as through critical review of results, and communication of those results through the writing of a primary research article. Biological Research Methods thus provides a foundation for the student to independently develop a strong thesis question or hypothesis and the skills necessary to critically evaluate current literature that addresses the thesis question.

During the third academic year, a Biology major is required to take Junior Seminar in Biology (BI290), which plays a dual role: it aids the student in career preparation, and provides guidance that allows the student to select a thesis topic and begin to develop a thesis question or hypothesis. During Junior Seminar, the student collects a minimum of twenty research articles pertinent to his/her topic, and tentatively chooses a thesis mentor from the Biology faculty. The student also develops a tentative thesis question or hypothesis,
and begins to write an initial draft of the thesis. A student pursuing a library-based thesis develops a synopsis of current literature that addresses his/her thesis question, whereas a student engaging in laboratory or fieldwork writes a first draft of the Methods and Results sections. These exercises initiate the process of thesis writing, and aid the student in identifying weaknesses, if any, in the development of his/her thesis. For example, a student may not be able to identify current literature relevant to his/her topic or may realize that his/her topic is too broad and that further refinement of the thesis question is necessary. BI242 and BI290, therefore, provide the student with the foundational knowledge, technical abilities, and critical thinking skills necessary to engage in an in-depth investigation of a relevant biological thesis question. Moreover, the writing skills acquired in BI242 and BI290 help to prepare the student to effectively communicate his/her findings in the form of a scholarly research paper.

**Overview of Senior Seminar in Biology**

The Capstone Project is completed in Senior Seminar in Biology (BI490), a four-credit course (typically taken in the Spring semester of the Senior year) in which the student uses the knowledge and skills acquired as a Biology major to explore, in great depth, a biological question of interest. This exploration results in the development of a biologically-based thesis, which includes an Abstract, Introduction, Current Investigations (library-based thesis) or Methods/Results (laboratory- or field-based thesis), Discussion and Bibliography (Figure 1). The student is also required to provide a non-technical summary of his/her thesis (in the Overview section). In developing the thesis, the student gains considerable skill in (1) summarizing introductory information from a vast number and type of sources in order to provide the necessary background to understand the results of the presented studies, (2) distilling and summarizing complex data, (3) discussing the relevance of his/her described studies to the advancement of knowledge in the field, and (4) presenting his/her work in both technical and non-technical formats. The student writes multiple drafts that undergo both mentor- and peer-review, which assists the student in processing the information into a clear and precise presentation of the material. The Capstone Project in Biology culminates with a translation of the thesis into a poster format that the student uses to defend his/her work to a committee comprised of two or more faculty members in Biology. The student also presents his/her work in a public forum that is modeled after a poster session at a scientific meeting. Communication of the thesis is of central importance to the Capstone Project. The thesis is not intended to be a tome that is read by one instructor and then simply placed on a shelf. Instead, the thesis takes on new life in its translated poster format and is used as a tool to aid the student in communicating his/her findings to a wide variety of audiences, including peers, faculty members from a range of disciplines, and the general public. Students are trained to fine-tune their presentations to these specific audiences, and thereby gain invaluable experience in communicating their ideas effectively, a skill that will serve the student well beyond graduation as he/she embarks on any of a vast array of scientific careers.

**A Brief History of Senior Seminar in Biology**

In the 1990’s, colleges became increasingly aware of the necessity to prepare students for life after graduation. Accordingly, the Biology Department initiated the Senior Seminar concept. The goal of the Seminar was twofold: 1) to encourage the senior student to prepare for post-graduate life and explore career and graduate school options; and 2) select and research a senior thesis topic and prepare for a poster presentation which would occur at the end of the spring semester senior year.

Initially, the program was offered in the senior year, with a two-credit course in the Fall semester followed by a four-credit course in the Spring. The Fall course was devoted to career preparation (graduate school applications, preparation of resumes, writing letters of job application) and selection of thesis topic. In the spring, further work was done on careers, with the major focus of thesis and poster presentation. Initially, Biology was one of only a few departments to require a thesis poster presentation. The presentation occurred within the walls of the Biology department, and involved poster displays to the public and a reception (including refreshments) for friends and parents. After the public opening, the student was required to defend his/her work in front of two Biology faculty members for evaluation. Later, poster presentations became a University-wide event, a tradition that continues today.

As the senior thesis program evolved, it became apparent that the career preparation material should be presented earlier in the student’s career, and accordingly, the fall semester course was moved to the spring of the junior year and became known as Junior Seminar. This course focused on career materials as well as selection of thesis topics. The student worked on post-graduate materials and in addition, was given experience in reading and interpreting scientific papers. The

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latter experience was established to prepare for thesis work. Junior seminar was then followed in the spring semester of the senior year with the senior seminar that focused on thesis and poster presentation.

**Design and Implementation of Senior Seminar in Biology**

Today, the Senior Seminar in Biology course is divided into two main phases: 1) the writing and revision of the thesis paper, and 2) the preparation and presentation of the thesis poster (Figure 2). Almost all of the work is done outside of the classroom; however, the class meets once weekly in a seminar format, where the course instructors review pertinent topics and provide students with guidance as issues arise. Topics covered during the weekly meetings include reviews of each of the thesis sections, plagiarism, peer review, poster production, and poster presentation. Prior to enrolling in Senior Seminar in Biology, the student is responsible for identifying a suitable topic and a faculty mentor from within the Department of Biology. This process is initiated in the Junior Seminar in Biology (BI290) course, typically taken in the spring semester of the Junior year. Figure 2 provides a graphic representation of the major assignments and their progression. Following is a detailed description of each of these assignments.

**Written Assessment.** At the first meeting of the class (week one), the student submits the Written Assessment, in which he/she reports on the status of his/her thesis topic to date. This assignment asks the student to identify his/her topic and thesis mentor, and to assess his/her progress in several key sections of the thesis. Specifically, the student provides outlines of the Introduction section (including a distinct thesis question or hypothesis) and Methods/Results (for a laboratory- or field-based thesis) or Current Investigations (for a library-based thesis) sections, as well as a list of references. The completed Written Assessment is distributed to the corresponding thesis mentors, who then use it to evaluate key parameters such as the appropriateness of the thesis topic, the completeness of the thesis statement, and the progress in researching the topic that the student has made thus far.

**Current Investigations / Materials and Methods; Results.** The first major thesis assignment is submitted prior to class during the fourth week of the semester. For a library-based thesis, this is the rough draft of the Current Investigations section, whereas for a laboratory- or field-based thesis, this assignment includes drafts of both the Materials and Methods section and the Results section (Figure 1). The requirement for submitting these sections first is modeled after a common approach to writing a scientific manuscript: the author typically writes the Results section first, and then formulates the Introduction to include information necessary to understand and better interpret the Results.

For the library-based thesis, the student is expected to have previously selected at least two articles from the primary scientific literature that either support or refute the thesis question or hypothesis. In most cases, these articles must have been published in the previous 2-3 years, and must be biologically-based (rather than clinical studies or reports). The articles must be from the primary literature, and not review articles. The student reports in detail the findings of these papers, using selected figures and tables (with paraphrased legends) from the papers. Interpretation of the findings is reserved for the Discussion section of the thesis.

For the laboratory- or field-based thesis, the Materials and Methods section describes in detail the methodology with which experiments, data collection, and analyses were carried out. In the Results section, the student provides a detailed description of the outcomes of the studies that were described in Materials and Methods section. This description is typically accompanied by figures and data tables (with legends) generated from the studies. Both of these sections are intended to mimic the corresponding sections of papers from the primary literature. Similar to the Current Investigations section of the library-based thesis, interpretation of the data is reserved for the Discussion section of the thesis.

Once submitted, the draft is reviewed by the student’s thesis mentor, who provides detailed constructive feedback so that the student can edit the section for inclusion in the first full draft of the thesis.

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1. Optimally, the selection of the Current Investigation articles occurs during Junior seminar; however, it is not uncommon for students to revise these selections during weeks 1-3 of the Senior Seminar class.
Introduction. At the beginning of week 5, students submit a rough draft of the Introduction section. This section is intended to serve as a focused review of the student’s chosen topic of study, and allows the student to demonstrate the breadth of knowledge that he/she has accumulated during the writing process. This deviates slightly from what is seen in the primary literature, where Introduction sections are typically shorter and more focused in their scope. In the thesis Introduction, the student is expected to begin broadly (i.e. he/she addresses why this topic is important in the general sense), and then gradually narrow his/her focus to the specific topic that he/she has researched. The Introduction ends with a distinct thesis question or hypothesis, which provides the basis for the selection of the Current Investigation articles (in the case of the library-based thesis), or for the experiments performed in a laboratory- or field-based thesis. The student’s thesis mentor reviews the draft, and the student incorporates the feedback into the first full draft of the thesis.

Discussion. The rough draft of the Discussion section is due at the beginning of week 6. In this section the student interprets the findings described in his/her Current Investigations or Results section. In addition, the student proposes future studies to address gaps or outstanding questions in the findings. The student is also urged to critique any questionable methodologies, and to propose improvements. For lab- or field-based studies, the student is encouraged to troubleshoot any issues they might have encountered during their studies, and to offer suggestions for improvements in the experimental design. This section not only allows the student to interpret the results within the larger context of the study, but it also allows the thesis mentor to evaluate the student’s level of understanding of his/her topic.

Full Rough Draft, Peer Review, and Final Thesis. Upon receipt of the critiqued rough drafts of the individual thesis sections from his/her mentor, the student is then able to begin incorporating suggestions and assembling the full rough draft. In addition to the sections described above, the full rough draft of the thesis also includes an Abstract, an Overview, and a complete list of references (Figure 1). The Abstract gives a succinct, technical summary of the thesis paper in no more than 300 words, similar to abstracts found in the primary literature. The Overview is a 2-3 page non-technical description of the thesis. While the other sections of the thesis are written scientifically, the Overview challenges the student to describe his/her work in a way that is easily accessible to a reader who lacks a scientific background.

Two copies of the full rough draft are submitted at the beginning of week 9: one copy goes to the thesis mentor, and the other copy goes to the student’s Peer Reviewer, another member of the Senior Seminar class randomly assigned to the student by the instructors. It is the duty of the Peer Reviewer to provide detailed, constructive criticism to the author. Upon completion of the review, the Peer Reviewer returns one copy of the reviewed paper to the author, and submits a second copy to the Senior Seminar instructors, who evaluate the quality of the review.

Finally, upon receiving the second round of critiques from his/her peer reviewer and thesis mentor, the student is able to revise his/her thesis and submit the final version at the beginning of week 11. This concludes Phase 1 of the senior seminar course.

Poster preparation and presentation. In addition to submitting the final thesis, the student submits a rough draft of his/her poster layout to his/her thesis mentor, thus beginning Phase 2 of the Senior Seminar course (Figure 2). The primary function of the poster draft is to 1) initiate discussion between the student and his/her thesis mentor about the poster, and 2) shift the student’s focus from thesis writing to poster production. With guidance from his/her mentor, the student then proceeds to develop and refine the poster over the next two weeks using desktop publishing software2. The final poster file is submitted no later than week 13, to ensure sufficient time for printing and poster board mounting prior to presentation.

At this time, the student is scheduled for his/her thesis defense, which occurs at some point between Monday through Thursday of week 14. During the thesis defense, the student uses his/her poster to give a 10-15 minute oral research presentation to two members of the Biology department faculty: one is the student’s thesis mentor, the other is a second faculty member selected by the student. After the oral presentation, the faculty members ask questions of the student, to examine the depth of that student’s knowledge and ability to answer questions. Finally, on Friday of week 14, the student presents his/her poster to the public at the University-wide Senior Capstone Day, where their family and friends can enjoy the fruits of the student’s labor.

2Students are provided with a template file for use with the software that acts as a general guide for poster production, to increase the likelihood that the students’ posters will maintain a degree of uniformity. Final poster design is ultimately at the discretion of the student and thesis mentor.
Reflections

At the conclusion of the course, most students report that Senior Seminar in Biology was beneficial to their overall education in biology, and that they not only gained important skills in scientific writing and presentation, but that the experience would aid them in future educational and employment endeavors, regardless of the field. They especially value the ability to work one-on-one with a faculty mentor. Students also report that the structure and organization of the course helped them to stay focused and to complete their assignments in a timely manner, and that the workload was relatively evenly spread over the length of the semester.

Faculty mentors also report satisfaction with the level of faculty-student interaction, as well as the ability to work one-on-one with the students. In general, mentors feel that most students make significant and impressive progress from the time that they begin the course until they present their posters at Senior Capstone Day.

Although the course involves a significant investment of time and effort for both student and faculty mentor, both parties typically value the outcome. As the number of Biology majors at Arcadia continues to grow, we constantly monitor student and faculty workload associated with Senior Seminar, and make adjustments to the structure of the course accordingly. We are committed to ensuring that the Senior Seminar in Biology Capstone Experience remains a transformative process, one in which the student transitions from undergraduate learner to professional.

About the authors:

Dr. Sheryl T. Smith earned her B.S. in Biology and B.S. in Psychology from King’s College in 1988, her M.A. in Biochemistry from The University of Scranton in 1993, and her Ph.D. in Developmental Biology and Teratology from Thomas Jefferson University in 2003. Her postdoctoral training was completed at the Wistar Institute, before joining the Biology faculty at Arcadia University in 2007. Dr. Smith’s research interests include 1) gene regulation during Drosophila development; and 2) the effects of environmental toxins (such as Bisphenol-A (BPA), PFoA, DHEP, and BHA) on Drosophila development.

Dr. R. Wesley Rose earned his B.A. in Biology from Franklin and Marshall College in 1994, his M.S. in Biomedical Chemistry from Thomas Jefferson University in 1998, and his Ph.D. in Biology from the University of Pennsylvania in 2003. His post-doctoral training was conducted at the Fox Chase Cancer Center in Viral Pathogenesis and Immunology before joining the Biology faculty at Arcadia University in 2006. Dr. Rose’s research focuses on understanding the unique negative regulatory mechanisms that control the interferon-gamma response in CNS neurons.

Dr. Raymond W. Rose, Jr. earned his B.S. in Biology from Bucknell University in 1963, his M.S. in Biology from Bucknell University in 1965, and his Ph.D. in Biology from Temple University in 1970. Shortly thereafter, he became a member of the faculty of Beaver College (which would become Arcadia University in 2001) until his retirement in 2007. Dr. Rose’s research focused on the genetics of tRNA aminoaoylation in Drosophila.

Photo credit:

The photo of Colby Stotesbury, Arcadia ’13, is reprinted courtesy of Dr. Lauren Howard. Colby’s thesis titled “Expression and activation of the STAT1 phosphatase SHP-2 in CNS neurons exposed to gamma-interferon”, was a laboratory investigation under the guidance of Dr. Wes Rose.
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NYCC Executive Vice President of Academic Affairs
A Subunit of BOTOX Reduces Pain and Inflammation during Chronic Migraines

Abstract: A subunit of BOTOX, Onabotulinum Toxin Type A (BoNT-A), has been approved by the FDA as a prophylactic treatment for chronic migraines. The exact pathophysiology of migraines remains unclear but researchers are examining the mechanism by which BoNT-A reduces the pain of migraines and associated symptoms. Studies have determined that BoNT-A injected into craniofacial muscles reduces glutamate and calcitonin gene related peptide (CGRP) concentrations by attenuating the release of these neurotransmitters from synaptic vesicles. Glutamate and CGRP are responsible for eliciting the inflammatory response and activation of nociceptors, proposed to be the sources of pain during chronic migraines. BoNT-A exhibits potential as being an effective prophylactic treatment for chronic migraines due to its ability to reduce craniofacial muscle nociceptivity and neurogenic inflammation.

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Headache pain, often accompanied by sensitivity to light and debilitating nausea, is the hallmark of migraine and 300 million people suffer from it each year. The pain is so intense that suffers, in the midst of an attack, have been known to suggest that the knowledge that no one actually dies from a migraine may be viewed as a mixed blessing. The historical record indicates that while migraine headaches have very likely affected humans for at least 7,000 years, they remain at the bottom of the list of inadequately treated medical conditions. Recent epidemiological evidence suggests that these excruciating, pulsing headaches are more common and more debilitating than previously believed. The duration of the headache and its recovery period, which can be lengthy, costs the economy an estimated $17 billion each year in disability payments, loss of work, loss of school time, and related health care expenditures. Application of non-invasive brain imaging technologies coupled with advances in molecular biology and genetics have begun to converge in the hope of facilitating the development of novel therapies, including the injection of BOTOX, which may prevent or even stop migraine pain once it has started (Dodick & Gargus 2008).

The average migraine attack lasts for one to two days. About 14% of sufferers experience chronic migraines suffering with headaches 15 or more days a month. Attacks typically have environmental triggers that, though different for everyone, may be related to such everyday things as alcohol consumption, physical exercise, stress, a change in weather patterns, allergies, fluorescent lighting, sleep deprivation or menstruation. Two-thirds of reported cases occur in women between the ages of 15 and 55 but migraines can occur in all age groups and in both sexes (Dodick & Gargus 2008, Katsarava , et al. 2011).

In ancient Greece, Galen attributed migraine headaches, which he called hemicrania because of their unilateral expression, to errant humors that periodically left the liver and made their way to the head. The word migraine itself can be traced from Galen's hemicrania to the Middle English term "megrim", meaning headache accompanied by depression, and finally to migraine, the term that is widely used medically and in vernacular speech today. In the 17th century, a vascular hypothesis was formulated that replaced humors as the source of migraine pain with disruption of cerebral blood flow as a more likely culprit. This hypothesis served as the basis of treatment, with very few exceptions, until the 1980’s. During this time period, pain was believed to be triggered by the stretching and dilation of blood vessels in the brain. The characteristic pulsing pain of migraine was thought to be most likely the result of vasoconstriction of these previously dilated blood vessels and the resulting drastic drop-off in blood flow to neurons of the brain (Dodick & Gargus 2008).

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Today it is possible, using an array of non-invasive imaging technologies, to actually observe the progression of vascular changes associated with migraine. For many people who have been observed using non-invasive imaging, the developing model points to an increase in blood flow around neurons preceding migraine pain rather than the previously theorized decrease in blood flow. In fact, increases in cortical blood flow of up to 300% have been calculated just prior to the onset of pain. As imaging continues into the pain phase of a migraine, blood flow can be seen to diminish and return to normal or slightly less than normal when the pain starts. As the understanding of blood flow patterns associated with migraine has changed, the understanding of the most likely root of migraine pain has also changed. Today, research is being directed to the nervous system, specifically the most ancient part of the brain, the brainstem, in an effort to understand the origin of migraines (Dodick & Gargus 2008).

New insight into migraines has centered on understanding the aura, which often precedes the pain, and the headache itself. Unlike most headaches, migraines move through predictable stages, although not everyone will experience all of the stages. A migraine headache is heralded, for about 60% of sufferers, by a prodrome that lasts anywhere from a couple of hours to several days. During the prodrome, people report fatigue, excessive yawning, difficulty in maintaining concentration and sensitivity to sound and light. The prodrome is followed by a set of sensory manifestations known as the aura. Typical of the aura, which affects about 30% of people, are visual sightings of patterns of light and sparks, which is frequently followed by dark spots or blind spots in the visual field. The aura is shorter than the prodrome and usually lasts for 20 to 60 minutes. All sufferers of classic migraine experience the headache, which is typically accompanied by nausea, vomiting, and sensitivity to light and sound. The pain can last up to 72 hours, often with little or no significant relief. The postdrome follows the actual headache in about 70% of people. It is characterized by light sensitivity, fatigue, and difficulty in focusing on everyday activities. The postdrome may last for just a few hours or for several days (Dodick & Gargus 2008).

Research into the aura has centered on a phenomenon known as cortical spreading depression, which has been described as a “brainstorm” or wave of heightened neuronal activity that spreads over a large area of the cerebral cortex, including the primary visual areas. Spreading cortical depression is followed by a quiet period of neuron inhibition, an extended refractory period during which the affected neuron cannot be made to fire. Research indicates that the periods of intense excitability followed by long periods of inhibition that are typical of spreading cortical depression can explain the changes in cerebral blood flow patterns that have been observed in migraine sufferers. For example, neurons that are very active require a huge blood supply to furnish them with needed nutrients from which to extract energy. During quiet periods, neurons do not need as many nutrients and therefore require less access to blood (Dodick & Gargus 2008).

Using advanced scanning technologies, it can be seen that the cortical spreading depression, a huge depolarizing wave that sweeps over the brain, fits nicely with a patient’s description of aura. Traveling across the cortex at one to three millimeters per minute, the depolarizing wave and the visual sensations of aura described by the patient undergoing a scan are seen to dovetail. As patients describe the changing sensations of their aura, from visual patterns of light to sensory or motor experiences, the wave of depolarization can be observed crossing the corresponding areas of the cortex. Even the dark spots, which patients often describe as following the patterns of lights and sparks in their visual field during aura, are consistent with neurons becoming refractory in specific regions of the visual cortex after experiencing a wave of intense depolarization (Dodick & Gargus 2008).

Along with the knowledge of migraine aura and its relation to cortical spreading depression, the focus of research has also been directed at finding the specific source of migraine pain. Most of the neurons in the brain are incapable of regulating or transmitting pain signals. However, there is a specialized region of nerve fibers known as the trigeminal nerve system, which is at the root of the trigeminovascular theory of migraine pain. The trigeminal nerve system transmits sensations of pain from the meninges and the blood vessels associated with the meninges. Vasodilator peptides are located in nerve cell bodies of sensory nerve fibers called nociceptors, which are located in the trigeminal ganglion. The trigeminal ganglion is the sensory ganglion of the trigeminal nerve, which is located in the dura mater near the apex of the petrous portion of the temporal bone. During a migraine, it is hypothesized that some type of abnormal brain activity, very likely cortical spreading depression, stimulates the trigeminal nerve, causing its sensory nerve fibers to release glutamate and calcitonin gene related peptide (CGRP). Upon their secretion, glutamate and CGRP induce neurogenic inflammation by acting on the smooth muscle lining of blood vessels causing vasodilation. They also recruit inflammatory mediators, such as mast cells, which alter the permeability of blood vessels causing protein extravasation. During extravasation, proteins move from the blood into surrounding tissue where their presence causes edema. The dilated blood vessels and swollen tissues press against sensory fibers of the trigeminal nerve, which ultimately elicits pain. The impulses from stimulated trigeminal nerve fibers travel to the brainstem for processing in the trigeminal nucleus (Continued on next page)
The trigeminal nucleus is the largest cranial nerve nucleus extending all the way through the medulla, the pons, and the midbrain. Sensation is relayed to the thalamus from this nucleus and from there to the sensory cortex where people become consciously aware of pain (Galletti et al., 2009, May and Goadsby 1999, Ramadan 2008, Richardson and Vasko 2002).

A phenomenon known as sensitization is a key component of migraine development. With the continued presence of inflammatory mediators, the trigeminal nociceptors are constantly activated and continuously sending signals to the brain. As a result, in a process known as sensitization, the degree of the stimulus needed to elicit an electrical response from the nociceptor diminishes. Once sensitization has taken place, trigeminal nociceptors will elicit increased electrical firing in response to lesser amounts of glutamate or CGRP. Consequently, pain is perceived more frequently and for a longer duration of time. Commonly, migraine pain is referred to as allodynia, which describes pain from a stimulus or a degree of stimulus that would not normally be painful. Understanding the process of sensitization may provide explanation for the increased frequency and duration of pain associated with migraines (Goadsby 2012, Richardson and Vasko 2002).

One of the subunits of BOTOX, Onabotulinum Toxin Type A (BoNT-A), was discovered accidentally to be a potential treatment for chronic migraine. Patients receiving facial cosmetic injections of BOTOX began reporting that they were experiencing reduced frequency and diminished pain with their headaches. Consequently, clinical studies were conducted using migraine patients to see whether injections of BoNT-A had beneficial effects on migraines. Two such studies were the Phase III Research Evaluation Migraine Prophylaxis Therapy I (PREEMPT1) and the Phase III Research Evaluation Migraine Prophylaxis Therapy II (PREEMPT2). Conducted from 2006 to 2008, participants for both studies were chronic migraine sufferers of ages 18 to 65. PREEMPT1 was conducted nationally in 56 North American sites, and PREEMPT2 expanded its participation globally encompassing 50 North American sites and 16 European sites. Based on survey results, both studies found that in comparison to the placebo group, those treated with BoNT-A experienced reduced days and hours per day of migraines and reported an elevated quality of life. Of the 341 participants who received treatment with BoNT-A in PREEMPT1 and the 347 participants who received treatment with BoNT-A in PREEMPT2, only 3.5% percent from each trial withdrew from the study due to adverse effects. Adverse effects were reported as being mild or moderate. The results from both studies determined that the usage of BoNT-A for migraines was effective and safe. Consequently, the FDA approved its administration as a prophylactic chronic migraine treatment on October 15, 2010 (Aurora et al., 2010, Diener et al., 2010, FDA 2010). The effect of BoNT-A on motor neurons has been thoroughly investigated and described. BoNT-A inhibits muscle movement by preventing the release of acetylcholine from synaptic vesicles at the neuromuscular junction. Associated with this process are soluble N-ethylmaleimide-sensitive factor attachment protein receptors, (SNAREs), which are responsible for docking the synaptic vesicles inside of the axon, as well as mediating the release of acetylcholine. BoNT-A cleaves a protein component of the SNARE complex, synaptosomal-associated protein 25 (SNAP-25). The cleaving of SNAP-25 from the SNARE complex prevents the synaptic vesicle from binding to the axonal membrane and releasing acetylcholine into the neuromuscular junction. Consequently, there is no muscle movement (Durham and Cady, 2011).

In an attempt to determine the possible effect of BoNT-A on chronic migraine pain, it has been hypothesized that decreased muscle movement would reduce the release of inflammation mediators, which would, in turn, decrease the sensitization of nociceptors. However, an increasing number of studies have found the paralytic effect on muscles to be independent of the mechanism by which BoNT-A prevents chronic migraines. Instead of reducing pain by decreasing muscle movement, BoNT-A is believed to act on neurons in the sensory system involved with transmission of pain. The exact mechanism by which BoNT-A acts on sensory neurons is not definitively known. However, it is believed to have a similar action in the sensory system as it does on motor neurons. Therefore it has been proposed that at the sensory neuron, BoNT-A damages SNAP-25 and prevents the release of synaptic vesicles containing the pain mediators glutamate and CGRP. A study conducted by Aoki in 2003, found that BoNT-A was indeed able to inhibit the release of glutamate. The inhibition of CGRP and glutamate acting in the peripheral sensory system would alter the perception of pain and could be a logical reason why BoNT-A has an effect on migraines (Aoki 2003, Durham and Cady, 2011, Oliver et.al., 2006, Meng et.al., 2009).

When BoNT-A is prescribed as a prophylactic migraine treatment, it is injected intramuscularly into seven craniofacial muscles using a 0.5-inch needle. The FDA has approved the regulations with which it is commonly prescribed. The recommended dose per treatment is 155 units (U), with treatments every 12 weeks. Injections are administered bilaterally in the following muscles of the face, neck, and upper back: corrugator, corrugator, procerus, occipitalis, temporalis, trapezius, and the cervical paraspinal muscle group. Dosage amounts vary in accordance with the size of the muscle, ranging from as little as 5 units in the corrugator muscles to 20 U in the temporalis muscles (ALLERGAN 2013).

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Once the mechanism by which BoNT-A reduces inflammation and nociceptivity during chronic migraines was elucidated, attention turned to discovering how it was being transported in the nervous system. Originally, it was believed that BoNT-A only acted locally in the region where it was injected. However, a few studies, including one conducted by Matak et al. in 2011, demonstrated that BoNT-A was producing bilateral effects. In response to this discovery, it has been suggested that retrograde axonal transport of BoNT-A, from peripheral sensory neurons into the central nervous system along microtubule tracts, is a possible mechanism of transport. To provide evidence of retrograde axonal transport, the researchers performed immunohistochemical testing to track a byproduct of BoNT-A’s action, cleaved SNAP-25. Not only was cleaved SNAP-25 found in the ipsilateral nucleus caudalis (TNC), it was also found in the contralateral TNC. This was evidence that although administered peripherally, BoNT-A travels into the central nervous system. Not only is BoNT-A reaching the CNS, it also seems to be eliciting its main effect there (Matak et al., 2011).

If BoNT-A does indeed travel into the central nervous system to elicit its antinociceptive effect, this piece of evidence could change the way in which BoNT-A is administered. At the same time, it is disturbing to realize that BoNT-A, a paralytic toxin, exhibits effects distant from its site of injection. These types of open-ended findings demonstrate refinements that may need to be made to the administration of BoNT-A in order to ensure the highest level of efficacy in treating chronic migraines, while simultaneously minimizing potential adverse side effects. Knowing that BoNT-A acts within the central nervous system raises the potential of its administration there. Under current therapeutic practices, needles are not inserted directly into regions of the brain as a treatment method; however, another form of administration may serve as an alternative to this. One such example is the ALZET Osmotic Pump. The ALZET pump is a small capsule that can be surgically implanted into tissues of the body to administer a drug (agent) at a consistent rate. The pump comes in three sizes ranging from 100 µL to 2mL depending on the quantity of the agent required and the length of the delivery period. The capsule itself is composed of three layers, an inner impermeable reservoir which holds the agent, a middle osmotic layer, and an outer semi-permeable membrane. The middle osmotic layer is called the salt sleeve. At one end of the pump is a flow moderator. The pump operates in response to the osmotic pressure difference between the salt sleeve, and the tissue into which the pump is implanted. The salt sleeve compartment has very high osmolality compared to the tissue that surrounds it. This osmotic difference causes water to flow through the semi-permeable outer layer of the pump. The semi-permeable layer controls the rate of delivery; consequently, this layer is made specifically for the amount of agent being administered. As water flows into the salt sleeve compartment it compresses the inner impermeable reservoir containing the agent. The agent will enter the flow moderator and be diffused out at a pre-determined rate, specific to the agent. Delivery rates range from 0.11 and 10 µL/hour and delivery durations range from 1 day up to 6 weeks. Once the pump has administered the contents of its agent, the drug reservoir cannot be refilled and it must be surgically removed. If another round of the treatment is required, a new pump must be implanted (ALZET 2013).

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If BoNT-A could be administered by this mechanism, it could be implanted near the trigeminal ganglion, where the cell bodies of sensory neurons from the trigeminal nerve are located. Since BoNT-A has been found to exert its effect in the central nervous system, use of the ALZeT pump would allow for a more direct administration. This would avoid the application of BoNT-A in the peripheral nervous system, doing away with the use of needles for injection. As it is administered now, BoNT-A injections are given intramuscularly which can cause discomfort. Additionally, a single treatment of BoNT-A is administered in small doses into both sides of seven different paracranial muscles, which may require as many as 31 separate BoNT-A injections. While the use of the ALZET pump may be more invasive, it would require one implantation per treatment in comparison to 31 injections (ALZET 2013).

Another advantage of the ALZET pump is its ability to deliver a consistent amount of dispensed material, which results in around the clock exposure to the agent at appropriate dosages. When BoNT-A is administered via injection, there are fluctuations in the dosage over time, ranging from potentially dangerous overdoses to ineffective under doses. The pump provides a consistent dosage amount over time as regulated by the semi-permeability of the outer layer and the flow modulator. Consistency of regulation is especially important in the mechanism of BoNT-A as a prophylactic chronic migraine treatment. BoNT-A reduces the levels of neurotransmitters, glutamate and CGRP, which are responsible for the inflammatory process that causes pain during a migraine. Increased levels of these neurotransmitters can cause sensitization of the nociceptors responsible for the sensation of pain. The sensitization process is a proposed mechanism for the evolution of chronic migraines, and so it is important to regulate glutamate and CGRP at consistent levels to prevent sensitization (ALZET 2013).

While the ALZET pump offers benefits including direct administration and consistent dosages of BoNT-A, other considerations must be taken into account. It is now known that BoNT-A can spread to sites other than that of its original administration. It is possible, therefore, that the BoNT-A from the ALZET pump might spread from its implantation site in the trigeminal ganglion, and act on higher order neurons innervating other regions of the brain, perhaps even making its way to the thalamus and cortex. So far, the ALZET pump has only been used in animal studies. If BoNT-A were an agent able to be administered through this mechanism, extensive research would have to be conducted to determine the efficacy and safety of the use of the ALZET pump, or a similar device, in humans (ALZET 2013).

There is a range of expectations for injections of BoNT-A for migraine pain as demonstrated by the results of the PREEMPT1 study. In this study, patients received BoNT-A injections every 12 weeks, and data was collected upon the second treatment during the 24th week. After two treatments with BoNT-A, days spent suffering from a migraine decreased by 7.6 days from a baseline of 19.1 days. The mean cumulative headache hours occurring on headache days decreased by nearly half from a baseline of 295.7 hours to 189 hours. Additionally, the days of moderate/severe headaches was reduced by 7.2 days, from 18.1 days at baseline measurements to 10.9 days. Based on the results from this study, those receiving BoNT-A for chronic migraines can expect the length of their migraine attacks to decrease by roughly 8 days, their hours spent with a migraine to decrease by half, and the severity of their migraines to be significantly reduced by their second BoNT-A treatment (Aurora et al., 2010).

While these are typical results, BoNT-A does not produce consistent effectiveness in everyone. A possible explanation for this is that all of the underlying causes of migraines and the exact pathophysiology of the condition have yet to be determined. Other neurotransmitters, like serotonin and dopamine, have also been found to be involved in migraine progression. As of now, BoNT-A has been found to reduce levels of only glutamate and CGRP. If other neurotransmitters and neurological mechanisms were responsible for the migraine, BoNT-A would not be expected to be effective. Additionally, adverse effects of BoNT-A have been reported. In the PREEMPT1 study, nearly 60% of patients treated with BoNT-A experienced some form of adverse effects; however only 3.5% found them intolerable and withdrew from the study (Aurora, 2010). The two most common side effects were neck pain and muscle weakness, which can be explained by the paralytic effect of BoNT-A on muscles. BoNT-A administration into the central nervous system by something like the ALZET pump may eliminate these side effects (Aurora et al., 2010).

Over the past three centuries, the botulinum toxin has undergone an amazing transformation from toxin to medicine. A subunit of botulinum toxin, BoNT-A, one of the most poisonous toxins known to humans, has been isolated and found to be useful in clinical medicine for treatment of neurological disorders such as chronic migraines. The prophylactic use with BoNT-A for the treatment of chronic migraines began as a serendipitously observed phenomenon and was deemed effective based on results from clinical trials. As its use became more prevalent, so did studies conducted on animals, seeking to understand the mechanism by which BoNT-A reduced pain associated with migraines. From these studies, it was determined that BoNT-A injected into craniofacial muscles reduced neurogenic inflammation and pain by attenuating glutamate and CGRP concentrations. These neurotransmitters elicit the inflammatory response and activation of nociceptors, believed to be the

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sources of pain during chronic migraines. Additional animal studies looked at the transport of BoNT-A, and determined that it undergoes retrograde axonal transport from the periphery into the central nervous system, where it elicits its antinociceptive effects. Presently, animal studies continue to be performed to confirm and clarify the mechanism and transport pathway of BoNT-A in migraine treatment. Clinical studies have found mixed results of its effectiveness and research must be continued to understand other mechanisms of BoNT-A and migraine pathophysiology. For now, current research has determined that BoNT-A acts as a prophylactic treatment for chronic migraines by reducing neurogenic inflammation and nociceptivity. These developments mark a breakthrough that may someday benefit millions of people who are currently experiencing this biologically complex and extremely debilitating medical condition.

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Photo credit:

DKart/istockphoto
**Abstract:** Bone fracture non-unions are often the result of high-impact injuries and are characterized by an inability to heal due to a reduced blood supply at the fracture location. Sufferers are often incapable of regaining the proper strength and function to carry out normal activities. Treatment options were limited mostly to medications and casting until research discovered the uses of adult stem cells. Human mesenchymal adipose derived stem cells (HMADSCs) and human bone marrow mesenchymal stem cells (hBM-MSCs) have been the basis of most non-union fracture research. By creating and managing inflammatory responses, promoting superior callus formation, and shortening fracture recovery period, adult mesenchymal stem cell injections heal fracture non-unions and normal fractures better than other conventional treatment methods during animal experimental studies.

In the modern world, most broken bones can be expected to heal without serious problems if they are professionally diagnosed, properly realigned, and expertly stabilized. If the patient is generally healthy and well nourished and the blood supply to the area is adequate, new bone tissue almost always forms to reconnect the broken pieces of bone. Occasionally a “delayed union” may take place in which the fracture eventually heals over a longer period of time than expected and, in rare instances, a broken bone fails to heal at all. When a broken bone does not heal, even after an extended period of time, it is called a “non-union”. A fracture non-union is a serious medical condition that can be difficult to treat (AAOS 2013).

The most probable cause of a fracture non-union is lack of stability at the fracture site coupled with a lack of an adequate blood supply. The risk of having a fracture non-union is highest in people who smoke or use tobacco in any form, in the elderly, in people who are anemic, in people with diabetes, in people taking anti-inflammatory drugs such as aspirin and ibuprofen, and in people with a current infection. The lack of an adequate blood supply to a bone may be due to the nature of the affected bone itself or it may be the result of severe trauma to the fracture site. The bones of the toes, for example, are very stable and this, coupled with the fact that they also have an excellent blood supply, is one of the reasons that toe fractures are likely to heal with minimal treatment or without treatment at all. The femur and the scaphoid, both commonly broken bones, possess a limited blood supply that is often disrupted when a fracture occurs. Fractures in these bones may take a little longer to heal. The blood supply to the tibia is considered to be moderate but when fractured, there may be difficulties with healing because the shaft of the bone is so close to the overlying skin and muscle, which can easily be destroyed when there is trauma to the leg. Trauma to the surrounding soft tissues can destroy the blood supply to the marrow cavity of the tibia. Rarely it may happen that bone fractures occur in people with no apparent risks for nonunion. These people may have access to proper treatment and appear to be healthy, but the fracture simply does not heal, even after surgical intervention. It is this last group that is most problematic (Shoji et al., 2013, AAOS 2013).

One of the signs that a fracture non-union has occurred is that pain is felt for a long time, months or even years, after the initial pain of the fracture has disappeared. Imaging studies, including X-rays, CT scans, and MRI scans, are used to diagnose a fracture non-union. The diagnosis of a non-union may be made based on an observable gap between bone ends at the fracture site, the lack of observable healing progress over many months, or an unacceptable length of time a patient feels pain associated with the fracture. Along with imaging studies, blood tests may be used to determine if the patient has an infection or another medical condition that might be slowing the repair process, such as diabetes or anemia. Traditional treatment for nonunion fractures may involve the use of electromagnetic and ultrasonic pulsed waves to the bone and surgical intervention. Surgical treatment options include bone grafting, bone substitute grafting, and internal or external fixation (AAOS 2013).

Surgery is both invasive and expensive and carries a significant risk of infection. One possible, less invasive, solution to the problem of fracture non-unions that has shown significant promise, involves (Continued on next page)
the injection of stem cells into the non-union site. The
limitations placed on embryonic stem cell research
combined with extremely limited funding in this area,
led to a renewal of interest in human bone marrow
mesenchymal stem cells and stem cells derived from
adipose tissue. Human bone marrow mesenchymal
stem cells (hBM-MSC) are a form of adult stem cells
that can be extracted non-invasively from an infant’s
umbilical cord or placenta and adult tissues such as
bone marrow and peripheral blood.

Much like embryonic stem cells, adult
stem cells have received their share
of criticism, presumably because
the term “adult” implies that they
are being removed from a living
human. hBM-MSCs are collected
from bone marrow via needle biopsy,
while donors are under general
anesthesia, and from the umbilical
cord after birth. When hBM-MSCs
are taken from peripheral blood,
they are removed through a catheter
into a machine that filters out the
stem cells and circulates the blood
back into the donor. An average
extraction from any of these three
cell sources contains only about one
human bone marrow mesenchymal
stem cell for every 34,000 cells
processed. Although this number is
very low, it takes only a few weeks
to grow a sufficient number of cells
for injection. Research collected
from many animal-model organisms
injected with hBM-MSCs has shown
that the cells have the ability to
treat or cure many common diseases
including red blood cell disorders
such as sickle cell anemia, many
 cancers including lymphoma and
leukemia, and even autoimmune disorders like multiple
sclerosis and Crohn’s disease. In addition, there are
now many studies that show the ability of hBM-MSC’s
to regenerate bone damaged by fractures and to repair
torn cartilage (cancer.org 2012, NSCF 2011, Prentice

One form of “adult” stem cell that is free from
controversy or ethical concerns is human multipotent
adipose derived stem cells (hMADSCs). These cells
were discovered in 2002 by researchers at UCLA and
they have emerged as the leading stem cell used in
current research. They possess the same multipotency
as bone marrow stem cells but they are much more
plentiful and less invasive to extract. The removal of
hMADSCs is done via liposuction, which has already
been established as a cosmetic procedure that enjoys
worldwide acceptance. The ability to extract a very
large number of cells at once means that the extracted
cells do not need to be grown in vitro for very long.

This saves a great deal of time, making the use of
adipose derived stem cells a more sensible solution
for clinical usage. There are roughly 500 times more
dense mesenchymal stem cells extracted from one gram
of adipose tissue than can be extracted from a gram of
bone marrow. While HMA DSCs have shown the ability
to treat cardiac muscle repair following heart attack,
and circulatory damage resulting from diabetes in
research animals, these adipose derived cells have
been most successful in repairing both
bone and cartilage following serious
injuries (NSCF 2011, Zuk, 2010).

The differentiation process for both
hBM-MSCs and HMADSCs into new
bone requires only a few steps, but
when examined on a molecular level
the process is quite complex. Stem
cells are isolated by centrifugation and
cultured with growth factors, inorganic
salts, vitamins, and amino acids.
Proliferation of the stem cells generally
takes between two and three weeks.
Following proliferation, the second
step involves commitment of the stem
cells to the osteoblast lineage. This
is accomplished by the introduction
of bone morphogenetic proteins
to the culture medium to direct the
differentiation of the stem cells. Fifteen
different bone morphogenic proteins
(BMPs) have been isolated and they
can be added to the culture medium
as needed, causing the stem cells to
differentiate into the appropriate cell
lineage. The third step requires lineage
progression into mature osteoblasts.
This progression is accomplished
using a medium that contains bone
morphogenetic proteins that are specific
for this purpose. The culture medium
is replaced with fresh medium every 48-72 hours for
a week. Once mature osteoblasts have been formed,
they are frozen in a special freezing medium until they
are needed for implantation. Freezing mediums slow
the freezing process of the stem cells to reduce the
crystallization rate. When needed, the differentiated
cells are quickly thawed in a warm water bath where
they can stay for up to 48 hours. The cells are treated
with phosphate buffered saline (PBS) that adjusts them
to the proper pH and osmolarity for implantation. They
are injected into a specific body location and they
are attracted to the fracture site by chemotaxis. The
fourth and final step requires the transformation of the
osteoblasts into osteocytes. Osteocytes are formed
when the osteoblasts become embedded in the bone-
forming matrix. New bone formation and the healing
process in general are important in several types of
bone injuries including fractures (Burastero et al., 2010,
Caplan & Bruder 2001, Violini et al., 2009).

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In natural bone healing, the damaged bone endings bleed immediately following a fracture and bleeding continues until a clot forms. This is followed by acute local inflammation, which is caused by the migration of histamine-secreting mast cells into the epithelium. Inflammation is important in the promotion of healing because it attracts neutrophils, macrophages, and mesenchymal cells to the site of the injury. Acute inflammation is followed by the “repair” stage. Since the vascular tissue surrounding the injured bone has been destroyed or partially damaged, fibroblasts begin laying down stroma, which allows the bone to become re-vascularized. Immediately following an established vascular system, a collagen matrix begins to form around the bone, which quickly becomes a callus. The callus bridges the cut ends of the bone encouraging the bone parts to fuse. The callus is generally very weak for 4 to 6 weeks and can easily re-fracture if stress is placed upon it. This is the reason a cast is required for most fractures. The final step for bone healing is termed the remodeling stage. During this stage the bone regains its form and strength. It takes from three to six months following a fracture for a bone to regain optimal strength following a fracture. Typically, the elderly require longer recovery periods. As many as ten percent of all bone fractures may require surgery in order to achieve proper healing (Hannouche et al., 2001, McKibbin, 1978, Kalfas 2001).

When fracture healing does not proceed along expected lines and healing is delayed, stem cell injection into the fracture site may address the limitations of natural bone healing. hBM-MSCs have been found to regulate and reduce the inflammatory response in non-union fracture sites where the fracture site may require more inflammation to establish a good blood supply or less inflammation to promote proper healing. In animal studies where fractures were induced in mouse tibias, the injection of hBM-MSCs promoted more callus volume and a stronger bone matrix than standard healing while simultaneously shortening the recovery time. In studies where fracture non-unions were induced in rat femurs, injection with hBM-MSCs resulted in the production of new bone with a significant ability to take on more torque and withstand more force than naturally healed bone. Biomechanical testing on non-union fractures in rat femurs that had been injected with HMADSCs also showed greater strength when compared with naturally healed bone. Femurs injected with HMADSCs showed the ability to withstand nearly triple the amount of stress placed on the bone and exhibited nearly quadruple the amount of percent energy failure, which is the ability to absorb mechanical energy until breakage occurs. These results strongly indicate the ability of stem cell injections to speed and enhance the recovery process of fracture non-union healing (Granero-Molto et al., 2009, Undale et al., 2011 Shoji et al., 2011).

Human bone marrow mesenchymal stem cells and adipose derived mesenchymal stem cells have shaped the field of regenerative bone repair for the future. Sometime in the near future healing time for many tendon, ligament, bone, and cartilage surgeries will be drastically reduced by the injection of adult stem cells. These cells will be able to effectively increase the vasculature at a fracture location, form osteoblasts around a callus, and allow the callus to become stronger, heal faster, and withstand greater forces than naturally healed bone. Best of all, everything will be accomplished with a significantly shortened recovery period.

* Dylan Marks graduated from Arcadia University in Spring 2013 and is enrolled in the DPT program at Arcadia University. Excerpts from his senior thesis titled “Stem cell / Bone Non-Union Fracture Healing” appear in this article.

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A Surgical Approach to the Correction of Pulsatile Tinnitus caused by a Sigmoid Sinus Diverticulum

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Abstract: The unwanted noises of tinnitus may affect over 36 million Americans at some time during their lifetime. A rare type of Pulsatile tinnitus, which coincides with one’s heartbeat and has its origin in the presence of a sigmoid sinus diverticulum, may be amenable to surgical treatment via a transmastoid approach. The goal of this relatively new surgical procedure is the reconstruction of the sinus wall and the resolution of the associated sounds.

Tinnitus, often described as ringing in the ears, is an annoying condition that can be expected to affect one out of every five people during their lifetime. Though not a disease in itself, it can be a symptom of problems with the auditory system. Common forms of tinnitus can be triggered or exacerbated by an array of substances including antibiotics, cancer medications, diuretics, antidepressants, quinine-based medications and high doses of aspirin. Risk factors for the disorder include repetitive exposure to loud noises, advanced age, smoking, being male, and having high blood pressure. The sounds, which may be intermittent or continuous, are frequently reported to diminish a person’s overall quality of life. People with tinnitus may have difficulty sleeping, suffer from fatigue and depression, complain of memory problems and exhibit anxiety and irritability (Tabuchi et al., 2011).

The most common type of tinnitus is called subjective or auditory tinnitus. In auditory tinnitus, sounds typically have their origin in the auditory nerve and the central auditory system, which may indicate problems with the outer, middle or inner ear. Only the person suffering from tinnitus is able to hear these sounds. The less common type of tinnitus is objective tinnitus, also known as somatosounds, which originates in structures in and around the ear. The examiner as well as the tinnitus sufferer can hear somatosounds. The most common sources of somatosounds are vascular

Figures 1 and 2: “Left sinus wall dehiscence with the air-on-sinus sign. The two images are a few millimeters apart on the same patient.”

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bruits, involuntary twitches of the muscles of the palate known as palatal myoclonus, a distended Eustachian tube, or sounds associated with the tempromandibular joint. A vascular bruit, from the French word for noise, refers to sounds that are made by blood turbulence as blood flows past an obstruction. The hallmark of vascular bruit is sound that keeps pace with the heartbeat, resulting in a rare condition known as pulsatile tinnitus (Otto et al., 2006).

Pulsatile tinnitus is associated with the vasculature of the head and neck and may occur in the arterial system when blood encounters a tumor pressing against a blood vessel or where atherosclerosis is present in blood vessels of the middle or inner ear. Atherosclerosis typically results in loss of blood vessel elasticity, which may have an affect on the sound blood makes. High blood pressure can also trigger unusual sounds in blood vessels as can blood turbulence resulting from stenosis of the internal carotid artery or the internal jugular vein. Unusual sounds may also have their origin in abnormal connections between arteries and veins in the dura mater known as arteriovenous malformations. Arteriovenous malformations associated with tinnitus usually result in the production of unilateral sounds. In the venous system, bruits most commonly originate from venous stenosis, small groups of abnormally coiled veins, or elevated intracranial blood pressure (Otto et al., 2006). It is possible to distinguish whether pulsatile tinnitus is of arterial or venous origin by gently compressing the internal jugular vein. If the tinnitus is of venous origin, the compression will cause the observed sound to stop. If the tinnitus is of arterial origin, the compression will make the sound louder (Gologorsky et al., 2009).

For the 25% of people who are severely affected by tinnitus, definitive cures are hard to come by. However, reconstructive surgery has recently become an option for a rare condition known as intramastoid sigmoid sinus diverticulum, a specific type of venous disruption that may be associated with pulsatile tinnitus. Individuals with this disorder are diagnosed using computed tomographic angiography, CTA. This type of imaging, in which contrast dye is injected into the blood stream prior to the scan, offers high resolution of both the temporal bone and its vascular anatomy. A typical CTA scan might begin coverage at the level of C6, include the bifurcation of the common carotid artery and extend through the Circle of Willis (Otto et al., 2006).

When a sigmoid sinus diverticulum is present, the associated increase in blood turbulence can cause the loss of the thin layer of cortical bone that normally separates the sigmoid sinus from the mastoid air cell system, a condition known as dehiscence. Loss of cortical bone to the level of the mastoid air cells may appear as an “air-on-sinus” sign on a CT scan (Eisenman 2013, Fig.1 & 2). One of the possible treatments for this condition is a surgical procedure known as transmastoid reconstruction of the sigmoid sinus. The goal of this procedure is to provide a smooth vascular surface for the sigmoid sinus and eliminate any audible sounds of blood turbulence by flattening out the sigmoid sinus diverticulum. In order to accomplish this, an incision is made behind the ear and a flap of skin and subcutaneous tissue is lifted from the region covering the mastoid portion of the temporal bone. Once the skin flap is securely anchored out of the way, a flap of periosteum is raised exposing the mastoid cortex. The sigmoid sinus, its adjacent dura mater and the diverticulum are exposed through careful dissection. The wall of the sigmoid sinus is reconstructed using either part of the temporalis muscle and its associated fascia or bone wax. Bone wax is beeswax to which a softening agent has been added. It can be used to apply pressure to bone in order to stop bleeding or, as in this case, it can function as a patching material. When a large diverticulum has been exposed, typically a piece of the temporalis muscle is used to cover the defective area of the sigmoid sinus. The temporalis muscle patch is then sutured to the adjacent dura with just enough tension to flatten out the diverticulum. Smaller diverticula can often be patched with just a sheet of bone wax, cut to proper size, and placed over the bulging area of the sinus. Care is taken during the surgery to conserve the normal diameter of the sigmoid sinus and the sinus is never ligated or obliterated. When everything has been completed to the satisfaction of the surgeon, the repaired section of the sigmoid sinus is covered with the periosteal flap, the skin is closed, and a compression dressing is applied to the area. Many patients whose pulsatile tinnitus is linked to sigmoid sinus diverticulum, and who are treated surgically, report complete resolution of the offending noise (Eisenman 2011, Otto et al., 2006). Along with the success that has resulted from surgical transmastoid reconstruction of the sigmoid sinus in the treatment of pulsatile tinnitus, there are still unanswered questions relating to the pathophysiology of sigmoid sinus diverticula. The direct cause of a diverticulum remains unknown as does its sequential natural history and the exact mechanism by which the sound is generated. The intracranial vascular abnormalities that are related to the diverticulum, and possibly contribute to its formation, have not yet been adequately investi-
Superficial Veins of the Head and Neck [Figure 22.21] Superficial veins of the head converge to form the temporal, facial, and maxillary veins (Figure 22.21). The temporal and maxillary veins drain into the external jugular vein. The facial vein drains into the internal jugular vein; a broad anastomosis between the external and internal jugular veins at the angle of the mandible provides dual venous drainage of the face, scalp, and cranium. The external jugular vein descends superficial to the sternocleidomastoid muscle. Posterior to the clavicle, the external jugular empties into the subclavian vein. In healthy individuals, the external jugular vein is easily palpable, and a jugular venous pulse (JVP) can sometimes be seen at the base of the neck.

Venous Return from the Upper Limb [Figure 22.22] The digital veins empty into the superficial and deep palmar veins of the hand, which interconnect to form the palmar venous arches (Figure 22.22). The superficial arch empties into the cephalic vein, which ascends along the radial side of the forearm, the median antebrachial vein, and the basilic vein, which ascends on the ulnar side. Anterior to the elbow is the superficial median cubital vein, which interconnects the cephalic and basilic veins. Venous blood samples are typically collected from the median cubital vein.
gated. The precise radiological criteria for assessing the amount of dilation of the sinus that is required in order to make the diagnosis of pulsatile tinnitus have not been established. Furthermore, it is not known if an actual diverticulum must be present in order to produce the tinnitus sound or if a wearing away of the cortex of the mastoid portion of the temporal bone is sufficient to produce the sound on its own (Eisenman 2011).

Anecdotal reporting from surgeons suggests that a disproportionate number of cases of sigmoid sinus diverticulum and related pulsatile tinnitus involve only the right ear. This suggests that the usual dominance of the right side of the venous drainage pathway from the brain may in some way play a role in the pathogenesis of the diverticulum. Most lesions in the sigmoid sinus are reported to occur immediately downstream from the junction of the transverse sinus and the sigmoid sinus, rather than further along in the sigmoid sinus. This might suggest that the velocity of the blood as it leaves the transverse sinus and hits the wall of the sigmoid sinus just distal to the curvature, may weaken the wall of the sigmoid sinus over time, resulting in the formation of a diverticulum. There are some associated vascular anomalies that may contribute to this phenomenon. These anomalies include the failure of the contralateral transverse sinus to form, the presence of very small contralateral sinuses and stenosis of the ipsilateral distal transverse sinus. These anomalies could serve to further increase the blood velocity in an already dominant side of the venous drainage or abnormally increase it on a nondominant side and thus influence the blood flow pattern. More research will have to be done to determine if these observed vascular anomalies contribute to the formation of sigmoid sinus diverticulum (Eisenman 2011).

The success of transmastoid reconstructive surgery, the relatively few reported complications associated with this surgery and the degree of patient postoperative satisfaction, indicate that this treatment may continue to be a viable option for those whose pulsatile tinnitus has its origin in the presence of a sigmoid sinus diverticulum.

The inspiration for this article came from Shaina John, a recent graduate of Arcadia University who suffers from tinnitus. Excerpts from her senior thesis titled “Pulsatile Tinnitus Caused by a Defective Sigmoid Sinus” are included in this article.

Literature cited:

Eisenman, David J. 2013. Associate Professor, Vice-Chairman & Residency Program Director, Department of Otorhinolaryngology-Head & Neck Surgery, University of Maryland School of Medicine. Personal Interview. May 27, 2013.


Illustration Credit:
Figure 22.21 “Major veins of the Head and Neck” is used with permission to reprint courtesy of Pearson Publishing. The illustration is taken from Human Anatomy by Martini, Frederic H., Timmons, Michael J., and Tallitsch, Robert B. 7/e. ISBN 0321688155. p. 594.

Scan Credit:
Figures 1 and 2 showing a left sinus wall dehiscence with the air-on-sinus sign, is reprinted with permission of:
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Figure 3 showing a relatively small but symptomatic right sigmoid sinus diverticulum shown in a CT in the axial plane, is reprinted with permission of:
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EDU-Snippets: Bones, Art Work, Excitation, and Neurotransmission

EDU-Snippets – A column that survives because you - the members - send in your Snippets

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EDU-Snippets is a column designed to let you, the members of HAPS, share your “ways to make sure your students get it.” Since EDU-Snippets began, our members have been continuously amazed at how many teaching and demonstration ideas pop up and are easily transferred from one instructor to another through Snippets. This edition is no exception. Hopefully you will be able to utilize what our colleagues have submitted.

For this issue, EDU-Snippets received three great hands-on (or brains-on) ideas for working through some of the basic points of anatomy and physiology. While these exercises were initially designed for introductory college classes, all of the ideas presented here can easily be modified or adapted for middle school, junior high, or high school classes. This is a good selling point for your college students with children in various educational settings. Also, if you have students in advanced (or even graduate) classes, these projects can be modified or upgraded for them too! EDU-Snippets encourages you to take these ideas and run with them!

I. Identity Crisis Snippet
Karen Groh (Good Samaritan College of Nursing and Health Science, karen.groh@email.gscollege.edu) starts us off with a basic identification exercise. We need to remember that sometimes our students understand the “machine” quite well but that they do not know where the “on/off” switch is. This learning experience is valuable for that very basic hardwiring. Karen explains...

To help the students review and consolidate their knowledge of histology, I created the game “Who Am I?”, modeled on the adult game SmartAss™. We play the game during lab after the material has been covered in lecture. I divide the class into three to five teams with three to four students per team. One student acts as scorekeeper for the class while still participating as a member of a team.

On Power Point slides, I put a series of clues which the students see one at a time. The first clue is general and each clue the students see becomes more specific. After each clue, I pause for about 15 seconds and all of the teams have the option of guessing the answer. If a team guesses and answers correctly, that team scores a point. If the team is incorrect, that team is not permitted to guess again until the next round. Additional clues appear on the screen until a team has come up with the correct answer.

The following is an example of one of the “Who Am I?” clues:

- I am a type of connective tissue.
- My cells are in lacunae.
- I have no blood vessels.
- My cells are called chondrocytes.
- You can find me in the discs between your vertebrae.

The correct answer is fibrocartilage. For this particular puzzle, some of the hints may include images of the tissue type as one of the clues.

Although I don’t give points toward a grade for this game, I often bring in a small prize like candy for members of the winning team. Students have responded positively to this game, often becoming quite competitive in trying to be first to figure out the answer.

Besides being fun, the game helps students to sort out complex categories. For instance, on the question above, students will sometimes guess “bone” after the second clue, forgetting that cartilage cells are also found in lacunae. Or they will guess hyaline cartilage after the fourth clue, forgetting that there is more than one type of cartilage. Students have remarked to me that they found this game has helped them put together all of the details about histology. After all of my sections have played the game, I post the game on the learning management system for students to play on their own. Several students have told me...
they have used the game to help them study for the exam.

I recently created a similar game for biologically important molecules. I will use this new game next semester. These games are quite easy to create; each one taking me only an hour or two to put together. Variations on this game would also be useful for hormones, spinal tracts, parts of the brain, and various other anatomy and physiology topics.

II. Building an Anatomical Snippet

Christine Boudrie (Lourdes University, cboudrie@lourdes.edu) sent in a really exciting idea that can be modified in so many ways for all sorts of students from kids to grad students! And, it can be made as simple or as complex as you wish. Chris uses simple kits – which she makes herself from inexpensive (or free) and readily available objects – for building complex anatomical structures. This “kit” idea can also be expanded to help conceptualize so many topics beyond those listed here – both anatomical and physiological. Chris writes…

I have students build things during A&P. I find this activity engages them intellectually. They ask themselves, “Where IS that structure, exactly?” Or, “What does it look like and how am I going to represent it?” Projects also engage students emotionally. A project is an individualized and playful way to learn! Project building works best in a small class. I can monitor and evaluate the building of each project for a grade using a pre-established rubric. Projects can be elementary or more complex depending upon the level of anatomic detail needed for the application involved. If it is elementary, the project can serve as a quick review for students who have had exposure to the (for instance) cardiovascular system before. I can also have the students present the projects orally to demonstrate some other skill. For a more complex application, the student can use a completed project as a point of departure for explaining related physiology topics. We use simple kits made up of readily available items. During tough economic times in higher education, the materials cost nothing or next to nothing whether the institution or the student is covering the cost. Here are some examples.

1. Build A Heart ♥:
Kit = 1 paper plate + 2 red pipe cleaners + 2 blue pipe cleaners. Markers, labels, and tape as needed.
Basic objective: Represent apex/base, 3 layers of the heart wall, 4 chambers, 4 valves, intake & output vessels, oxygenated versus deoxygenated blood, and directional flow of blood.
More complex objectives: Represent the coronary circulation and the conducting system. Orally present the events of the cardiac cycle using the completed project.
Expectation: I give this project as a take-home. Structures must be complete and correct to receive full credit.
Sample Student Project:

3. Build An Alimentary Canal:
Kit = cardstock cut into long strips (2 inches wide) + Post-It tabs + paperclips + marker.
Basic objective: Represent in 3-D the hyoid, 3 single & 3 paired cartilages (and a tracheal cartilage or two.) The vocal folds and glottis can also be built on the inside of the tube with a fold of cardboard.
More complex objectives: Demonstrate the response of the larynx during swallowing. Demonstrate intubation.
Expectation: I use this as a quick-build at the beginning of the respiratory anatomy lab. We do the cutting and marking together and it goes very quickly. Subsequently, students can more easily appreciate the complexity of models and specimens of the larynx.
Sample Student Project:
III. Muscle and Joint Coordination Snippet

Hilary Engebretson (Whatcom Community College, hengebre@whatcom.ctc.edu) has a practical idea for helping the students understand the relationship between the muscles and the joints. Again, this idea can be made as simple or as complex as you wish. Hilary explains...

I teach 200-level A&P at a community college, and I use the following assignment as I am introducing muscles and the terms of movement that go along with them. I found that I had been assuming that students could easily picture the connection between a muscle shortening and the occurrence at the associated joint. Once I realized that many students were struggling, and not having their “a-ha!” moment until much too close to exam time, I came up with the following assignment:

(See example next column)

What is great about this assignment is that although the students can (and should) use the textbook and other resources to discover the needed information, they will have to think and search and cannot simply copy a paragraph or look up a direct answer from anywhere, even from the internet! I also encourage the students to go through the actions, at least mentally in order to get a picture and a feel of the muscles and joints in action.

IV. And We Hope You Will....

Keep those cards and letters coming! Thank you all for your EDU-Snippet contributions. The influx of Snippets has been good! Please keep it up because more are always needed! Your ideas are tremendous! If you have thoughts or ideas, or any interesting ways to help our students understand anatomy and physiology, EDU-Snippets would love to hear from you! Once again, EDU-Snippets encourages new submitters to submit – and regulars to keep on submitting!

For the next issue of the HAPS-Educator, send your EDU-Snippet experiences and ideas to biology@ctos.com as soon as possible. You will also find a reminder on the HAPS-L list. Plan ahead. You can even submit your ideas now and maybe next issue you too will see your EDU-Snippet in print!

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**Muscle/Joint Action Assignment**

The purpose of this assignment is to help you learn basic terms of kinesiology and to help you become comfortable using those terms when referring to actions used during common body movements.

This assignment is due on __________. It should be typed and headed with your name, class info, and instructor’s name. (For my classes this assignment is worth 10 points. Of course, other instructors may choose a different point value.)

1. Think of an action that you perform a lot in your daily life
   a. You are looking for a definable action that requires movement in more than one direction to complete
   b. Consider...pedaling a bike, opening a door, rowing a kayak...etc.
2. Name the synovial joint or joints involved in that action
3. Separate that action into steps
   a. Notice that each different direction of movement will require a separate step, as it requires different muscles to execute
   b. Be sure to use correct kinesiology terms to describe each step
4. Name the muscles that contract at each step of the action
5. Use the following example to help you get started...

I try to keep the sample action short so that the students do not feel as if I have presented them with a magic formula.

**Action:** swinging and releasing a bowling ball

**Joint(s) involved:** glenohumeral joint and acromioclavicular joint (shoulder)

**Steps:**

1. Shoulder is (hyper) extended to move humerus posteriorly
   a. Latissimus dorsi and posterior fibers of deltoid contract as the prime movers of the humerus at the glenohumeral joint
   b. Teres major and long head of triceps brachii also contract as the secondary movers of the humerus at the glenohumeral joint
   c. Rhomboid major and rhomboid minor contract to rotate the scapula at the acromioclavicular joint inferiorly to assist movement of arm posteriorly
2. Shoulder is flexed to move humerus anteriorly (and release ball)
   a. Pectoralis major and anterior fibers of deltoid contract as the prime movers of the humerus at the glenohumeral joint
   b. Coracobrachialis also contracts as a secondary mover of the humerus at the glenohumeral joint
3. Shoulder is extended to return humerus back to resting position at the side of the body
   a. Latissimus dorsi and posterior fibers of deltoid contract as the prime movers (agonists) of the humerus at the glenohumeral joint
   b. Teres major and long head of triceps brachii also contract as the secondary movers of the humerus at the glenohumeral joint
   c. Rhomboid major and rhomboid minor contract to rotate the scapula at the acromioclavicular joint inferiorly to assist movement of arm posteriorly
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