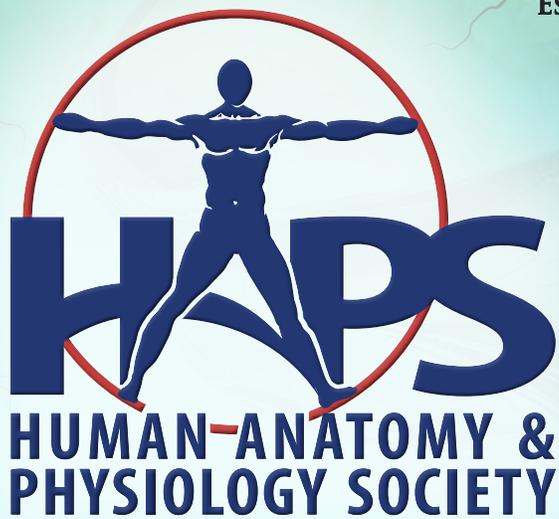


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Letter to the Editor

Student Justification for MCQ

New Treatment for Rabies

Sickle Cell Trait

Arthritis Simulation Activity

Challenging Courses and Performance Based Funding

Teaching Skeletal Anatomy

Ultrasonography in Anatomical Education

Benefits of Faculty-Authored Course Materials

Promoting Excellence in the Teaching of Human Anatomy & Physiology

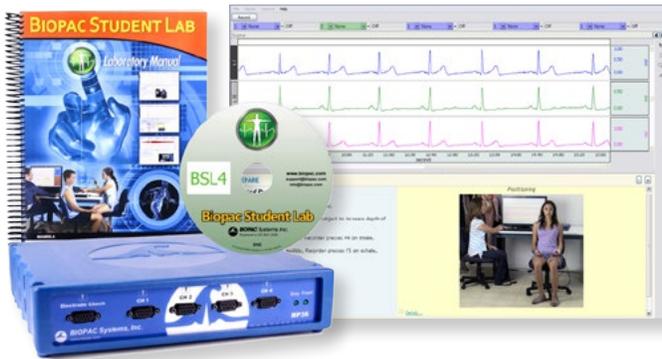


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• SPRING 2017 HAPS EDUCATOR TABLE OF CONTENTS •

LETTER TO THE EDITOR

The Tyrannical Demands of Statistical Power

Jon Jackson, PhD5

EDUCATIONAL RESEARCH

Student Justification of Responses to Multiple-Choice Questions

By: *Jacqueline A. Carnegie, PhD and John J. Leddy, PhD*6

CURRENT TOPICS IN ANATOMY AND PHYSIOLOGY

New Treatment for Rabies Uses Short Interfering RNAs (siRNAs) to Silence The Post Transcriptional

RNA of the Rabies Virus

By: *Sarah Cooper, MEd and Jessica Watson*17

Sickle Cell Trait Is Not Always Asymptomatic

By: *Tracy L. Ediger, PhD*25

PERSPECTIVES ON TEACHING

Analysis of an Arthritis Simulation Activity Developed as a Laboratory Exercise for Allied Health Students

By: *Anna E. O'Connor and Carol A. Britson*30

Are Challenging Anatomy and Physiology Courses Detrimental to Colleges at a Time of Performance-based Funding?

By: *Peter Reuter, MD, PhD, Valerie Weiss, MD, MS*40

Boning Up on Active Learning Exercises for Teaching Skeletal System Anatomy: Pre-Class Accountability is Key

By: *Justin Shaffer, PhD*44

From Conference to Classroom: Ultrasonography in Anatomical Education

By: *Theodore Smith, MS*48

The Benefits of Faculty-Authored Course Materials for Students and Faculty

By: *Peter Reuter, MD, PhD, Valerie Weiss, MD, MS*51

Addendum to the December 2016 edition of the HAPS Educator:

A methodology of Optimizing Abstraction in Anatomy and Physiology Infograms: Abbreviations and Acronyms By: Vasiliy Kolchenko, MD/PhD and Rachel Offer, was supported by the National Science Foundation under Grant #1245655.

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Letter to the Editor

The Tyrannical Demands of Statistical Power

Jon Jackson, PhD — Columbus, OH

The tyrannical demands of statistical power are uncompromising. If one hopes to show a “treatment effect” or the strong association of two events with one another, or conclusively rule out the same, then the sample sizes in a given study must be of sufficient stature to ensure that garden-variety type I and type II statistical errors are not made for lack of effort.

Kerry Hull and I (with the guidance of Rachel Hopp, Audra Schaefer, and Sam Wilson), have been working on collecting responses to a survey that seeks to better understand pre-requisite courses and their connection with academic retention (i.e., people staying in their programs of study). Although the demographic data that HAPS routinely collects with these types of surveys is useful and interesting (in that it shows that HAPSters teach a lot of different types and levels of courses), we have not reached a sufficient sample size to allow us to reach any definitive conclusions with the necessary statistical power. Bottom line: we need YOU! If you haven't already done so, we invite you to visit the survey website at <http://survey.ubishops.ca/ls/index.php/742277/lang-en>. To fill out the survey, you need to do a little prep work: you need to make a table of As, Bs, etc., given out in each of your A&P 1(or A&P2, anatomy alone, physiology alone, etc.) courses over the past few years. It may take a bit of digging to find your historic grade data — but we want it. Once you get to the site, you will note that we're using a different kind of survey engine, and it will take another 10-20 minutes to get all of your data entered in. But there's a reward: once you've entered your survey data, if you're interested, you can leave your name and email in the comments section of the survey for a chance to be one of 6 lucky people who will win \$50 Amazon gift cards. We'll start drawing on April 25th, and draw on the 25th of each month through the next 5 months of spring and summer.

What we're trying to do with this survey is get information from as many HAPS instructors about as many iterations of their many and different courses as possible. Why? We want to show conclusively with solid data, 95% confidence intervals, and sufficient statistical power, exactly what typical D-F-W rates are across the world of all A&P courses. And if we listen to the barking demands of sample size and statistical power, we might get enough responses to allow us to parse out the effects of having pre-requisites on student success in

A&P courses. Effect sizes with Cohen's d attached to them. Heck, with enough responses, we might even be able to determine which type of courses impact student success in A&P (and vice versa). Wouldn't it be nice? (to quote the Beach Boys).

Alas, each student does not represent a unique sample. According to how the survey was designed and constructed, each iteration of a COURSE represents a unique sample. In this way, if you've taught a single section of A&P 1 each fall for 8 years, and have entered 8 years' worth of data on that course, our sample is $n+8$ richer. But we need a rather robust sample size to have the statistical power to make scientifically valid assertions from what might otherwise seem to be subtle differences. Such is the tyranny of statistical power. But I hope you join in the fight to help with the battle by joining forces, not in resisting the power, but rather, by adding your data to the database, and thereby increasing the power of the work that HAPS is doing. Thanks!

Don't hesitate to get in touch with me if you have questions about the survey or about the mechanics of entering your data.

About the author

Jon Jackson, PhD is the Western Regional Director of HAPS, and a member of the Pre-Requisite Survey Task Force. He is currently Visiting Professor of Anatomy at The Ohio State University College of Medicine, where he teaches Gross Anatomy to Dental, Graduate, and Medical students. He is also a Fellow in the History and Philosophy of Science at the Institute for Philosophy in Public Life at the University of North Dakota.

Student Justification of Responses to Multiple-Choice Questions

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Abstract

The large sizes of many undergraduate classes in anatomy and physiology necessitates that summative evaluation rely extensively on multiple-choice questions (MCQs). Student reasoning while answering selected physiology-based MCQs was explored using a second question in which students were asked to justify their answer. The questions explored concepts pertaining to Rh factor during pregnancy, dead space and the regulation of respiration, and alkalosis plus possible compensation. While 48%-60% of students answered their MCQ correctly, only 12-41% of correct respondents could fully justify their responses. Analysis of the written answers identified important student misconceptions and a potentially misleading component in one question stem. While the current climate of heavy teaching loads and large classes deters evaluation of students' written work, it is important to find ways to sample their thinking. This allows modification of teaching approaches and the design of discriminating MCQs that provide optimal learning combined with valid student assessment.

Key Words: assessment, MCQ, two-tier question, teaching, justification

Introduction

The large sizes of many undergraduate medical and health sciences classes in anatomy and physiology necessitate that summative evaluation of students relies extensively on the use of multiple choice questions (MCQs) to test recall and comprehension of fact-dense basic science content (Lowe 1991, Pepple *et al.* 2010, Roediger III and Marsh 2005, Tarrant *et al.* 2009). Unfortunately, some students prepare for these exams by using primarily surface study approaches, such as listing and memorizing many pieces of factual information, without obtaining a deep understanding of concept linkages (Marton and Säljö 1976, Scouller 1998). They then look to recognize the correct answer to each MCQ from a list of suggested responses when writing the summative exam. Examination answer sheets are subsequently marked by computer and professors are provided with statistical data pertaining to question difficulty and discrimination as well as exam reliability (Lowe 1991). However, while this data includes the percent of students selecting each of the answer choices provided, professors do not obtain feedback regarding the reasoning employed by each student when choosing each of their answers (Tamir 1990). Hence, for a given question, an instructor will know that a certain percentage of students did not choose the correct answer, but not why their reasoning led them to pick one of the distracters over the correct response. A final complicating factor exists because the correct answer, by necessity, has to be included in the list of choices. This means that some students who do not know the right answer may still select it with a lucky guess, either from the original set of four to five possibilities or from a list that they have been able to shorten to two or three candidates by eliminating obvious distracters (Harper 2003, Kuechler and Simkin 2010, Tamir 1990).

Physiology is a discipline that not only requires students to assimilate a considerable volume of factual information, but also to link concepts as they construct a scaffold of related course content. These scaffolds need to be assembled in an orderly and accurate manner, so that students can subsequently retrieve and correctly associate these facts and concepts during exams when explaining how the various body systems function and how they adjust their level of activity in order to maintain body homeostasis (Kirschner 2002, Kirschner *et al.* 2006, Sweller *et al.* 1998, Terrell 2006). The purpose of this study was to explore student reasoning when answering selected physiology MCQs that asked them to correctly retrieve and link relevant pieces of information. This was accomplished by extending the question to a two-tier format in which an open-ended part 2 required students to provide written justification for the answer selected in part 1, the original MCQ (Amir *et al.* 1987, Tamir 1990). It was hypothesized that part 2 would distinguish between students who utilized primarily surface learning or a lucky guess to arrive at the correct answer for part 1 from those students who acquired a more thorough understanding of course content via the use of deeper learning approaches (Crowe *et al.* 2008, Scouller 1998).

Needless to say, only certain types of MCQs lend themselves to this format of questioning. They have to be cognitively higher-level questions (Anderson *et al.* 2001, Harper 2003, Tamir 1990) that ask students to evaluate a given physiological situation and determine the appropriate body response by linking and applying several previously-learned physiological facts and/or principles in context. The follow-up question was designed to provide insight as to the patterns of thinking

continued on next page

employed by students, either when choosing the correct response or when being led astray by a misconception (Michael 2002).

METHODS

Student populations. This study involved Faculty of Health Sciences and Faculty of Science undergraduate students studying anatomy and physiology (ANP) at the University of Ottawa. Three student populations in three different ANP courses (ANP1101, ANP1303 and ANP1304) took part in this study, as summarized in Table 1. The three class populations consisted of combinations of Faculty of Health Sciences students enrolled in the Bachelor of Science in Nursing, Bachelor of Human Kinetics and Bachelor of Health Sciences programs as well as Faculty of Science students studying for their Bachelor's degree in Biomedical Sciences. All students had to successfully complete ANP1101 before continuing on to take ANP1303 and, finally, ANP1304. The collection of student-outcome-related data for this research project was approved by the University of Ottawa Human Ethics Committee (File H09-06-10B).

The two-part examination question.

The final summative examinations for these courses consisted of a mix of different types of questions. MCQs comprised 67-81% of each exam, with the remaining questions requiring some written work (fill-in-the-blank and diagram labeling, provision of definitions and some very short-answer questions in which physiological processes had to be explained). Each exam also included a single content-specific two-tier question (Table 1) in which part 1 was an MCQ and part 2 was an open-ended question that asked the student to construct a concise justification for the answer selected in part 1 (Table 2). For ANP1101, the two-tier question targeted a blood-related topic (Rh factor) while for ANP1303 and ANP1304, respectively, the two-tiered questions targeted aspects of respiratory system

regulation (dead space volume) and the integration of renal and respiratory function in the regulation of blood pH.

Rh factor lent itself well to the two-step approach because it provided a clinical example of the application of basic science knowledge while requiring students to distinguish antibody production related to Rh factor from that occurring in the ABO blood system. The question on dead space used a physiological example, rather than a clinical scenario, but was designed to direct students toward recognizing the tube as an additional source of dead space and, through their understanding of the regulation of lung ventilation, realizing that the respiratory system would compensate by adjusting depth of breathing.

For the final ANP course, where students are learning to link concepts relating to different organ systems, a question pertaining to acidosis or alkalosis was ideal because it not only has significant clinical application, but also necessitated integration and application of physiological concepts pertaining the cardiovascular, respiratory and renal systems. This question required students to recognize a blood pH above 7.45 as alkalosis and to then interpret the blood CO₂ and bicarbonate levels (normal values supplied) in terms of identifying the body system (respiratory) causing the alkalosis and determining whether or not the other body system (renal) had activated a compensatory response.

Students were required to answer both part 1 and part 2, although the two parts were corrected separately. Part 1 was marked by computer, along with the rest of the MCQs, and so provided data on the percent of students selecting the correct answer (question difficulty) as well as the discrimination, a parameter calculated as the ratio of higher-scoring versus the lower-scoring students choosing the correct answer section for each question (Lowe 1991, Sevenair and Burkett 1988). Part 2 was hand-corrected anonymously by one of the authors (JC) using a standardized marking grid, with the students awarded a mark of 0, 0.5 or 1 (out of 1) for their answer.

Table 1. Student populations and ANP course descriptions.

Course Code	Number of Students	Course Description	Exam Question Group
ANP1101	188	Introduction to Basic Cell Biology, Biochemistry, Anatomy & Physiology of Neurons, Muscles & Blood	Rh Factor
ANP1303	179	Systems I: Anatomy & Physiology of the Endocrine, Cardiovascular, Lymphatic & Respiratory Systems	Dead Space
ANP1304	202	Systems II: Basics of Nutrition, Anatomy & Physiology of the Digestive, Reproductive & Renal Systems	Acid-Base

continued on next page

Table 2. The two-part questions (correct answers for Part 1 indicated in bold).

Exam Question Group	Part 1 (1 mark)	Part 2 (1 mark)
Rh Factor	<p>The father is Rh⁻ and the mother is Rh⁺. They have had three children without adverse problems due to the Rh factor. The mother is pregnant again. In terms of the Rh factor, the risk to the fetus now within the uterus:</p> <p>A. is less than before B. is greater than before C. never was a problem D. is the same and remains relatively moderate</p>	In one sentence, justify your answer to question 1.
Dead Space	<p>Julie decides to try to get into the record books by sitting under water for as long as possible. She fixes a mouthpiece to a long plastic tube, weights herself down and sits at the bottom of an 8-foot pool with the top of the plastic tube 5 cm above the water. After a few minutes, she finds that:</p> <p>A. she is breathing more deeply B. she is able to breathe more shallowly C. her depth and rate of breathing are the same as they were when she was above water D. her tidal volume has decreased</p>	In no more than two sentences, justify your answer to question 1.
Acid-Base	<p>A person whose blood pH is 7.47, whose pCO₂ is 31 mm Hg (normal range = 35-45 mm Hg) and whose levels of bicarbonate ion in arterial blood are 23 mEq/L (normal range = 22-26 mEq/L) is in:</p> <p>A. compensated metabolic alkalosis B. uncompensated respiratory acidosis C. uncompensated respiratory alkalosis D. uncompensated metabolic acidosis E. uncompensated metabolic alkalosis</p>	For one mark, justify your answer to question 1 in the space below. Confine yourself to two sentences.

Data collection and analysis.

Student outcomes on each of part 1 and part 2, as well as details of their responses to part 2 (correct concepts as well as key misconceptions) were tabulated, sorted and analyzed using Microsoft Excel. Comparisons of student outcomes when answering part 2 were made between students who chose the correct answer versus those who chose an incorrect answer for part 1. Answers to part 2 were also evaluated for their rate of inclusion of key physiological concepts related to the question or of misconceptions that may have led certain students to choose an incorrect answer for part 1.

RESULTS

A comparison of the three student populations revealed that 47.9 to 59.9% of students chose the correct answer for the multiple-choice portion (part 1) of their respective two-part questions (Table 3, Figure 1). With regard to the influence of the distractors for the Rh factor question, the remaining

students tended to favor distractor B or distractor D with only 4 (2.13%) of the 188 students considering the possibility of a reduced fetal risk of Rh-related problems (Table 3). For the question on dead space and lung ventilation, those students who did not select the correct answer were similarly drawn to each of the three distractors regarding rate and/or depth of breathing (Table 3). Finally, for the students answering the question on acid-base disorders, comparable numbers of students erroneously evaluated the clinical situation as compensated or uncompensated metabolic (rather than respiratory) alkalosis, while far fewer students made an error involving the recognition of a pH of 7.47 as being alkaline (distractors B and D, Table 3).

Discrimination indices for the MCQs in these exams ranged from 0.04 to 0.71 with the lower indices often, but not always, linking to easier MCQs that were answered correctly by almost all students. The discrimination indices for the three MCQs targeted in the current study were 0.40 (Rh factor), 0.04 (dead space) and 0.25 (acid-base disorders), indicating that the Rh factor and acid-base balance MCQs were answered correctly

continued on next page

Table 3. The distribution of student responses expressed as a percent of each student population.

Group	Question	Choices	Selected by (%)
Rh factor (n=188)	The father is Rh ⁻ and the mother is Rh ⁺ . They have had three children without adverse problems due to the Rh factor. The mother is pregnant again. In terms of the Rh factor, the risk to the fetus now within the uterus:	A. is less than before B. is greater than before C. never was a problem D. is the same and remains relatively moderate	2.1 23.4 47.9 26.6
Dead space (n=179)	Julie decides to try to get into the record books by sitting under water for as long as possible. She fixes a mouthpiece to a long plastic tube, weights herself down and sits at the bottom of an 8-foot pool with the top of the plastic tube 5 cm above the water. After a few minutes, she finds that:	A. she is breathing more deeply B. she is able to breathe more shallowly C. her depth and rate of breathing are the same as they were when she was above water D. her tidal volume has decreased	52.0 15.6 14.0 18.4
Acid-Base (n=202)	A person whose blood pH is 7.47, whose pCO ₂ is 31 mm Hg (normal range = 35-45 mm Hg) and whose levels of bicarbonate ion in arterial blood are 23 mEq/L (normal range = 22-26 mEq/L) is in:	A. compensated metabolic alkalosis B. uncompensated respiratory acidosis C. uncompensated respiratory alkalosis D. uncompensated metabolic acidosis E. uncompensated metabolic alkalosis	16.3 5.9 59.9 2.5 13.4

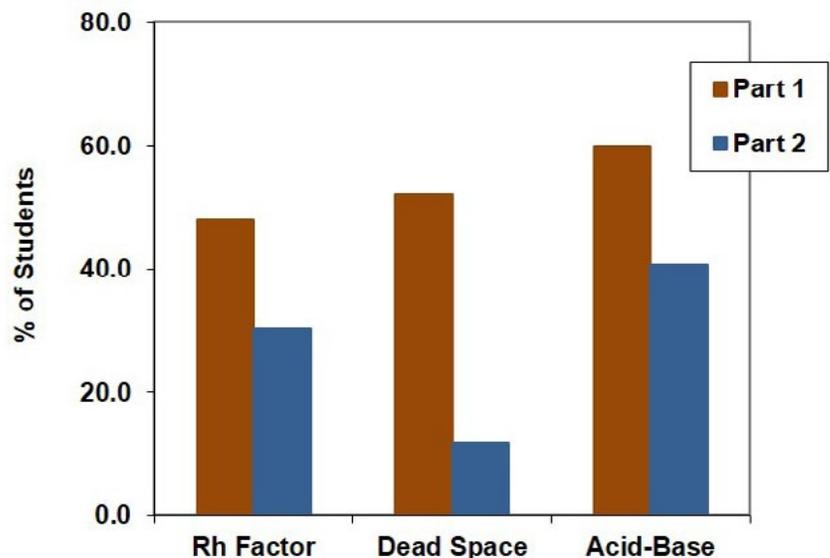


Figure 1. Student performance on the two-tier questions. Data shows percent of students who obtained full marks on the MCQ (part 1) and the justification of their answer (part 2), respectively, for the Rh factor (n = 188), dead space (n = 179) and acid-base (n = 202) questions.

more frequently by the stronger students while the dead space MCQ did not really distinguish between the stronger and weaker student populations.

Interestingly, students did not tend to perform as well when asked to provide written justification (part 2) for their correct answer to the MCQ (part 1). Only 11.7 to 40.6% of students were awarded the full mark for this part of the exam question and the provision of an accurate justification appeared to be particularly challenging for the students answering the question on dead space (Figure 1). The corresponding class averages (out of 1) for the justification of answers (part 2) on Rh factor, dead space and acid-base disorders were (mean \pm SD): 0.36 ± 0.45 ($n = 188$), 0.30 ± 0.35 ($n = 179$) and 0.56 ± 0.41 ($n = 202$), respectively. Finally, there was a small number of students who chose the correct answer for part 1, but were unable to even attempt a justification of that choice and left the answer space for part 2 of the question completely blank (1 student each for the Rh Factor and Dead Space groups and 6 students for the group answering on acid-base disorders).

A closer scrutiny of the subpopulation of students who answered part 1 correctly revealed that, while some of those students could justify their choice completely, others were completely unable to apply physiological concepts in support of the answer they had chosen (Figure 2). The Rh factor and acid-base disorder student subpopulations had similar positive outcomes in that at least 60% of those students who chose the correct answer for part 1 also received the full mark for their written answer to part 2. However, within those same two populations, 20.0% of the Rh Factor and 12.4% of the Acid-Base students scored 0/1 in the justification section of this question. The results were more disappointing for the Dead Space students. Only 22.6% of Dead Space students who answered part 1 correctly obtained the full mark for their written answer to part 2. This dismal outcome is somewhat ameliorated by the fact that 47% of these students did obtain 0.5/1, indicating that at least some of their reasoning was presented correctly. However, it also meant that 31.2% of Dead Space students scored 0 on this section of the exam question.

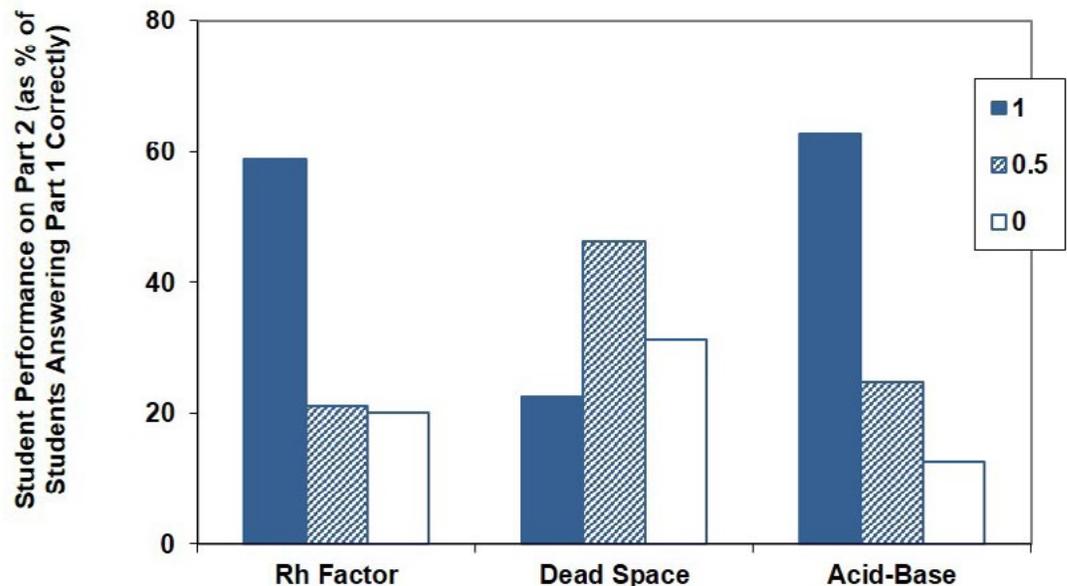


Figure 2. Student performance on part 2 of the 2-part question expressed as a percent of those students who answered part 1 correctly (Rh Factor: $n = 90$, Dead Space: $n = 93$ and Acid-Base: $n = 121$). Students could obtain 1/1, 0.5/1 or 0 for their answer to part 2.

The frequency with which key components that could have contributed to a complete answer to each of these questions were omitted from all student responses is summarized in Table 4. The first three model components listed for the Rh factor question are interrelated and, indeed, not all three had to be present in a good answer. However, at least one of those model components had to be mentioned in order to have a chance at receiving the full mark for that answer. The fourth component was not viewed as an essential component of a correct answer, but it did represent a fact relating to the inheritance of Rh factor that, if included in a student's answer, had the potential ability to raise a poorly-worded or incomplete answer to a higher score.

With regard to the other two questions (dead space and acid-base balance), the model components listed in table 4 (two and three, respectively) really were required components of a complete answer. The results for the dead space question were disappointing. Less than 5% of students recognized the tube as an applied example of increased dead space volume and only 15% of students linked reduced lung ventilation with a build-up of CO_2 gas leading to a resultant increase in the rate and depth of breathing. The majority of students answering the acid-base question recognized the clinical condition as alkalosis, but less than half of them indicated that it was caused by low blood CO_2 levels and only about one-third of them identified a lack of compensation for the alkalosis via metabolism (bicarbonate).

continued on next page

Table 4. Per cent of students who omitted key facts when writing the justification portion of their answer.

<i>Rh Factor Group: Question on Rh factor during pregnancy</i>	
Omission	% of Students
Mother will not produce antibodies to Rh factor	73.9
Mother has Rh antigens on her red blood cells	91.5
We need to be concerned only if mother is Rh-	82.4
The fetus can be either Rh+ or Rh-	80.9
<i>Dead Space Group: Julie sitting underwater and breathing through a tube</i>	
Omission	% of Students
The tube is an additional source of dead space volume	95.5
There will be a build-up of CO ₂ that will drive a change in breathing	84.9
<i>Acid-Base Group: Question on uncompensated respiratory alkalosis</i>	
Omission	% of Students
The person is in alkalosis	16.3
Low levels of CO ₂ are the cause of the alkalosis	53.5
This is uncompensated because bicarbonate levels are normal	64.4

Table 5. Prevalence of misconceptions among students indicative of a misunderstanding of some basic physiological concepts.

<i>Rh Factor Group: Question on Rh factor during pregnancy</i>	
Misconceptions	% of Students
A factor exists called Rh-	11.7
An Rh+ mother will produce antibodies to Rh factors	13.3
Confusion between an antigen and an antibody	3.2
<i>Dead Space Group: Julie sitting underwater and breathing through a tube</i>	
Misconceptions	% of Students
Decreased compliance due to being underwater will result in uncompensated reduction in ventilation.	29.1
Increased airflow resistance due to breathing tube will result in uncompensated reduction in ventilation.	16.8
Lack of oxygen seen as the major force driving an increase in ventilation.	16.2
<i>Acid-Base Group: Question on uncompensated respiratory alkalosis</i>	
Misconceptions	% of Students
Alkalosis caused by metabolism rather than by respiration	12.9
Do not distinguish between cause and possible compensation	59.4
Associate the pH value with acidosis rather than alkalosis	4.0

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Qualitative analysis of the written answers also allowed the identification of fundamental misconceptions expressed by some students (Table 5). Within the group answering the Rh Factor question, close to 12% of students misunderstood the nomenclature pertaining to Rh factor and thought that there exists a second factor referred to as “Rh-negative” factor. While only a very small number of students (3.2%) confused antigens and antibodies, four times that number thought erroneously that a mother who expresses the Rh antigen on her red blood cell is capable of producing antibodies to that same antigen.

Within the group answering the Dead Space question, a proportion of students were misled in their interpretation of the regulation of lung ventilation by the fact that Julie was underwater and that she was breathing through a tubular

structure. Hence, close to 30% of those students felt that lung ventilation would decrease in an uncompensated fashion simply because the pressure of the water would decrease her thoracic compliance. The key role of blood CO₂ levels in driving respiration was ignored by 16.2% of students who suggested, instead, that a lack of oxygen would cause Julie to breathe more deeply. A similar proportion of students incorrectly viewed the tube as an important source of resistance to airflow, despite its large internal diameter.

Within the group answering the Acid-Base question, close to 13% of students were unable to see the reduced blood CO₂ levels as a potential cause of alkalosis and almost 60% of students did not recognize a blood pH imbalance to potentially reflect two sequential processes: the initial cause of the alkalosis and a possible attempt by the body to correct

Table 6. Distribution of part 1 choices by those students who showed sufficient correct reasoning in the justification section (part 2) to earn 0.5 marks (correct answers indicated in bold)

<i>Rh Factor Group: Question on Rh factor during pregnancy (n = 23)</i>	
Choices	% of Students
A. The risk to the fetus is less than before	0
B. The risk to the fetus is greater than before	8.7
C. The risk to the fetus never was a problem	82.6
D. The risk to the fetus is the same and remains relatively moderate	8.7
<i>Dead Space Group: Julie sitting underwater and breathing through a tube (n = 65)</i>	
Choices	% of Students
A. Julie is breathing more deeply	66.2
B. Julie is able to breathe more shallowly	10.8
C. Julie’s depth and rate of breathing are the same as when above water	1.5
D. Julie’s tidal volume has decreased	21.5
<i>Acid-Base Group: Question on uncompensated respiratory alkalosis (n = 64)</i>	
Choices	% of Students
A. The patient is in compensated metabolic alkalosis	21.9
B. The patient is in uncompensated respiratory acidosis	4.7
C. The patient is in uncompensated respiratory alkalosis	46.9
D. The patient is in uncompensated metabolic acidosis	0
E. The patient is in uncompensated metabolic alkalosis	23.4
No answer was selected by the student	3.1

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that pH imbalance (compensation). While the number is small, it should still be noted that 4% of students who were completing their fourth course in anatomy and physiology at the time of writing this exam actually misread a blood pH of 7.47 as acidosis, rather than alkalosis.

There was a small number of students in each group (Table 6) who made an incorrect choice when completing the multiple-choice section of their question, yet showed some correct reasoning when answering part B (obtained a score of 0.5/1). Of the 4 students who chose either B or D, instead of C, for the question dealing with Rh factor, their answers included some scattered relevant data (mixing of maternal and fetal blood occurs only at birth, the fetus can be Rh⁺ or Rh⁻ and/or one only needs to worry if the mother is Rh⁻), but not one of them was able to coordinate enough relevant pieces of information arrive at the conclusion that there was never a risk to the fetus (choice C). However, the inclusion of some relevant pieces of information combined with the fact that none of these four answers contained any of the basic misconceptions summarized in Table 5, allowed a score of 0.5/1 to be awarded.

With regard to the question on dead space, many students who chose B (Table 6) thought that Julie would simply breathe more shallowly because the pressure of the water pushing on her chest from the outside would make it more difficult for her to ventilate her lungs. They did not credit the body with making an adjustment so as to ensure adequate maintenance of lung ventilation, and uniformly did not suggest that a build-up CO₂ gas in the bloodstream (due to the increased length of the conducting zone) plays a key regulatory role in depth of breathing. Likewise, the 14 students who chose the similar response, D, that Julie's tidal volume would decrease, displayed much of the same reasoning as those who chose B. Eleven of these students suggested that the work of breathing would be increased but did not address how lung ventilation would be affected while only one introduced the term of dead space volume, only one suggested that there was a build-up of CO₂ in the bloodstream, and three were distracted by the tube as a source of resistance to airflow.

The final question on acid-base disorders (uncompensated respiratory alkalosis) required that students recognize the alkaline state of the blood, identify which system (respiratory or body metabolism) was responsible for the alkalosis and determine if the other system, the one not responsible for causing the shift in blood pH, was being activated to try to correct the pH imbalance. With very few exceptions, the students who scored 0.5/1 on this question did recognize a blood pH of 7.47 as an alkaline condition. However, even though they were informed within the question that blood CO₂ levels were low, those students who chose answers A or E (Table 6) uniformly did not recognize these low CO₂ levels as the cause of the alkalosis. Furthermore, many of them had difficulty distinguishing between two sequential events: an initial event that caused the shift in blood pH followed by possible compensation by the other system to try to restore pH homeostasis.

DISCUSSION

The consistently lower performance by students in part 2 (the justification part) of the questions assessed in the current study is not surprising. Tamir (1990) presented the argument that MCQs tend to overestimate student knowledge because points can be acquired through lucky and/or strategic guessing while written answers require students to clearly formulate arguments in favor of a particular answer choice. Zimmerman and Williams (2003) also suggested that the reliability of MCQ test outcomes is negatively impacted by guessing and that the extent of this impact is inversely proportional to the size of the exam and the number of answer choices per question.

Indeed, students can follow a number of different paths to arrive at the correct answer for an MCQ. Some of them will be fully cognizant of the basic physiologic concepts pertaining to that question and will recognize the correct answer with confidence. Many of those students would then have the necessary knowledge and understanding to be able to fully justify their MCQ answer choice. On the other hand, those who chose the correct response in part 1, but received only a partial score for part 2 may have been struggling to remember some of the key concepts pertaining to that physiological scenario, or, were aware of the concepts, but simply unable to express their thoughts in a coherent and complete manner (Frery *et al.* 1977, Frery 1980). Often undergraduate students find the transition from answering MCQs that assess primarily recall of factual information to answering questions that ask them to actively synthesize a coherent written answer that demonstrates their ability to apply and link appropriate basic science principles to be a significant hurdle (Bailin 2002, Crowe *et al.* 2008, Zoller 1993).

Indeed, the results of this research emphasize the importance of providing opportunities for students to practice developing explanatory answers to content-based questions before they are challenged to do so on summative exams. To address that deficiency, feedback-oriented online exercises can be used, even with classes with large enrollments, to provide formative opportunities for practicing the selection of answer elements and using them to build well-organized responses to physiologically-based short essay questions (Carnegie, 2015).

Within the current study, an example of misunderstanding a key concept would be incorrectly ascribing the major role of regulating lung ventilation to oxygen, rather than carbon dioxide when justifying a response to the dead space volume question. Related to the question on acid-base balance, an example of the omission of a key piece of information in the answer construct would be not mentioning that the alkalosis was caused by abnormally low blood levels of CO₂. Finally, those students who selected the correct answer in part 1, but obtained 0 in part 2, either because an answer was not attempted or the answer that was provided included no relevant and useful information, likely represent the students who were able to obtain the correct answer to the MCQ only

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by guessing. This may have been completely random guessing (unable to eliminate any of the distracters; Frary 1977) or strategic guessing after some of the distracters had been discarded through careful thinking (Frary 1980, Harper 2003, Kuechler and Simkin 2010; Tarrant *et al.* 2009).

Each of these questions required more than the knowledge of just a single physiological fact. Rather, students needed to assemble and link a number of related pieces of information and then apply that knowledge within the confines of a physiological or clinical scenario. This type of assessment matches well with some of the learning characteristics of adult students who have been described as learning best when that knowledge is task-oriented rather than simple memorization (Knowles & Associates 1984, Pratt 1993). And certainly these are questions that required a higher level of cognitive function (Anderson *et al.* 2001). For example, the question that provided the greatest justification challenge to students was the one involving Julie sitting underwater and breathing through a tube. In order to arrive at a correct answer, students needed to first recognize that the tube added to the dead space volume of the respiratory system. Secondly, they needed to realize that, given that the dead space volume had increased, less gas exchange would occur if the depth of breathing was not adjusted, leading to both a reduction in blood O₂ levels as well as a rise in blood CO₂. Finally, they had to remember that it is the blood level of CO₂, not O₂, that drives lung ventilation and that the body will not simply let this gas accumulate in the bloodstream. Rather, an increase in the depth of breathing would be stimulated to compensate for the lengthened conducting zone so that the body could continue to maintain blood gas homeostasis.

Differences in student approaches and attitudes toward learning likely contributed to the variable outcomes for the justification portion of the two-tier questions. Learning comprises three events: input, processing and output. It is the middle event, the processing, that is of interest because of its effect on the quality of the educational experience and of the quantity and quality of the output (Biggs 1979). At opposite ends of the spectrum, there are deep learners and there are surface learners (Entwistle 2001, Marton and Säljö 1976). The former actively engage with the course content in an effort to maximize their comprehension while the latter tend to memorize isolated pieces of information and recognize key words without really understanding the interrelationships (Entwistle 2001). Deep learners would have been able to fully explain the orderly progression of events that would have led Julie to breathe more deeply so as to adequately clear CO₂. On the other hand, the surface learners may have been able to recognize that two of the choices described similar reductions in the depth of breathing and therefore eliminate them. This would allow them to improve their chances of choosing a correct answer because they had narrowed the field by half.

A third type of learner has been proposed, the strategic learner (Biggs 1979). This learner is achievement-oriented and

gears the learning to be done around anticipated milestones to be achieved when answering examination questions. This learner will have strong, short-term recall of factual information deemed to be important for the exam, but will not be as able as the deep learner to show comprehensive understanding as to how these facts are interrelated or apply their newly learned information in a context outside that which has been learned in the classroom (Biggs 1979, Entwistle 2001). The strategic learner may fill the space in part 2 with factual information related to lung ventilation and regulation of breathing, but will have difficulty incorporating the breathing tube, something that was not discussed in class, into the evaluation of the problem. This learner will likely follow the tangents of uncompensated effects of water pressure or airway resistance on lung ventilation because those are concepts that were covered in class. But neither the strategic learner nor surface learner will be likely to see the breathing tube as contributing additional dead space volume.

During exam writing, the elimination of effective distracters associated with a given MCQ has the potential to require as much higher-level thinking as the recognition of the correct answer for a given question (Harper 2003). Truly effective distracters must relate sufficiently to the question that a student must take a moment to reason through why that particular choice is not correct. Indeed, it has been suggested that distracters that are chosen by less than 5% of students are ineffective and should either be rewritten or discarded (Tarrant *et al.* 2009). While the distractors for the dead space question all functioned well, the Rh factor and acid-base questions each included one ineffective distractor and those distractors will be edited based on feedback obtained in part 2 with regard to common student misconceptions. However, it is equally important that distracters or elements of the question stem not confuse students during exam writing by introducing information that has some physiological value and detracts from the concept being examined.

The Dead Space group students who were distracted by the potential for increased atmospheric pressure on Julie's chest due to the fact that she was underwater were not entirely wrong and this distraction may have contributed to the low discrimination index for that MCQ. They had also been taught that pressure increases by one full atmosphere (760 mm Hg) for every 33 feet one travels below sea level in water (Marieb and Hoehn 2016). The recognition of the potential for the scenario to confuse as revealed by the feedback from students has allowed the question to be revised so that the child breathing through the tube is no longer underwater, but rather hiding in a wooden box with his breathing tube extending via a hole in the side (Carnegie 2009). Hence the potential exists for MCQs to be improved, both by the revision of ineffective distracters as well as by the elimination of extraneous sources of confusion.

Misconceptions are disturbing to instructors because, by their very nature, educators favor a deep approach to learning

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because it builds toward increased understanding and the ability to apply new knowledge in a variety of contexts (Entwistle 1997). Once identified, it would be important to address these fallacies; although how that occurs that will depend on timing. If a misconception comes to light during the writing of a midterm exam, then the topic can be revisited during a post-exam lecture. However, if it is revealed during the writing of a final summative exam, then the instructor has lost all opportunity to clarify this concept with that particular class.

That being said, it is still important to be aware of the misconception so that the teaching approach for that topic can be modified for future student populations and the frequency of subsequent misunderstandings minimized. For example, our teaching of topics such as these has evolved over the years and in response to these findings. Cognizant of the fact that these topics present significant challenge, we have consciously slowed down when presenting that content in class, encouraged students to participate more actively in the discussion, pointed out misconceptions encountered in previous years and explained the underlying fallacies, and involved students in problem-solving activities in class.

While large classes sizes do tend to render discussion and the identification of learning errors somewhat difficult, the in-class use of online class polling systems combined with practice questions during a pre-exam review session could not only support the identification of learning errors in a timely manner, but also provide the opportunity to immediately address them with the students and correct the misinformation before the summative exam is written (Broida 2007). Finally, the identification of key misconceptions may also support the development of online learning tools that devote additional time, outside the lecture room, to the review of selected concepts and how they are influenced by one another (Carnegie 2009).

In summary, it is important to find ways both inside and outside the classroom to not only assess student retention of factual information, but to also continually sample their thinking when they have been prompted to connect and apply physiological concepts within the context of real-life situations. While the current situation of large undergraduate class sizes presents a significant challenge to the implementation of such an approach, the value of the feedback obtained can justify the investment of time and effort. Awareness of student misunderstandings and the resultant modifications to teaching approaches should then allow students to build strong scaffolds of correctly-associated physiological principles that improve their ability to predict body responses as it strives to maintain homeostasis in the face of changing environmental conditions.

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New Treatment for Rabies Uses Short Interfering RNAs (siRNAs) to Silence The Post Transcriptional RNA of the Rabies Virus

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Abstract

Rabies remains one of the most important public health concerns worldwide. It is a life-threatening disease that causes tens of thousands of deaths every year through its ability to attack the central nervous system. Rabies causes a variety of recognizable symptoms including hyperexcitability, hallucinations, hyper-salivation and hydrophobia. This article examines the virology, pathogenesis, vaccines and diagnosis of rabies in addition to traditional and novel treatments for the disease. The article focuses on the newest treatment modalities that make use of short interfering RNA (siRNA), which allows for post-transcriptional silencing of rabies virus genes by cleaving complementary mRNA transcripts. It is hoped that siRNA will become an effective treatment for reducing the virulence and multiplication of the rabies virus. The article includes a description of the survival of a 15-year-old girl who survived clinical rabies in 2005 after being treated with the Milwaukee Protocol.

Key Words: rabies, rabies treatment, short interfering RNA (siRNA), hydrophobia, public health, Milwaukee Protocol

Introduction

Rabies is a type of encephalomyelitis that is virtually 100% fatal without pre- and/or post-exposure vaccination treatment. It is an ancient disease characterized by symptoms so extraordinary that modern day clinicians would be able to make a presumptive diagnosis based on the writings of Democritus and Aristotle in 500 - 400 BC (Smith 1996). Once introduced into the body through the contact of virus-laden saliva with a wound, scratch, or mucous membrane, the virus kills by interfering with the ability of the brain to regulate breathing, heartbeat and the rate of production of saliva. Victims either drown in their own saliva or blood or die as a result of diaphragmatic muscle spasms so severe that breathing becomes impossible. Twenty percent of victims die from fatal heart arrhythmias (Lite 2008). Observable symptoms include nervousness, paresthesia at the wound site, extreme anxiety and hydrophobia followed by seizures, paralysis, coma and death (Smith 1996). The hydrophobia that is a hallmark of rabies is a result of throat irritation coupled with painful contractions of the pharynx, diaphragm and sternocleidomastoid muscles when the patient tries to swallow water (Jackson 2013).

The rabies virus is the prototypical member of the genus *Lyssavirus* of the order *Mononegavirales*, and family *Rhabdoviridae*. The order *Mononegavirales* is characterized as a non-segmented, negative-stranded RNA virus that is encapsulated in ribonucleocapsid structures (Smith 1996). There are six known genotypes in the genus *Lyssavirus* all of which cause clinical diseases indistinguishable from rabies encephalitis (Smith 1996). Reservoirs for rabies are distributed throughout the world with the notable exceptions of the continents of Australia and Antarctica. In the United States, Hawaii and Alaska remain rabies free (Smith 1996).

Louis Pasteur and Emile Roux developed the first anti-rabies vaccine in 1885 and research into rabies treatment remains an active area targeted by modern public health research programs. Many of these programs are focused on rabies in dogs since the World Health Organization estimates that 99% of human rabies cases worldwide come from dog bites (WHO 2017a). Vaccination programs for the control of rabies that were instituted in the United States in the 1940s and 1950s are credited with eliminating domestic dogs as a viable reservoir for rabies in the US. The introduction and consistent use of immune globulin and increasingly powerful vaccines have ensured such successful post-exposure treatment for humans in the United States that 21st century clinicians in the US are unlikely to ever see a case of rabies in humans (Smith 1996). Over the past hundred years, human deaths from rabies have declined in the United States from approximately 100 a year to an average of only one to two a year (Smith 1996).

In much of the rest of the world, however, rabies continues to be a devastating disease that claims the lives of tens of thousands of people each year. Most of these deaths occur in Asia and Africa with the greatest numbers reported in India (WHO 2017a). As many as four in ten reported deaths from rabies are in children under 15 years of age and fifteen million people worldwide receive post-bite exposure prophylaxis (PEP) (post-bite vaccination) each year (WHO 2017a).

The Pathogenesis of Rabies

Once introduced into the body, the rabies virus is transported to the central nervous system (CNS) via retrograde axoplasmic flow through the axons of the

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peripheral nervous system. Rabies virus enters the neurons at the neuromuscular junction by way of nicotinic acetylcholine receptors (nAChRs) (Jackson 2013, Smith 1996). For endocytosis to occur, the G protein of the rabies virus must reconfigure, switching from a hydrophilic to a hydrophobic state, allowing for the formation of a vesicle (Jackson 2013). Following this, the M protein is dismantled allowing for the tight coil of RNA to be pulled apart. The genes of the rabies virus are then transcribed individually and repackaged into the bullet shape before travelling further (Jackson 2013). It is unlikely that the virus replicates during the transport phase since neuron axons lack ribosomes. Transport of the rabies virus can take place inside of sensory and motor fibers (Smith 1996).

Transport of the virus into the CNS is followed by intra-axonal spreading, which distributes the virus over a large area, often before symptoms are apparent (Smith 1996). There is no known pattern in the spreading virus that is correlated with the symptoms of rabies. It is not unusual for the electroencephalogram readings to remain normal even in the end stages of the disease (Smith 1996).

The incubation period for rabies virus (RABV) is dependent on the bite location. If the laceration is close to the CNS an individual risks quicker death as the virus travels at speeds of one to two centimeters per day towards the blood brain barrier, evading immune cells as it goes (Jackson 2013). Rabies is highly neurodegenerative, stripping the myelin off of the neurons in the CNS, leading to acute encephalomyelitis in as few as 20-90 days after the introduction of the virus (Jackson 2013). Following CNS infection, the virus can travel to the eyes and salivary glands to cause the hydrophobia and foaming at the mouth that characterizes rabies. Once RABV reaches the CNS, symptoms become an amalgamation of hallucinations, hyper-production of saliva, and the inability to swallow, often followed by violent outbursts or complete paralysis (Jackson 2013).

In some rabies infections, the virus exits the CNS via anterograde axoplasmic flow, moving to distant regions of the body at an estimated rate of one to four centimeters per day (Smith 1996). As the disease progresses, rabies virus can be found in autonomic fibers, sensory fibers, motor fibers, and in both myelinated and unmyelinated neurons. In the late stages of the disease, virus is released at axon terminals and enters surrounding non-nervous tissue. Movement into non-nervous tissue is not known to have an effect on the progression of the disease (Smith 1996).

There is typically no evidence of an acquired immune response in victims until very late in the progression of the disease. The end stage symptoms such as cardiac arrhythmias, hypoventilation and hypotension are generally attributed to advanced neuritis (Smith 1996).

Clinical Forms of Rabies

Encephalitic

Encephalitis is common in 80% of all cases of rabies (Jackson 2013). The symptoms associated with this form include hyperexcitability, hallucinations, biting, a fever that can exceed 107 degrees, hyper-salivation, dilated pupils, seizures, hydrophobia, autonomic dysfunction, and violent outbursts following sensory stimuli induction (Jackson 2013). The virus can remain in the mouth of the infected host and is easily transferred when the individual develops aggressive biting behaviors.

Paralytic

Paralytic rabies is seen in only about 20% of rabies cases (Jackson 2013). It results in flaccid paralysis of all muscles in the body of an infected host. This form of rabies causes patients to be mute since the laryngeal muscles are incapable of contracting (Jackson 2013). This form of rabies is sometimes confused with anarthria from a brain lesion, poliomyelitis, or Guillain Barre Syndrome. Muscle paralysis moves through the body as the virus moves, resulting in paraplegia in the victim (Jackson 2013).

Diagnostic Techniques

The preferred test used for diagnosing rabies is the direct immunofluorescent-antibody (dIFA) test that detects the presence of rabies virus antigens in the brain tissue of animals suspected of having rabies (Jackson 2013, Smith 1996). Real time polymerase chain reaction analysis can be used to detect rabies virus RNA in saliva, brain tissue, or cerebrospinal fluid and in certain cases, skin biopsies can be tested for rabies virus antigens (Jackson 2013).

Traditional Vaccines

Vaccines for rabies have historically been among the first to benefit from progress in the production and control of vaccines. In 1955 a transition was made from developing rabies vaccines using animal nerve tissue to preparing it using embryonated eggs. This was followed in the 1960s with rabies vaccines that were made using cultures of human diploid cells. In the 1970s and 1980s another transition took place that favored the production of rabies vaccines from various cellular substances such as fibroblasts from chicken embryos and explant cells from fetal calf kidneys (WHO 2017b). Ultimately rabies vaccines were cultured using cells from continuous lines known as Vero cells. Production of many of the highly experimental rabies vaccines stopped in the 1980s and after that time, three broad categories of vaccines took over the rabies vaccine market and they continue to be widely produced and administered to millions of people (WHO 2017b).

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Modern vaccine types

The following three vaccine types represent the majority of the modern vaccines that are produced and used worldwide:

1. A rabies vaccine made from inactivated rabies virus was first developed in cell culture lines in 1964. In 1966, it was established that human diploid cell (HDC) strain WI-38 could be used effectively in the propagation of the Pitman-Moore (PM) strain of fixed rabies virus. First licensed in France in 1974, commercial production of a vaccine made for humans prepared in human diploid cells began in 1978 (WHO 1027b).
2. Purified Vero cell rabies vaccines (PVRV) are prepared in continuous human diploid cell lines. This is a safe process with high immunogenicity but is plagued by relatively low titer of virus production by human diploid cells. This serves as a limitation to the much sought after large-scale production of cheap rabies vaccine that the market craves (WHO 2017b).
3. Purified chick-embryo cell vaccine is made from primary chick embryo cells that come from specific pathogen-free SPF eggs. The vaccine, which contains inactivated, concentrated and purified rabies antigen is freeze-dried after preparation (WHO 2017b).

Traditional Treatment

Since 1980, the most commonly used treatment option for rabies is post exposure prophylaxis (PEP), which consists of an injection of human rabies immune globulin (HRIG) directly into the wound site and four sequential shots of rabies vaccine that are injected into the deltoid muscle (Jackson 2013, Maryland DHMH 2011). Two rabies vaccines, the Human Diploid Cell Vaccine and the Purified Chick Embryo Cell Vaccine (PCEC), have been licensed for post-exposure vaccination (Maryland DHMH 2011). The first dose of vaccine is given as soon as possible after exposure to rabies. Additional doses are given on the 3rd, 7th, and 14th day after the first injection (Maryland DHMH 2011). Human rabies immune globulin is given only once, typically at the same time as the first dose of the vaccine. Minor local reactions, such as localized pain, itching, swelling, and redness at the injection site, may occur within 24-28 hours after receiving the vaccine. A few people may experience systemic reactions such as headache, nausea, abdominal pain, muscle aches and dizziness. Recovery from local and systemic reactions is typically rapid. No deaths or lasting effects have been reported with the use PEP injections (Maryland DHMH 2011).

Along with the rabies vaccine, antiviral medications, such as ketamine, ribavirin, and amantadine, are injected directly into the muscle that was exposed to the virus

(Brandao *et al.* 2007, Jackson 2013). The action of ketamine is currently being debated. Ribavirin increases the mutation rate of the rabies virus, which makes the virus less effective, and amantadine elevates the pH inside of endosomes, which prevents the unraveling of the viral genome (Brandao 2015). Adenoviruses and lentiviruses have also been used to express the genes of the rabies virus, which allows a plasmid containing the complementary base pairs to denature the resulting mRNA (Jackson 2013).

If the biting incident involves apparently healthy dogs or cats in the United States, the animal is confined and observed by its owner for a period of ten days. If no sign of rabies appears in that time, the animal need not be killed and prophylaxis is not required (Smith 1996). Outside of the United States, where rabies in dog populations is common, prophylaxis is often started immediately after a biting incident and stopped if the animal does not display rabies symptoms during the period of quarantine (Smith 1996).

In cases of bites from non-domestic animals in the United States and other countries, the animals are killed and their brain is biopsied to determine if rabies virus is present. If the virus is present, PEP treatment is started immediately (Smith 1996). There is currently no treatment for rabies that has progressed to the CNS other than the Milwaukee Protocol (below).

A Case of Survival from Rabies Treated with the Milwaukee Protocol

Survival from rabies without having received a preventative vaccine was unheard of until 2005 when a case was reported by physicians from the Departments of Pediatric Infectious Diseases, Pediatric Critical Care Medicine, Pediatric Anesthesiology and Pediatric Neurology at the Medical College of Wisconsin in Milwaukee and the CDC in Atlanta (Willoughby *et al.* 2005). Untreated, rabies usually results in death within five to seven days after the appearance of the first symptoms. Aggressive medical management may increase the survival time for up to 133 days but there is little evidence that any medical treatment changes the median survival time (Willoughby *et al.* 2005). Currently, there are only five known people who have survived after receiving immunoprophylaxis following the diagnosis of clinical rabies but prior to the onset of symptoms (Willoughby *et al.* 2005).

Jeanna Giese (Gee-See) is documented as the first person ever to have survived rabies without receiving a preventative vaccine. Jeanna was fifteen years old when she picked up a bat outside of her hometown church in Fond du Lac, Wisconsin (Lite 2008). The tiny, superficial wound she received on her left index finger from handling

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the bat was washed with hydrogen peroxide. The wound was so small that no one considered the possibility that it might be problematic and no effort was made to seek further medical advice or treatment (Lite 2008, Willoughby *et al.* 2005).

Jeanna continued to do well at school and to maintain an active sports schedule for a month following the incident. After a month she started to complain of excessive tiredness and numbness in her left hand. Over the next several days she gradually developed nausea, vomiting, blurred vision, weakness in her left leg, difficulty maintaining a normal gait, slurred speech and fever (Willoughby *et al.* 2005). She was admitted to the Medical College of Wisconsin in Milwaukee where her symptoms continued to progress rapidly. By the time she arrived at the hospital, she could no longer talk, stand without support, or balance herself while sitting, and she was experiencing intermittent unconsciousness, uncontrolled salivation and uncoordinated swallowing behavior. She was immediately intubated to protect her airway (Willoughby *et al.* 2005).

Physicians offered Jeanna's parents a choice between hospice care leading to certain death or aggressive treatment that would be based on a strategy that had never been tested. The treatment strategy called for a combination of anti-excitatory and antiviral drugs augmented with intensive supportive care. Jeanna's parents gave the doctors permission to undertake the aggressive, untested treatment (Willoughby *et al.* 2005).

The physicians at the Medical College of Wisconsin searched the available literature in regard to neurotransmitters in rabies and identified ketamine as an N-methyl-d- aspartate (NMDA)-receptor antagonist, which had been shown to have specific anti-rabies virus activity in animal models (Willoughby *et al.* 2005). A therapeutic coma was induced using g-aminobutyric acid (GABA)-receptor agonism (using benzodiazepines and barbiturates) along with NMDA-receptor antagonism (using ketamine and amantadine) to reduce excitotoxicity, autonomic nervous system reactivity, and general brain metabolism (Willoughby *et al.* 2005). The antiviral drug ribavirin was also administered. Using this strategy, in consultation with the DCD, the doctors hoped to protect the brain from further injury while waiting for the body's own immune system to mount a natural response to the rabies virus (Lite 2008, Willoughby *et al.* 2005).

The doctors started to taper off the medications as soon as Jenna's body showed signs of mounting its own immune defense. Neither rabies vaccine or rabies immune globulin was administered since it was known to be ineffective once symptoms appeared and doctors feared it might interfere with Jeanna's own immune response (Lite 2008, Willoughby *et al.* 2005).

Jeanna survived with only her own naturally acquired immunity although she had some neurological impairment. She was extubated after 27 days in the hospital and discharged to her home on day 76. During a clinical visit that occurred 131 days after her initial hospitalization she was able to interact with the examining physician and to smile and laugh (Willoughby *et al.* 2005). Jeanna recovered most of her cognitive functions in the first few post-discharge months and most of her mobility and sensory skills in the first post-discharge year (Lite 2008).

The physicians who treated Jeanna theorized that her survival might have been enhanced by the small, superficial nature of the bat bite she received, the absence of trauma at the bite site, and the apparently small amount of rabies virus entering her system via the bite (Willoughby *et al.* 2005). Physicians were unable to exclude the possibility that Jeanna survived due to a rare, weakened variant of the rabies virus that was carried by the particular bat she had handled (Willoughby *et al.* 2005). It was believed to be fortunate in terms of her survival that Jeanna's condition was diagnosed relatively early and her medical treatment was very aggressive. The physicians who treated Jeanna were quick to note that the surprising survival of a single patient under these circumstances does not change the bleak statistics on rabies survival, which has the highest fatality ratio of any known infectious disease (Willoughby *et al.* 2005).

This method of treatment became known as the Milwaukee Protocol for the treatment of rabies. Due to the high technological demands required for its implementation, the constant monitoring of patient responses, and the dependency on the rapid availability of specific drugs, the Milwaukee Protocol is not a feasible treatment for use in developing countries where rabies is endemic and most cases are currently being diagnosed (Willoughby *et al.* 2005).

New Areas of Rabies Treatment Research

Inhibition Of Rabies Virus Replication By RNA Interference

The genome of the rabies virus consists of negative sense RNA contained within a bullet-shaped casing (Jackson 2013). Genes P and L, which are most interior, are used for polymerase activity post-infection, while gene G is used for trans-synaptic passage of the virus. Gene M is used for the budding of progeny and condensing of the helix, and N is used for nucleocapsid assembly (Jackson

2013). The N and G genes are the most critical to the rabies virus for multiplication and spread and thus serve as the targets for a newly proposed short-interfering RNA treatment.

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Short interfering RNAs (siRNAs) have been shown to silence the post transcriptional RNA of the rabies virus by cleaving complementary mRNA transcripts with a multicomponent nuclease complex called the RNA-induced silencing complex (RISC), which leaves the virus incapable of multiplying (Ono *et al.* 2013). As the siRNAs are highly specific for certain nucleotide sequences, destruction of host cell RNA is also spared in this treatment method (Singh *et al.* 2013). The G gene that controls viral uptake, passage of the virus through the axons of neurons, and replication, and the N gene that reassembles the nucleocapsid of the virus, are targeted for silencing most frequently since they are vital for RABV's virulence (Singh *et al.* 2013). It is hoped that targeting and silencing these genes might help to reduce viral titer and prove to be a potential antiviral treatment for rabies.

The specific mechanism of action of short interfering RNA consists of two steps: the initiator step and the effector step (Ma *et al.* 2007). The initiator step begins with the production of double-stranded RNA (dsRNA) by endogenous genes (Ma *et al.* 2007). Then the cellular complex RNase III-like Dicer cleaves the dsRNA to yield siRNA duplexes, which are typically 21-25 nucleotides in length (Leonard and Schaffer 2005, Ma *et al.* 2007). The effector step begins with an RNA induced silencing complex (RISC), which includes the siRNA that was previously generated (Ma *et al.* 2007). This complex targets the mRNA of the rabies virus with sequences complementary to the siRNAs that are being utilized (Gitlin and Andino 2003). The mRNA generated by the rabies virus is then spliced by RISC and becomes nonfunctional (Gitlin and Andino 2003).

In an article published in 2013 titled, "In Vitro And In Vivo Inhibition Of Rabies Virus Replication By RNA Interference", Ono *et al.* describe the need for a rabies treatment other than the Milwaukee Protocol. The authors highlight the successful treatment of other viral infections, such as HIV and HPV, with short-interfering RNAs (siRNAs). The

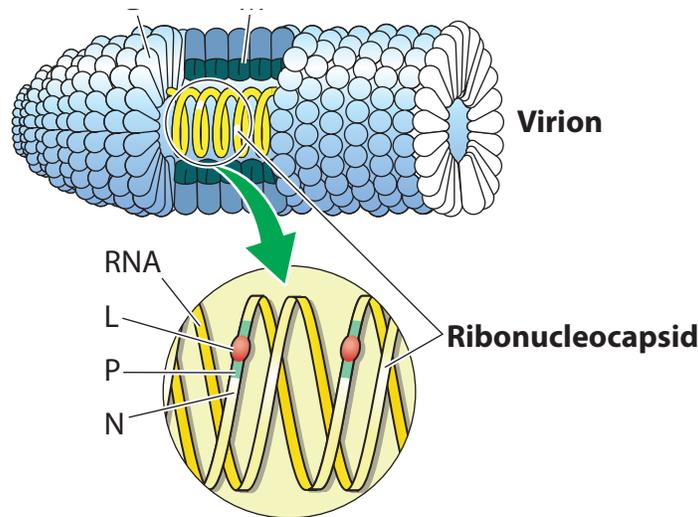


Figure 1. The rabies virus consists of RNA contained within a bullet-shaped casing, the ribonucleocapsid. Genes P and L, which are most interior, are used for polymerase activity post-infection, while gene G is used for trans-synaptic passage of the virus. Gene M is used for the budding of progeny and condensing of the helix, and N is used for nucleocapsid assembly. Adapted from Jackson, Alan C (Editor) (2013) *Rabies: Scientific Basis Of The Disease And Its Management*. Edition 1, illustrated by Kelly Paralis, Penumbra Design, Inc.

goal of their research is to decrease the overall titer of the rabies virus (RABV) by using siRNAs to silence the genes in RABV that allow it to multiply and travel through the PNS to the CNS. Ono *et al.* believe that this treatment method can be applied intracerebrally. The intracerebral injection of siRNA, without the use of a vector, would ideally act as an antiviral strategy and reduce risk of permanent damage to the brain and death from rabies.

This experimental protocol began with procuring siRNAs that were complementary to the mRNA translated as a result of N nucleoprotein gene sequences 124, 750, and B in the rabies virus genome. The N gene was

selected to be silenced due to its role in nucleocapsid assembly of RABV and its regulation in the switch from viral gene transcription to viral genome replication. Three siRNAs were designed with anti-sense strands complementary to the constrained portion of the RABV N nucleoprotein RNA derived from GeneBank (Table 1). The N protein mRNA was translated in duplex format with two deoxitimidines at the 3' end of all sense and anti-sense strands.

The siRNA was evaluated at a range of temperatures that a person infected with rabies might experience in order to ensure that the proteins remained viable at those temperatures (35 = 95F, 37, 49, and 42C = 107F). *In vivo* and *in vitro* assays were carried out with the Pasteur Virus (PV) strain of RABV grown in Baby Hamster Kidney (BHK-21) cells with titres of 6.0 logTCID₅₀/mL and 7.0 logTCID₅₀/30mL (the lethal dose of RABV by 50% in mice). *In vitro* studies were conducted using 24-hour-old BHK-21 cells that were grown in 96 well plates. These samples were then inoculated with 200 microliters of 100 to 0.1 TCID₅₀ of PV in 10 fold dilutions in MEM. After 2 hours (to allow for viral penetration) virus dilutions were discarded and 200 microliters of MEM was added and 100 microliters of 1:50 Lipofectamine 2000 combined with 10 micromoles of siRNA. Following 24h for RABV to multiply at least twice. Plates were then tested by

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direct immunofluorescence assay (DFA) with anti-RABV nucleocapsid rabbit fluorescein isotiocyanate conjugate.

In vivo assays were conducted using 21-day-old albino Swiss mice that were inoculated intracerebrally by PV diluted ranging from 10,000 LD50, 1000 LD50, 100 LD50, 10 LD50, and 1 LD50 in 30 microliters. Two hours after inoculation the treated group was injected intracerebrally with 30 microliters of siRNA along with lipofectamine 2000. The treated groups were observed for 30 days for clinical signs of Rabies including seizures, ataxia, hyperesthesia, paralysis, and death. Results of the *in vitro* study concluded that the highest drop in viral titre was found for the siRNAB group with an 87% reduction, while siRNA 124 and siRNA 750 followed close behind with 72% and 78% reductions, respectively (Table 2).

In the *in vivo* study, mice with 1,000 and 10,000 LD50 had a 0% survival rate and mice with 100 LD50 treated with siRNA had a 30% survival rate. Mice given 10 LD50 treated with siRNA had a 70% survival rate while mice given 1 LD50 treated with siRNA had a 100% survival rate. All animals that died tested positive for RABV antigen and all animals that lived tested negative for the RABV antigen. Due to the fact that the titers of the PV strain post treatment with siRNAs was significantly reduced, one can conclude that siRNA delivery is an efficient treatment option to reduce multiplication of the virus and severe infection.

siRNA	Sequence	Initial position
RNA124	sense 5' GCCUGAGAUUAUCGUGGAG 3' anti-sense 5' AUCCACGAUAAUCUCAGGC 3'	123
RNA750	sense 5' GCACAGUUGUCACUGCUUC 3' antis-sense 5' UAAGCAGUGACAACUGUGC 3'	749
RNAB	sense 5' GACAGCUGUCCUCACUCG 3' anti-sense 5' AGAGUGAGGAACAGCUGUC 3'	903

Table 1: The three siRNAs used in the study that are complementary to the N nucleoprotein gene's specific sequences from the RABV genome. These sequences allow for the silencing of the mRNA generated from the RABV-N gene and thus prevent nucleocapsid formation and replication of the virus. This table was reproduced with permission from Ono *et al.* 2013.

Treatment	Titer (logTCID ₅₀ /mL)	Titer difference regarding the control
siRNA 124	5.71	0.72
siRNA B	5.56	0.87
siRNA 750	5.65	0.78
Control	6.43	

Table 2: In the *in vitro* study this table depicts the Pasteur Virus titers following treatment with the three siRNAs (denoted in Table 1) in BHK-21 cells that had been injected with virus previously. This table was reproduced with permission from Ono *et al.* 2013.

Targeting Rabies Virus Glycoprotein And Nucleoprotein Genes For Inhibition Of Virus Multiplication

In an article titled, "Evaluation Of Single And Dual siRNAs Targeting Rabies Virus Glycoprotein And Nucleoprotein Genes For Inhibition Of Virus Multiplication *In Vitro*" Meshram *et al.* elaborate on the use of siRNA as a treatment option for rabies, but instead of injecting the siRNA directly into the cerebrum they performed plasmid cotransfection of both the rabies gene and the siRNA that was complementary to it. Meshram *et al.* theorize that direct injection of siRNA is inefficient in precision targeting of the complementary RNA and leads to the damage of host RNA. The treatment proposed by Meshram *et al.* makes use of both the N and G genes, since the G gene also plays a large role in transsynaptic passage of the virus. Their targeting procedure resulted in an 86% reduction in rabies virus *in vitro* compared to single gene targeting and an 87.4% reduction in virus as a result of dual G and N gene targeting. The results suggest that the G gene, as well as the N gene, is essential to the multiplication of rabies virus and needs to be targeted to reduce the titer of the rabies virus. The addition of an adenoviral vector significantly increased the precision of targeting and the eradication of the virus in this study.

Short Interfering RNAs (siRNAs) Delivered Through A Lentiviral Vector

Singh *et al.*, in an article titled, "Protection Of Mice Against Lethal Rabies Virus Challenge Using Short Interfering RNAs Delivered Through Lentiviral Vector" described a new technique using a lentivirus vector to ensure that siRNAs precisely target RABV transcripts. Singh *et al.* targeted the N gene of the rabies virus as well as the P gene, which plays a role in polymerase activity. In an *in vitro* challenge, using the RV Pasteur Virus PV-11, Singh *et al.* demonstrated a reduction in the number of RV foci indicating inhibition of RABV multiplication. This experiment demonstrated that slightly more than 62% of mice survived after being treated with the lentivirus vector Lenti-N, while the control mice died within 7-10 days following a PV-11 intramuscular injection. This research suggests that lentiviral vector plasmid cotransfection is an efficient means of targeting genes that play a role in rabies virus multiplication.

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These three studies suggest that the intracerebral delivery of a dual siRNA that targets both the N and G RABV genes by way of a lentiviral vector might be the most efficient method to clear the rabies virus, before or after it reaches the CNS, by depleting the gene transcripts necessary for its multiplication and virulence.

Conclusion: Strategies for the Elimination of Rabies

The World Health Organization has declared that freedom from dog-mediated rabies on a global basis is feasible in our lifetime (WHOc 2017). To this end the World Health Organization has established global partnerships, the goal of which is to eliminate human deaths from rabies by 2030 (Mohammadi 2016). The action is predicated on the belief that effective vaccines for both humans and dogs exist today and that it is easier than ever before to travel into remote areas.

The impetus has never been greater for the elimination of the estimated 59,000 deaths that occur as a result of rabies each year; most of which occur in underserved populations of Asia and Africa. The elimination protocol calls for extensive and coordinated intervention including vaccination programs for both humans and dogs with a strong emphasis on community awareness programs (WHO 2017c).

It is hoped that a combination of political will, sufficient vaccine resources and cutting edge research, perhaps focused on dual gene targeting siRNAs, will be brought to bear on this problem in order to consign rabies once and for all to history.

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Sickle Cell Trait Is Not Always Asymptomatic

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Abstract

Sickle cell trait is a genetic condition in which individuals carry one normal β -globin gene and one β -globin gene with the "S" mutation. This heterozygous carrier state, common in tropical regions where malaria is endemic, is generally asymptomatic. However, during intense exercise, individuals with sickle cell trait may experience exertional sickling, with muscle weakness, tissue damage, and even sudden death. Learning about sickle cell trait is important, as it affects one in twelve African-Americans. Sickle cell trait is an interesting socially-relevant phenomenon that allows anatomy and physiology teachers to discuss many essential concepts related to hematologic and respiratory physiology, as well as to review basic principles of genetics and protein chemistry. Learning about sickle cell trait allows students to connect cellular physiology to situations of health and disease.

Key Words: sickle cell trait, hemoglobin S, exertional rhabdomyolysis, sudden death

Introduction

When I was in school, students were taught that sickle cell trait is asymptomatic. People who were carriers of the sickle cell gene, heterozygous for the hemoglobin S gene, were not known to experience any related problems. Carrying the hemoglobin S gene was simply described as being protective against malaria, a parasite commonly found in the tropical regions where the sickle cell gene can be found. I learned that sickle cell trait is not always asymptomatic when a student asked a question about it in class and I was prompted to do further reading. I have since discovered that a person with sickle cell trait can, under certain circumstances, experience enough sickling to cause problems. Sickle cell trait is especially dangerous for athletes who train in short, intense bursts. Sickle cell trait can also become problematic in low oxygen environments such as might be experienced in high altitude locations. Learning about sickle cell trait is important because one in twelve African-Americans carries the gene. Because the effects of sickle cell trait show up clinically under specific physiological conditions, teaching about sickle cell trait may help anatomy and physiology instructors make a connection to aspects of cardiovascular and respiratory physiology that will give our students deeper, more lasting knowledge about these systems.

Sickle cell trait has been associated with exercise-related sudden death in athletes and military recruits. The most common scenario involving an athlete occurs during pre-season conditioning when a football player collapses on the field while running repeated short sprints. From 2000 to 2010, there were sixteen deaths in NCAA Division I football, and ten of them were associated with sickle cell trait. Three to four percent of Division I football players are known to carry the sickle cell gene. Most reported cases of sickle cell related problems in the literature are

related to football but there have also been instances of basketball players, runners, boxers, and swimmers affected by sickle cell trait. Sickle cell problems reported by the military often involve soldiers during training runs. An analysis of two million military recruits that were engaged in basic training between 1977 and 1981, identified twelve sudden unexplained deaths of African-American recruits who suffered from sickle cell trait out of a total of 42 sudden deaths among all recruits. (Anzalone *et al.* 2010, Eichner 2010b, Harmon *et al.* 2012, Harris *et al.* 2012, Kark *et al.* 1987)

It has been estimated that there are somewhere between 100 and 300 million people worldwide with sickle cell trait (Goldsmith *et al.* 2012, Tsaras *et al.* 2009). In parts of Africa where malaria is prevalent, sickle cell trait may affect between ten and forty percent of any sample population. In Nigeria, for example, twenty-four percent of the population carry the sickle cell gene (World Health Organization 2006). In 1987, the National Institutes of Health (NIH) recommended universal screening for all newborns born in the United States. Seven point three percent of African-American newborns screened by the NIH in 2010 tested positive for sickle cell trait compared to one point six percent of all newborns that were screened. In this report, sickle cell trait in Hispanic newborns ranged from 0.2% to 6.3%, depending on the state (Ojodu *et al.* 2010). In addition to equatorial Africa, sickle cell trait can be found in people of Caribbean, South and Central American, Arab, East Indian, and Mediterranean descent (Ashley-Koch *et al.* 2010).

Sickle cell trait represents a topic of clinical and social relevance to our students. Teaching about sickle cell trait can help students learn foundational concepts of biology and physiology. In order to understand why (and how) sickle cell trait can be deadly, it is necessary to understand

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how sickle cell trait works, starting with a review of genetics and protein biochemistry.

Demonstrating Principles of Genetics, or the Central Dogma of Biology

Hemoglobin S is a common genetic variant of the β -globin gene, which codes for one subunit of the hemoglobin protein. Hemoglobin is a globular protein consisting of four subunits, two α subunits and two β subunits. Normal hemoglobin is known as hemoglobin A. Hemoglobin S has a different β -globin protein that is the result of a single A to T substitution in the sixth codon of the β -globin gene on chromosome eleven. This substitution changes hydrophilic glutamic acid residue to a hydrophobic valine (Ashley-Koch *et al.* 2000).

Genetic conditions may be homozygous or heterozygous. In this case, having two copies (homozygous for) the hemoglobin S gene produces a condition known as sickle cell anemia, or HbSS, with the SS meaning two copies of the hemoglobin S gene. The heterozygous condition consists of one S-type β -globin gene and one normal β -globin gene; this carrier state is HbAS or sickle cell trait.

Whether a trait is dominant or recessive depends on the expression of the gene. In sickle cell anemia both the normal β -globin and the S-type β -globin proteins are expressed, meaning that the two alleles are co-dominant. When developing red blood cells start making hemoglobin, they make β -globin subunits based on the sequence of both of the genes present on the two separate copies of chromosome eleven. Interestingly, each red blood cell has slightly more HbA than HbS (typically 60/40) because α -globin subunits bind preferentially to normal β -globin proteins over S-type β -globin (Eaton 2003, US Department of Health and Human Services 1993).

Balanced polymorphisms may confer a selective advantage. In parts of Africa where malaria infects 100% of the children by the age of ten months, sickle cell trait is common, and noteworthy for being protective against malaria. This confers a selective advantage because resistance to malaria correlates with increased childhood five-year survival rates (Allison 1954).

Protein structure influences function. The function of hemoglobin is to bind oxygen. An iron atom, in the center of the heme group, binds one diatomic oxygen molecule. As each β -globin and α -globin subunit contains one heme group (with iron in the center), each hemoglobin protein can hold four oxygen molecules.

Hemoglobin becomes 98% saturated when red blood cells pass through the capillaries of the lung. When red blood cells move through the systemic circulation and enter oxygen-deprived tissues, hemoglobin releases oxygen.

Oxygen then diffuses through the tissues, enters cells, is used for oxidative phosphorylation, or binds to molecules like myoglobin that have a higher affinity for oxygen. This process is the same for hemoglobin A and hemoglobin S.

The problem comes once hemoglobin S has released oxygen and become deoxyhemoglobin S. In this state, deoxyhemoglobin S does something that normal deoxyhemoglobin does not do. Deoxyhemoglobin S polymerizes, with one deoxyhemoglobin S attaching to the next, forming linear strands of deoxyhemoglobin S proteins. Normally, deoxyhemoglobin has a different conformational state than oxyhemoglobin (T versus R). In the T state, the α and β subunits are shifted, and one of the two abnormal Valine β_6 residues found in the mutated β -globin comes in contact with a pocket in the neighboring β subunit. This pocket does not exist in the R state of oxyhemoglobin. With deoxyhemoglobin A, the glutamic acid normally at position six is too large and too hydrophilic to fit into the pocket, and deoxyhemoglobin A does not make polymers. When hemoglobin S releases oxygen and shifts into the T state, Valine β_6 contacts a neighboring hemoglobin molecule and holds on by sitting in this special pocket. At first, deoxyhemoglobin S molecules attach to each other slowly, until they form a critically-sized "nucleus". After this point, polymerization happens quickly and the fibers, which are fourteen hexagonally packed and helically twisted strands of deoxyhemoglobin S molecules forming parallel pairs (seven sets of two) extend the length of the cell (Voet and Voet 1990).

The shape of the red blood cell depends on the hemoglobin inside it. Red blood cells have a characteristic biconcave disc or "donut" shape. A single red blood cell is only eight to ten μm in diameter, but may contain 250 million hemoglobin molecules and a billion oxygen molecules. One drop of blood has approximately 260 million red blood cells, so the five Liters of blood of an average adult contain 25 trillion red blood cells. Put another way, one in three cells in an adult body is a red blood cell (Martini *et al.* 2015).

When the deoxyhemoglobin S proteins form chains, these linearized proteins force the shape of the red blood cell to morph from a nice round donut to a "crescent or holly" shape, creating the sickle cell. Normal round, flexible, red blood cells can squeeze through tiny capillaries, sometimes even capillaries smaller than themselves, such as the tiny splenic capillaries, only three μm across. Sickled cells can not do this. They have lost the round shape and are no longer flexible. Sickled cells get stuck in tiny blood vessels and create logjams. Since the sickled cells are blocking the way, no normal red blood cells carrying oxygen can get through to service the distal oxygen-starved tissues.

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Illustrating Concepts of Respiratory Physiology

Normally, we live at the top of the oxygen-hemoglobin saturation curve. Our red blood cells pass through the lungs, encountering 100 mmHg oxygen, and 98% of the hemoglobin has oxygen bound. Red blood cells then head out through the systemic circulation to areas of the body with minimal or moderate oxygen requirements. The pressure of oxygen in the blood may drop as low as 40 mmHg, but still hemoglobin is 75% saturated with oxygen. In these conditions, a person with HbAS will have less than one percent of red blood cells sickling and for all intents and purposes sickle cell trait is asymptomatic (Bergeron *et al.* 2004, Martin *et al.* 189, Martini *et al.* 2015).

Exercising muscle requires more oxygen. Blood flowing through exercising muscle releases more oxygen. The pressure of oxygen in this blood leaving the skeletal muscle may drop to fifteen or twenty mmHg, which correlates with 20-35% saturated hemoglobin (Martini *et al.* 2015). In other words, the majority of hemoglobin will now be deoxygenated. This is exactly the situation which can create problems for people with sickle cell trait.

Additional environmental factors that promote sickling also occur during exercise. In addition to severe *hypoxemia*, other factors increase the likelihood that red blood cells containing some hemoglobin S will turn into sickle cells. *Metabolic acidosis*, from the lactic acid produced by the working skeletal muscles, shifts the oxygen-hemoglobin saturation curve to the right, so that for the same pressure of oxygen gas molecules, more hemoglobin proteins will be deoxygenated.

Hyperthermia, due to heat produced by working skeletal muscle, which converts 60% of its ATP energy into heat, also shifts the oxygen-hemoglobin saturation curve to the right, with similar effects.

A fourth factor is the *dehydration* of the red blood cells, which lose water as they travel through the hyperosmotic environment of the lactic acid-producing skeletal muscle. The loss of water from a red blood cell shrinks the cell, concentrating the hemoglobin, making it easier for Valine $\beta 6$ to find its binding pocket, and decreasing the time to onset of deoxyhemoglobin S polymerization (Eichner 2007, Voet and Voet 1990).

Living with Sickle Cell Trait

The upshot of all of this physiology is this: **Exertional sickling is an “intensity syndrome” that may affect HbAS athletes** (Eichner 2010a). When exertional sickling happens, bystanders such as coaches or physical trainers may think that the athlete is experiencing heat exhaustion, but the symptoms are different. An athlete with sickle cell trait may exercise very intensely for a short period of time and collapse on the track or field, often while running. The most common complaint is of pain and/or weakness in the working muscles. For these athletes, any cramping should be considered sickling.

The differential diagnosis of sudden collapse during exercise includes cardiac conditions, heat illness, asthma, and sickling. With sickling, the collapse may come early in a workout, before heat exposure may be considered to have its effects. Also, with sickling there are no mental status changes, unlike heat-related exhaustion, which may include mental status changes. When cardiac conditions cause collapse, there is no cramping, and no talking, as the cardiac function has been compromised. With asthma, there is shortness of breath, chest tightness, and wheezing (Eichner 2007).

Sickling has no prodrome, no warning that it is coming. It presents differently than regular muscle cramps in which the contracted muscle is often described as being “lock-up.” Sickling pain is milder and accompanied by weakness as the muscles just do not work. An athlete experiencing sickling muscle weakness often feels better after a ten to fifteen-minute rest in a cold tub, with access to supplemental fluids and oxygen. The spontaneous recovery indicates that the sickled cells have managed to get back to the lungs, gain oxygen, and revert to their previous biconcave disc shape (Eichner 2007).

Exertional sickling can be fatal because of rhabdomyolysis. When skeletal muscle fails to get the oxygen it needs for contraction because sickled cells are stuck in the blood vessels, myocytes may die. Ischemia of the skeletal muscle may lead to necrosis, which causes myocytes to release their contents into the surrounding tissues and eventually into the bloodstream. As a result, potassium floods into the bloodstream. This leads to hyperkalemia, which can cause fatal cardiac arrhythmias. If a person makes it through the immediate post-sickling period, kidney failure is a possibility as myoglobin from dead myocytes damages the kidneys.

Standard training precautions for SCT athletes. Athletes can exercise safely if they follow specific guidelines with respect to hydration, treatment for cramping, and heat-related exercise guidelines. Hydration increases the volume of red blood cells, decreases the concentration of hemoglobin S, and decreases the risk of sickling. In one study of two HbAS men walking on a treadmill for 45 minutes, ingestion of fluid for three hours prior to and during a 45-minute walk prevented cells from sickling. Without hydration, sickle cells increased from a baseline of 0.5% to 1.0% to a maximum of 3.5% to 5.5% (Bergeron *et al.* 2004).

Additional guidelines include conditioning throughout the year, and adopting reasonable pacing during training. If a person with sickle cell trait experiences any “cramping” during exercise, the assumption should be that sickling is occurring and exercise should be halted immediately. Supplemental fluids, an ice bath, and the use of supplemental oxygen will encourage sickled cells to revert. Failing immediate recovery, emergency measures may become necessary to treat rhabdomyolysis (Eichner 2007). For a complete set of guidelines and a “chain of survival” flow chart, see O’Connor 2012.

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Litigation over the death of 19-year-old freshman football player who died after a 2006 practice session led to the NCAA adopting mandatory screening for sickle cell trait in Division I athletics as of April 13, 2010 (Bonham *et al.* 2010), and Division II in 2012 (O'Connor *et al.* 2012). The military screens for sickle cell trait according to "Service-specific" guidelines (Department of Defense 2015). The Army does not routinely screen for sickle cell trait, but has instituted heat-related service guidelines for everyone. Standard heat-related exercise precautions include adjusting the exertion level based on potential heat exposure, conducting high-intensity training in the cooler morning hours, and avoiding consecutive days of high-intensity activity (Nelson *et al.* 2016, O'Connor *et al.* 2012).

Concerns about routine screening have prompted discussion of whether screening for sickle cell trait leads to unnecessary restrictions and possible discrimination. Because adverse effects of sickle cell trait are rare, some have argued that routine screening is not warranted and that a better approach is to institute standard precautions for everyone. Groups that favor standard precautions for everyone include the American Society of Hematology and the Sickle Cell Disease Association of America (O'Connor *et al.* 2012). A recent analysis of the records of almost 48,000 African-American soldiers on active duty in the Army from 2011 to 2014 found that sickle cell trait was not associated with an increased risk of death, although there was a slight increase in the risk of exertional rhabdomyolysis. However, these soldiers were subject to standard heat-related exercise precautions and anyone with a previous history of rhabdomyolysis had been automatically excluded (Nelson *et al.* 2016).

Should we routinely test for sickle cell trait? This is an ethical issue which students could debate in class. Is it right for the NCAA to require athletes to be tested? Does allowing an athlete to opt out by signing a waiver signify that this is a liability issue more than a health issue? Or would knowledge of sickle cell trait encourage greater adherence to safety guidelines?

Potential treatments are in clinical trials. Other than preventive exercise-related measures, there are no currently approved treatments for sickling. However, two drugs that function as allosteric modifiers of hemoglobin's affinity for oxygen are now in Phase I/II clinical trials. One of them, GBT440, appears to decrease *in vitro* sickling and may increase the delay time to the sickling event. Since cells do not sickle instantly upon achieving a critical mass of deoxyhemoglobin S, the objective of increasing the delay time is to give the red blood cells enough time to return to the pulmonary circulation and bind oxygen again before red blood cells sickle due to the presence of deoxyhemoglobin S (Dufu *et al.* 2016).

Summary

Sickle cell trait can be deadly. Early analyses of the effect of sickle cell trait on morbidity and mortality concluded that sickle cell trait does not affect lifespan (Voet and Voet

1990). More recently, it has become clear that specific sudden deaths during intense exercise fit a pattern of exertional sickling followed by rhabdomyolysis and either cardiac arrhythmias or kidney failure. Thankfully, such events are uncommon and are triggered by a preventable "perfect storm" of events (Eichner 2010b).

Sickle cell trait is an interesting socially-relevant phenomenon which allows anatomy and physiology teachers to discuss many essential concepts related to hematologic and respiratory physiology, as well as to review basic principles of genetics and protein chemistry. The context of sickle cell trait brings clinical relevance to a discussion of the oxygen-hemoglobin saturation curve, and the shifts in this curve that happen with changes in pH and temperature.

About the Author

Tracy Ediger is an Assistant Professor of Biology who spends most of her professional time teaching anatomy and physiology and chatting with students about course choices, career plans, and life outside the classroom. Tracy is interested in how people learn, and how students make decisions about life direction.

Appendix I

Plasmodium falciparum has evolved a mechanism to help it pass unscathed through tiny splenic capillaries. *P. falciparum* lowers the intracellular pH of the red blood cell by as much as 0.4 pH units, which makes red blood cells more adherent to the walls of the capillaries, escaping destruction. Unfortunately for *P. falciparum*, this acidic microenvironment also encourages hemoglobin S to polymerize, and as many as 40% of the red blood cells may sickle. These sickled red blood cells lose the ability to control the intracellular potassium concentration and potassium leaks out. If *P. falciparum* does not have enough potassium, the parasite dies. In other words, the parasite causes sickling, which then kills the parasite. (Voet and Voet 1990)

Appendix II

In addition to exertional sickling, which is the focus here due to the link to red blood cell structure and function, sickle cell trait has also been associated with clinical conditions that can be fatal involving the kidneys (renal medullary carcinoma, hematuria, renal papillary necrosis, and hyposthenuria) and the spleen (splenic infarction). Serious conditions that affect the kidneys and spleen are presumably due to sickling in the hypoxic capillaries of the kidney or occlusion of the tiny capillaries of the spleen. For more potentially serious complications of sickling see Tsaras *et al.* 2009.

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Analysis of an Arthritis Simulation Activity Developed as a Laboratory Exercise for Allied Health Students

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Abstract

We developed an arthritis simulation learning and sensitization activity for a Human Anatomy and Physiology I laboratory. The protocol allowed 318 students to experience some of the physical limitations of aging, specifically arthritis, by asking them to perform activities of daily living (ADLs) while wearing simulation equipment that inhibited their range of movement. Students completed a pre-simulation survey, which assessed student knowledge about the elderly and arthritis. For the ADLs, students completed four simple tasks with and without taped hands that were designed to simulate arthritis. For each task, time to completion significantly increased ($p < 0.001$) with the addition of tape. Students then completed a post-simulation survey, which assessed the success of the simulation. Most students agreed that completing each task was more difficult with the tape and that the simulation was interesting, which suggests the tape was an effective method to simulate arthritis for allied health students.

Introduction

Ageism is defined as prejudice or discrimination based solely on a person's age, resulting in a stereotype specifically associated with decline and disability (Butler 1969, Hale 1998). Unlike other prejudices, ageism has been poorly studied and there is little known about its origins and consequences (Robbins 2015). Ageism in health care professions could interfere with diagnosis and treatment of older patients. Palmore (1999) argued that health professionals share the same ageist attitudes that are present in society, compounded by a disease-oriented education. According to Lorraine *et al.* (1998), both physicians and medical school students had negative attitudes about older patients, believing them to be inflexible, unproductive, and difficult to treat. A similar disconnect was found from the patient's point of view where patients often complain that physicians are insensitive and lack understanding and concern for them as individuals (Lorraine *et al.* 1998). Survey research found that older people experience ageist attitudes such as disrespect and being ignored and patronized. They had encountered assumptions by health professionals that health issues were caused by age (McGuire *et al.* 2008, Palmore 2001). Health profession training schools have begun to incorporate programs in their curriculum that sensitize students to geriatric issues, which aim to teach students how to help or treat older patients (Lorraine *et al.* 1998).

In order to reduce the prevalence of ageism in the health professions, it is necessary to understand the root of the problem. A possible explanation for these negative attitudes could be the types of exposure medical students have to the elderly. Students interact with the elderly in a hospital setting when they are acutely ill and at their

most vulnerable (Duke *et al.* 2009). In accordance with the Contact Hypothesis, stereotyping is not predicted to be higher among individuals who neither identify with nor have contact with the elderly (Hale 1998). Hale (1998) also found that knowledge of aging and application of aging stereotypes were affected by the quality of contact experienced. Those who experienced high levels of contact with elderly achieved higher knowledge scores and lower stereotype scores.

During their educational career, students learn the logistics of growing old without learning how it feels to grow old. Lorraine *et al.* (1998) found that among the major roadblocks facing students caring for elderly patients are personal feelings of helplessness and frustration at being unable to make a difference in the long run. These feelings often result from a combination of ignorance about what the elderly actually face on a daily basis, as well as student fears about their own aging and end-of-life issues. Many institutions have started to incorporate a geriatric curriculum into their programs. A typical program includes a one-week geriatric experience that includes an aging game, a mentoring program with healthy seniors, and the use of standardized patients, all of which have been proven to improve student relations with the elderly (Douglass *et al.* 2008, Duke *et al.* 2009). The "aging game" is a sensitization exercise that uses cards and the performance of acts of daily living (ADLs). It was inspired by an aging game created by faculty at Eastern Virginia Medical School (Douglass *et al.* 2008), which was made mandatory for fourth-year medical school students. In this sensitization exercise, students are assigned an illness common to the older population. The illness is simulated using simple techniques such as

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wearing clouded glasses to simulate glaucoma. Students are asked to perform ADLs, such as paying bills, while the appropriate simulated impairment is in place (Lorraine *et al.* 1998). Even though these interventions are helping with the healthcare of the older population, the Association of American Medical Colleges still reported that 38% of graduating medical students nationally felt they had not received geriatric education during the four years of their medical school (Duke *et al.* 2009).

The aim of this experiment is to develop and assess a arthritis simulation learning activity for a Human Anatomy and Physiology I lab exercise on joint structure and function. In an emotionally oriented arthritis sensitization exercise, students can experience some of the physical limitations associated with the arthritis of aging. Arthritis is considered the number one cause of disability in the United States. It encompasses a wide variety of inflammatory and non-inflammatory joint diseases [Arthritis Foundation (AF) 2016]. Osteoarthritis, also known as “wear and tear” arthritis, is a degenerative joint disease caused by a progressive loss of protective cartilage that cushions the ends of bones. It causes pain and swelling as the inner bone surfaces become exposed and rub together, which ultimately results in damage to muscles and nerves, pain, deformity, and difficulty moving (AF 2016, CDC 2015). The number of Americans who live with arthritis will grow as the number of older Americans continues to increase. At present, as estimated one in five (22.7%) adults in the United States report having doctor-diagnosed arthritis (AF 2016, CDC 2015).

We have not found any documented cases of aging “games” used in undergraduate education. Our new simulation will allow students to understand and experience the physiology of aging joints and the functional limitations resulting from arthritis. We hypothesize that simulated constrictions applied to the fingers and hands will increase the amount of time needed to complete ADLs. We also hypothesize that students will find the simulation interesting. It will be a successful educational experience, allowing students to feel more comfortable with the elderly.

MATERIALS AND METHODS

Three hundred and eighteen students enrolled in Human Anatomy and Physiology I at the University of Mississippi were recruited to participate in this study. All

were traditional undergraduate college students between the ages of 18 and 23. The students, varying with respect to race and gender, were healthy, and did not experience any physical injury or negative side effects as a result of this study. The experimental protocol was approved by the University of Mississippi Institutional Review Board (IRB #15-059). Students were not compensated in any way or awarded course points for participation in the experiment.

A pre-simulation survey was given to students to identify their future profession and assess their familiarity with and attitudes about the elderly. Questions were chosen to identify feelings of ageism and knowledge of arthritis. The survey was designed mostly with questions answered using the Likert scale, which asked participants to give a rating from strongly agree to strongly disagree in response to each statement (Fowler 2009).

The experimental protocol (Appendix A) required students to work in pairs with one student taking the role of Subject and the other the role of Attendant. If there were odd numbers of students in the laboratory sections, the extra student could choose to assume the role of Subject or Attendant. There were a total of 147 Subjects and 171 Attendants in this study. The Subject was first asked to perform four tasks while the Attendant was instructed to time the tasks from beginning to end, using a stopwatch or smartphone. The four tasks (tying their shoe, signing their name, opening a pill bottle, and texting a message) were chosen as ADLs because these tasks may be difficult to complete as one ages. Subjects were encouraged to perform each task as they normally would. The Attendant was then instructed to tape the Subject’s dominant hand with self-adhesive tape, which is a cohesive elastic wrap made of nonwoven material and synthetic elastic fibers (3M™ Coban™). In order to imitate arthritis effectively, and therefore make the simulation effective, we consulted a professional hand therapist, Dr. R. Parish; University of Mississippi Medical Center, for a concise description of the taping method. Dr Parish directed the Attendant to



Figure 1. Taped hand models used to develop joint dysfunction simulation (photos courtesy of R. Parish).

wrap the thumb so that it is pointed slightly inwards after placing a button over the first carpometacarpal (CMC) joint to remind the student of the pain that usually occurs in that location. The remaining fingers and palm of the hand were wrapped tightly enough to limit movement but not to the point of discomfort (Fig. 1). An instructional video, picture, and Teaching Assistant's verbal instruction were used to help with the taping. The Subject was then asked to perform the same four ADLs again while being constricted with the tape and being timed by the Attendant. There was little to no risk involved in the lab protocol except for possible numbness in the fingers as a result of wrapping the fingers too tightly with athletic tape. Stress balls were available to help alleviate any hand discomfort following the experiment.

A post-simulation survey was given after students completed the lab exercise to assess the success of the experiment as a sensitization exercise and as a potential laboratory exercise for the future. The survey asked the participant to identify their role in the experiment, either Subject or Attendant, and to evaluate their experience with the simulation either with the Likert survey or by a scale of percentages from 0-20% to 80-100% in response to each statement.

Descriptive statistics, including mean and standard error, were calculated for all data collected including the pre- and post-simulation surveys and the simulation exercise. Chi-square tests (Siegel and Castellan 1998) were used to analyze the responses for the Likert style questions asked in the pre and post simulation survey. Data from the simulation exercise (time to completion before and after tape was added to the hand) were analyzed using paired, two-sample for means, t-tests. Analyses were conducted using Microsoft Excel and the level of significance was set at $\alpha = 0.05$ for all tests.

RESULTS

Pre-Simulation survey data

Of the 318 students, 79.2% are pursuing a career in the health profession, aspiring to become a nurse, a physical therapist, or an occupational therapist (Fig. 2). Most students (74.8%) responded that they have family members who have experienced joint pain or immobility. When asked on a scale of 1-10 how comfortable the student was with the elderly, with 1 being not comfortable at all and 10 being very comfortable, 100 students rated their comfort level with an 8, 58 students reported a level of 10, 54 reported a 9, and 14 students rated below a 5 (Fig. 3).

In response to the statement, "As people grow older they become less organized and more confused", 108 students Agreed with the statement, 107 responded neutrally, and 79 students Disagreed with the statement ($X^2 = 148.1$, $df = 4$, $p < 0.001$; Fig. 4). In evaluating the statement, "Older

people don't contribute much to society," 154 students Strongly Disagreed and 135 Disagreed, only 7 students Agreed ($X^2 = 349.2$, $df = 4$, $p < 0.001$; Fig. 4). Finally, students were asked to evaluate the statement, "Arthritis is a problem only experienced by the elderly." One hundred and forty-five students Disagreed and 141 Strongly Disagreed ($X^2 = 332.8$, $df = 4$, $p < 0.001$; Fig. 4).

Laboratory Exercise data

Time-to-completion data from the simulation exercise were analyzed using a two-tailed, paired t-test for each of the four tasks (Fig. 5). Times increased significantly for each task ($p < 0.001$ for each test) when the hands were taped as compared to when hands were not taped.

Post-Simulation survey data

When Subjects were asked if they experienced difficulty with the tasks with taped hands, 87 of 147 subjects Agreed and 38 Strongly Agreed while 15, 6, and 0 students respond with Neutral, Disagree, or Strongly Disagree, respectively. Responses to this statement were significantly different than expected ($X^2 = 171.6$, $df = 4$, $p < 0.001$). Subjects estimated their decrease in mobility while performing the tasks with taped hand using percentages ranging from 0-20% (17 Subjects), 21-40% (48), 41-60% (56), 61-80% (24), and 81-100% (1). Attendant responses to the statement, "I observed the Subject experiencing difficulty performing the tasks with taped hands," were significantly different than expected ($X^2 = 153.8$, $df = 4$, $p < 0.001$) with 54, 89, 13, 14, and 2 Attendants responding Strongly Agree, Agree, Neutral, Disagree, or Strongly Disagree, respectively.

When Subjects and Attendants were asked if they found this simulation exercise to be interesting to which almost all students Agreed or Strongly Agreed ($X^2 = 419.7$, $df = 4$, $p < 0.001$; Fig. 6). One hundred thirty-three students Agreed that they believed this simulation would be useful in their future professions ($X^2 = 164.5$, $df = 4$, $p < 0.001$; Fig. 6). When students were asked if this simulation exercise increased their level of understanding of the difficulties experienced by people with joint mobility disorders, 154 students Agreed and 134 Strongly Agreed with this statement ($X^2 = 346.0$, $df = 4$, $p < 0.001$; Fig. 6). Most students responded Neutrally (129) when asked to evaluate the statement, "I feel more comfortable interacting with the elderly after completing this simulation exercise" ($X^2 = 145.3$, $df = 4$, $p < 0.001$; Fig. 6).

DISCUSSION

As anticipated, most students have a family member who has arthritis. When a high percentage of people already possess a personal context and image of arthritis, simulation exercises can be an effective means of developing empathy for family members and potentially patients who experience immobility in their day to day

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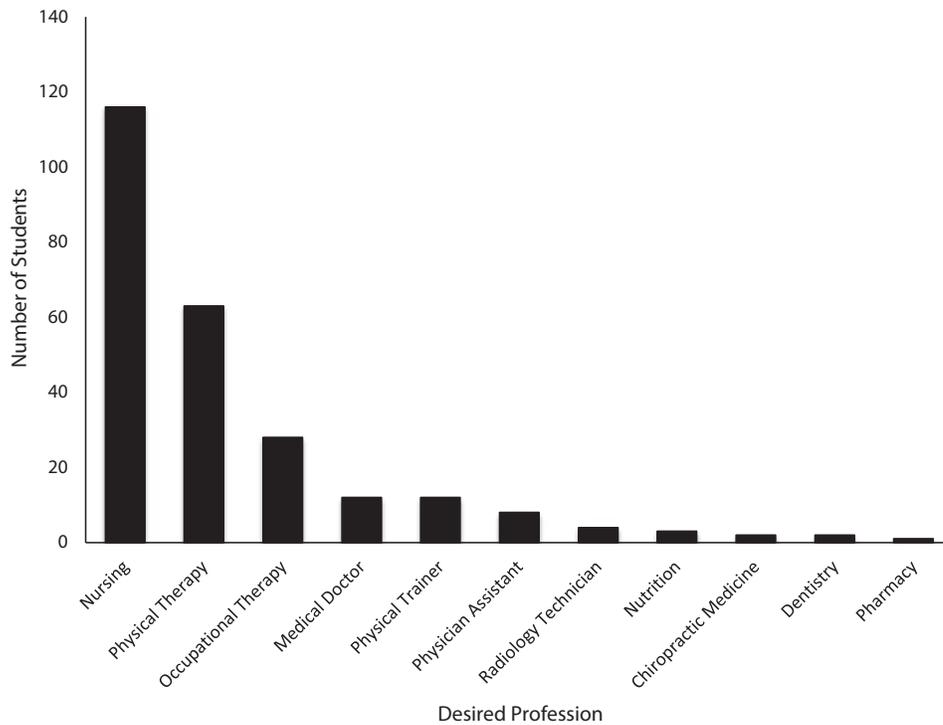


Figure 2. Common future health professions for students enrolled in Human Anatomy and Physiology I at the University of Mississippi during the fall semester of 2015.

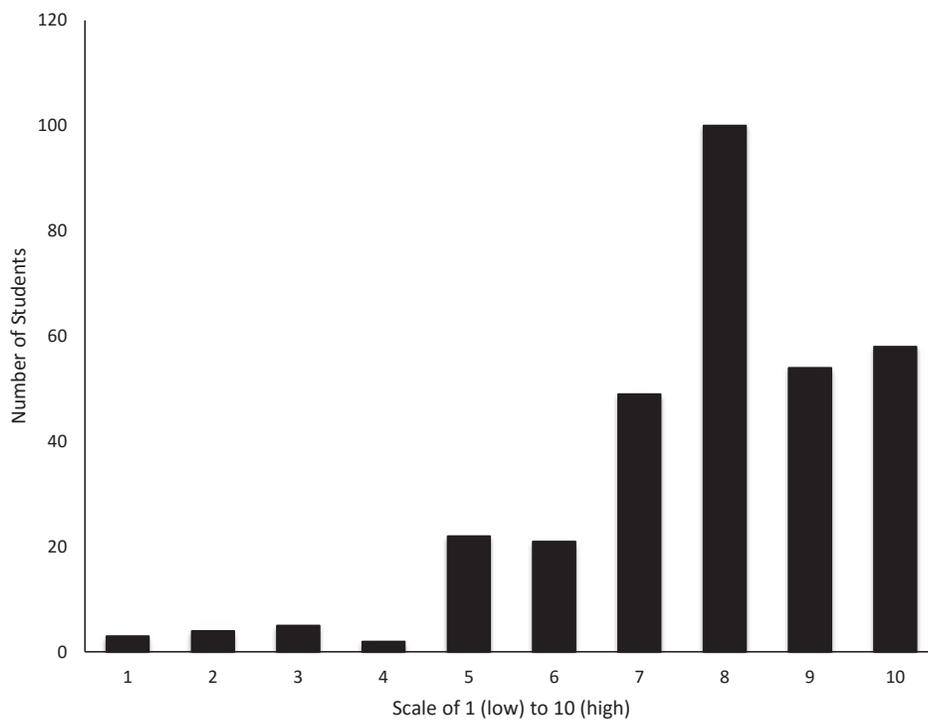


Figure 3. Student responses to Question 3 on the pre-simulation survey, "How comfortable are you with the elderly (aside from your grandparents)?"

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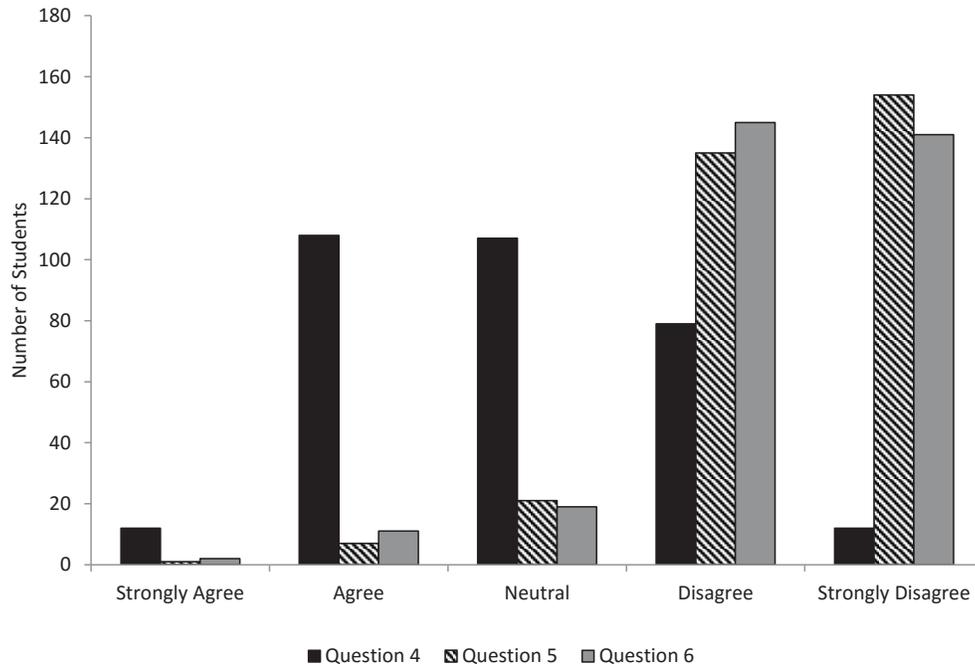


Figure 4. Student responses to Pre-Simulation Likert-style question 4 (As people grow older they become less organized and more confused), question 5 (Older people don't contribute much to society), and question 6 (Arthritis is a problem only experienced by the elderly).

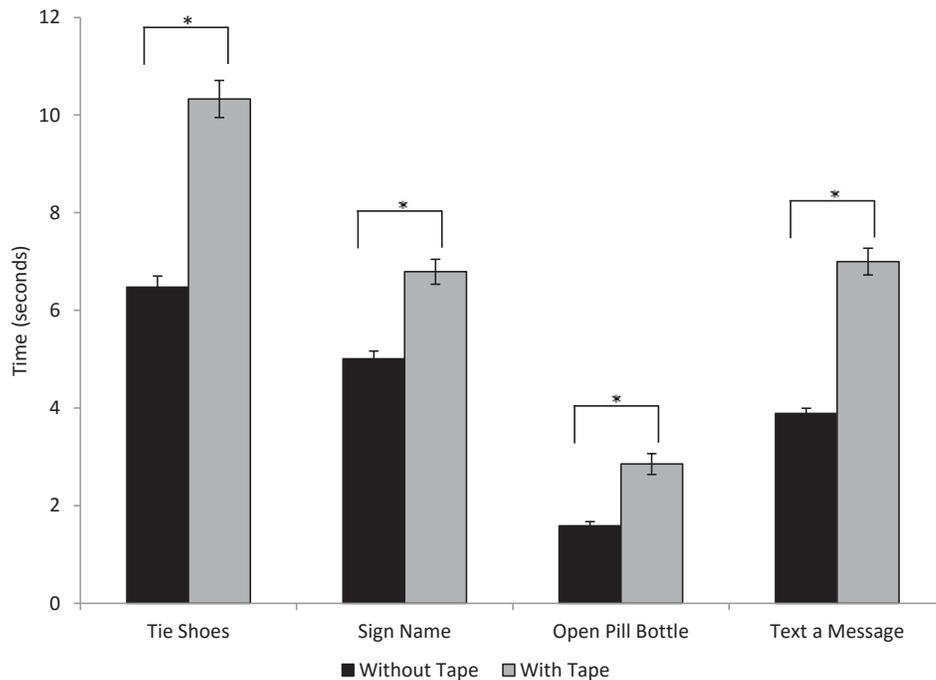


Figure 5. Mean (\pm 1SE) time-to-completion for four daily living tasks without and with the addition of restrictive tape on the hands. An asterisk represents a significant paired t-test result at $\alpha = 0.05$ ($df = 151$).

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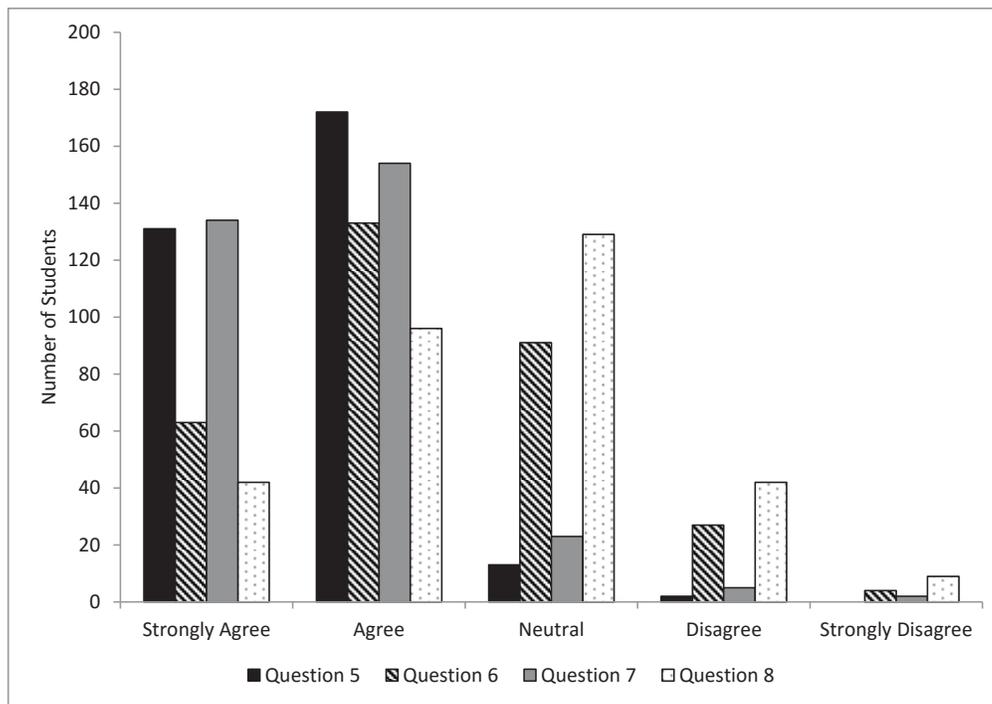


Figure 6. Student (both Subjects and Attendants) responses to Post-Simulation Likert-style question 5 (I found this simulation exercise to be interesting), question 6 (I feel that this simulation exercise will be helpful in my desired profession), question 7 (This simulation exercise increased my level of understanding of the difficulties experienced by people with joint disorders), and question 8 (I feel more comfortable interacting with the elderly after completing this simulation exercise).

lives. However, the students reported degree of comfort with the elderly was not expected. We expected more students to respond with a score below 5, meaning that they were not very comfortable with the elderly. According to Hayslip *et al.* (2013), younger individuals tend to have more negative attitudes towards aging when compared to their older counterparts. Students in this study may have felt obligated to say they were comfortable with the elderly given their future profession. Another possibility could be more exposure to the elderly from job shadowing opportunities students may pursue for their future careers in the health professions.

It was unexpected that more students were willing to Agree that, "as people grow older they become less organized and more confused", and more ready to Strongly Disagree that, "older people don't contribute much to society." Students may believe that older people become less organized and more confused because they are relying on a negative assumption instead of seeking out facts about the elderly and the aging process or

considering other possibilities that could lead to the lack of organization or confusion (Hale 1998). However, current students in college are not yet in the workforce, so their version of contributing to society may be much different than their parent's generation. Hayslip (2013) suggested that individuals of all ages tend to judge older people more negatively when compared to younger people in an industrial/organizational setting. The disconnect between different ages, which is evident in the responses in the pre-simulation survey, could also be described using the Social Identity Theory (Hogg 1987). Members of the in-group (in this case younger individuals) tend to favor positive characteristics within their group and stereotype members of the out-group (in this case older individuals) with less favorable characteristics thus enhancing the individual's personal identity (Hale 1998).

Laboratory exercise

There was a significant increase in the time it took students to complete the ADL with a taped hand versus the time it took students to perform the task normally,

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which was expected given the obvious handicap associated with the addition of tape. The biggest increase in the length of time required to perform a task was seen when students attempted to tie their shoes with tape on their hand. This was expected because of the multiple finger and hand motions used in this ADL. Some possible errors in Subject participation were observed during the completion of the simulation. When students were being timed, we noticed that some of the students were not performing the activities at a normal pace. Instead it seemed that some Subjects were racing to try and get quick times from their Attendant. Also, when the tape was added to their hand, some Subjects were trying to compensate for the restriction by trying to go even more quickly and forcefully through the activities. Some groups at the same table were racing each other even after prompting to perform the tasks as they normally would. However, the time-to-completion data collected were still significantly higher when the hands were taped for all tasks. When talking with and assisting students during the simulation, we noticed that most students seemed to enjoy the simulation and some expressed that it was a nice change in pace from the usual lab activities. Interactive learning allows students to think about the activities they are doing and to understand the purpose of each activity (Hofstein and Lunetta 2004). By creating an engaging simulation, a valuable opportunity is presented for students to experience what their patients could feel on a daily basis.

Some students were surprised by the feeling when the restrictions were added, sympathizing with their family members who have arthritis. While the general reaction to the simulation was observed to be a positive one, there were also some difficulties in the labs during the simulation. The instructional video for the proper way to wrap the hands was not consistently available for student viewing and as a result, some groups had problems with hand wrapping using only a picture to guide them. When this occurred, the course instructor and Teaching Assistants provided assistance in hand wrapping. Some groups seemed to go through the tasks quickly, trying to leave lab early and some students may not have taken the simulation seriously because it was different and seemed to be more entertaining than the usual lab activities.

Post-simulation survey data

When Subjects were asked whether they experienced difficulty with the tasks performed, most Agreed or Strongly Agreed, which indicates that the restrictions were successful. The restrictions were not meant to hinder hand movements too much because individuals with arthritis still have mobility in their hands. The difficulty and frustration experienced by the Subjects could stem from the decreased range of motion they experienced,

making them feel less in control. It could also be a result of the obvious increase in time-to-task completion. Similar to the Aging Simulation developed by Lorraine *et al.* (1998), this simulation gave students a realistic look at the frustrations that elderly persons may experience and increased their awareness of what it is like to be functionally impaired.

Most students either Agreed or remained Neutral when asked if they thought this simulation would be useful in their future profession. Improvement may be made in this area by simulating activities associated with going to see a doctor or activities associated with a hospital stay. Most students agreed that the simulation helped them understand the difficulties experienced by individuals who experience arthritis. However, students did not respond as enthusiastically when asked if this simulation helped them feel more comfortable when interacting with the elderly. Improving the link between the arthritis simulation and the ability to interact with older individuals in the future could be improved by applying more patient-to-provider role-playing activities for the Subject and Attendant. A major goal of the simulation exercise was to allow students to feel more comfortable with the elderly by allowing them to gain knowledge about the everyday lives of the elderly in the hope that student attitudes toward the elderly might increase in a positive manner (Hayslip *et al.* 2013).

Modifications and Future Considerations

Even though verbal and visual directions were given to students, there was room for error in the consistency of hand taping that resulted in varying degrees of hand and finger constriction. Due to the time constraints of the lab, it was not possible to allow all of the students to play the role of Subject during the simulation. Consequently there were some students in each lab who did not have a chance to directly experience the simulation activity. However, these students did participate in the simulation by taping the Subject's hand and by measuring time-to-task. The Attendants may have not have gotten as much knowledge from the simulation as the students who played the Subject did. When there were groups of three, more groups chose to have two Attendants and one Subject, which could have led to "social loafing" (Silverthorn 2006), in which case the second Attendant would not have had a rich simulation experience.

When we spoke with students in the laboratory and explained the research behind the simulation, they were very intrigued and began to think about the activities more thoughtfully. If health care professionals are more sympathetic to people who have arthritis, it might help with patient treatment by improving the relationship between care providers and patients and encourage patients to feel more comfortable sharing their pain with

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their care provider. Enhancements to the lab protocol could be made to simulate different degrees or types of arthritis by using other methods of taping not only hands but also other joints of the body. This can be done by consulting more hand therapists or by observing individuals who actually have arthritis and their degree of motion. More activities of daily living, specifically ones that older individuals have difficulty with, could also be added so that students can more fully understand the connection between the simulation and the aging process.

Acknowledgements

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APPENDIX A

Arthritis Simulation Exercise

1. Work in groups of two, one of you will be doing the activities (Subject), the other will be assisting (Assistant).
2. The Subject will do the following tasks and the Assistant will time from beginning to completion of each task (e.g. time-to-completion). The Assistant will need to have a watch or phone ready to time the Subject as they are performing acts of daily life.

Task	Time *from beginning to end of task* (sec)
Tie your shoes	
Write your name in cursive	
Open a pill bottle	
Text “hey, how are you?” on your phone	

3. Open the instructional video on your computer. You will need to cut 5 short pieces of tape (3”) and a long one (12”). The Assistant will tape the subject’s dominant hand with self-adhesive tape using the instructions contained in this instructional video. Wrap **each** finger first with a small piece of tape and then place a button (shown as a quarter in the video) on the subject’s hand above the thumb. The purpose of the button is to add some amount of discomfort in the first carpometacarpal joint, which a common occurrence with arthritis. Next, use the long piece of tape to wrap along the base of the hand and around the knuckles so that the thumb is tucked tightly in. The tape should be tight enough to restrict mobility but not tight enough to stop blood flow.
4. Repeat the tasks previously performed and time them from beginning to completion. After each task, check the tape to make sure it did not loosen and re-tape the hands as described in step 3 if necessary.

Task with taped hands	Time *from beginning to end of task* (sec)
Tie your shoes	
Write your name in cursive	
Open a pill bottle	
Text “hey, how are you?” on your phone	

5. Remove the tape from the Subject’s hands. If the Subject feels any soreness in the hand, he/she should squeeze the manual therapy ball provided until soreness is relieved.

6. Both Assistant and Subject will complete the post-simulation survey



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Are Challenging Anatomy and Physiology Courses Detrimental to Colleges at a Time of Performance-based Funding?

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Abstract

Many states use performance-based funding models to allocate a varying portion of the state funding to two and four-year institutions. Because our university struggles with two metrics, 2nd Year Retention Rate and Six-Year Graduation Rate, we may lose some funding for next year. In order to do our part in the quest to improve both metrics, Florida Gulf Coast University introduced new curriculum maps for all majors to ensure timely progression toward graduation. The new milestones push more students to take Anatomy and Physiology I as freshmen, although first year students have historically struggled in this course. We followed 30 freshmen that failed to earn a passing grade in anatomy and physiology in spring 2016 to see what happened to them. Our study found that all 30 freshman students who had failed to get a passing grade in anatomy and physiology were still enrolled at the University the beginning of the fall 2016 semester.

Introduction

Over the past two decades many states have shifted funding for colleges and universities from a system based on how many full-time equivalent (FTE) students are enrolled at the beginning of a term or academic year to performance-based funding models. Performance based funding models use metrics such as graduation rates, the number of degrees awarded overall or in special areas, and the number of low-income or minority graduates to determine the allocation of state funding resources (McLendon and Hearn 2013). According to the National Conference of State Legislatures, 37 states already have some form of performance-based funding or are in the process of introducing it (NCSL 2015). Some states only have performance-based funding models for two-year or four-year institutions, but the majority (currently 20 states) use the model to allocate a varying portion of the state funding to both two and four-year institutions.

While there are people who question the wisdom and efficacy of performance-based funding (Fain 2016, Douglas-Gabriel 2016, Hillman 2016), faculty and administrators have to adjust to this new reality in order to keep state funding levels sufficiently high.

Florida is one of the states with a metrics-based model for both two and four year institutions. The Florida Board of Governors website (FL BOG 2017) states that "[t]he model has four guiding principles:

- 1) use metrics that align with SUS Strategic Plan goals
- 2) reward Excellence or Improvement
- 3) have a few clear, simple metrics
- 4) acknowledge the unique mission of the different institutions"

The model currently uses ten metrics; eight of them apply to all eleven State Universities (with the exception of the

eight metric, which is different for New College). The ninth metric is chosen by the Board of Governors specifically for each university, while the last metric is selected by the Board of Trustees of each institution. Points are awarded for each metric based on a scoring sheet, with a maximum score of 10 points for each metric. Points can also be earned for either excellence or improvement. The model is rather complex and not easily explained in the context of this article. More information can be found at: www.flbog.edu/board/office/budget/performance_funding.php.

To be eligible to receive its share of performance-based funding, each institution has to score at least 51 out of 100 points. However, regardless of the absolute score, the three institutions with the lowest cumulative score each financial year will not receive a share of the State Investment. For the financial year 2016-2017, the total performance-based funding for the Florida State University System was \$500 million, with \$225 million in State Investment and \$275 million in Institutional Investment (FL BOG 2016). The three institutions with the lowest scores from the 2014-15 Final Metric Score Sheet (New College Florida, University of North Florida, University of West Florida) did not receive any allocation of State Investment.

Our institution (Florida Gulf Coast University, FGCU) received a total score of 67 on the 2014-15 Final Metric Score Sheet, which put us in sixth place overall. However, because of changes made to the scoring sheet for 2015-16 to account for the special status of New College, we started the year in seventh place. Our weak spots were, and still are, Metric 4 Six Year Graduation Rate (Full-time and Part-Time FTIC) and Metric 5 Academic Progress Rate (2nd Year Retention with a GPA above 2.0). On the 2014-15 Score Sheet we received 0 points for Metric 4 and only 3 points for Metric 5. We will most likely receive 0 points for both metrics on the 2015-16

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Score Sheet and may be in danger of slipping into the bottom three, which would lead to reduced funding for 2017-2018.

In order to do our part in the quest to improve both metrics our college (Marieb College of Health and Human Services, formerly College of Health Professions and Social Work, CHPSW) revised its Student Guidebook for Lower Division Undergraduates (CHPSW 2016) and introduced new curriculum maps for all majors to ensure timely progression toward graduation. The college also defined milestones students must achieve at a certain point for each major. Students missing a milestone have a hold placed on their account and they are required to meet with an advisor to work on and agree to a new plan toward graduation. If a student misses the same milestone for the second time, the student will be forced to switch into a different major that does not require the same milestone at the same stage.

While that may all sound reasonable in light of our low six-year graduation rate of 43.0%, the devil is in the details for our anatomy and physiology courses. We teach about 1200 A&P I and II students per year and approximately 80% are pre-nursing or pre-athletic training majors. They are now supposed to complete BSC 1085C (A&P I with lab) with a minimum grade of "C" by the end of the second semester. Students in other majors have until the end of their third semester to complete A&P I and II. More than 90% of our first time in college (FTIC) students start in the fall term so they have to take and pass A&P I in the spring semester of their freshman year. Unfortunately, freshmen have struggled in our courses in the past. From 2013 to 2015 we had on average of 15.1% freshmen in our A&P I courses and their passing rate (final grades A-C) was 55.7%. Our worry is that, based on previous years, between 100 and 110 freshmen may fail to earn a passing grade in Spring 2017. If a good portion of them give up and withdraw from FGCU, our 2nd Year Retention Rate, which currently stands at about 73%, may further decline.

Methods

To get an idea whether we may have reason to worry about students leaving our institution after failing to pass A&P I, we decided to examine the data for the spring 2016 A&P I courses. In the first step we looked at the passing rates and D/F/W rates for the different subgroups (freshman, sophomore, junior, senior, post-baccalaureate, non-degree seeking). In the second step we identified students who had failed to receive a passing grade and checked university records for fall 2016 and spring 2017 to find out whether they were still enrolled and active at FGCU.

Results

We offered 11 sections of A&P I in spring 2016. All sections met twice a week, once for a lecture and once for a lab section. Overall 349 students were enrolled in the class at the beginning of the second week, 260 students (74.5%) were female, 89 students (25.5%) were male. The percentage of freshmen (19.77%) was slightly higher than in the past because academic advising had already started to push students to take A&P I as freshman in anticipation of the changes to come (although we were not made aware of this). The majority of students were sophomores (56.73%), but we also had a good percentage of juniors (18.62%) and seniors (3.75%). Those "older" students, just like the few post-baccalaureate, non-degree seeking students, were mainly taking A&P I as a prerequisite course before applying for graduate programs.

The overall passing rate for students earning a final grade of A, B or C was 69.34%, which was in line with previous years. Freshmen had the lowest passing rate (56.52%) and, by far, the highest percentage of students withdrawing during the term (27.64%). Sophomores and juniors performed on or about the same level, while seniors had the highest passing rate as one would expect.

(Table 1)

Table 1. Student success rates A&P I spring 2016 for the different student populations

	n	Final grade of D or F	W	Total D/F/W	Passing rate
All students	349	55 (15.76%)	52 (14.90%)	107 (30.66%)	69.34%
Freshman	69 (19.77%)	11 (15.94%)	19 (27.64%)	30 (43.48%)	56.52%
Sophomore	198 (56.73%)	32 (16.17%)	23 (11.62%)	55 (27.78%)	72.22%
Junior	65 (18.62%)	11 (16.92%)	8 (12.31%)	19 (29.23%)	70.77%
Senior	13 (3.75%)	1 (7.69%)	1 (7.69%)	2 (15.38%)	84.62%
Post-bac, non-degree seeking	4 (1.15%)	--	1 (25%)	1 (25%)	75%

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The main question for us was what had happened to freshman students who had failed to earn a passing grade in anatomy and physiology I? Had they returned to try and pass the course a second time round? Or had they withdrawn from our institution?

Half of the students (n = 15) repeated the course and 13 of them stayed in the same major in our college or the College of Arts & Sciences (mainly biology). The other half either switched to a different major inside or outside our college that did not require successful completion of A&P I (11 students) or did not sign up for classes for fall 2016 (4 students). (Table2)

About the Authors

Peter Reuter, MD, PhD is an Assistant Professor at Florida Gulf Coast University where he teaches undergraduate and graduate Anatomy and Physiology courses. He is also the Chair of the Editorial Board of Aquila, The FGCU Student Research Journal, as well as a Co-Director of the Institute for Technological Innovation (i-Health Training Innovations).

Valerie Weiss, MD, MS is an Adjunct Professor at Florida Gulf Coast University where she teaches undergraduate anatomy and physiology to students in the pre-health professions. She is also a medical illustrator, contributing to the course companion and lab workbook used in the course.

Table 2. The status of freshman students who had failed to earn a passing grade in spring 2016 at the beginning of the fall 2016 semester

o All 30 students were still enrolled at the beginning of fall 2016 semester
● 9 students stayed in the same major in our college (CHPSW)
● 4 students stayed in the same major at the College of Arts & Sciences (CAS)
● 2 students switched to a different major within the CHPSW that requires A&P
● 10 students switched to a non-CHPSW major that does not require A&P
● 1 student switched from a non-CHPSW major to another non-CHPSW major that does not require A&P
● 4 students did not sign up for classes in fall 2016 (and spring 2017)

We also looked at sophomore to junior retention and the numbers are almost identical. All 55 D/F/W students were still enrolled at the beginning of fall semester 2016. However, 12 students did not sign up for classes. Altogether, 93.94% were still actively trying to earn a degree at FGCU.

Discussion

From a retention and performance-based funding point of view it is good to see that all 30 freshman students who had failed to get a passing grade in spring 2016, were still enrolled at the beginning of the fall 2016 semester. However, four students have not signed up for classes since the end of spring semester 2016 and will be inactivated at the end of this term. Those four students still counted for our 2nd Year Retention Rate, but they will count against our Six Year Graduation Rate, unless they decide to come back and get a degree at our university.

Based on these results we can say that the changes our college made to improve our Six Year Graduation Rate most likely will not have a negative impact on our 2nd Year Retention Rate. However, the total number of students we followed was rather small. We will look again at the data for our spring 2017 students at the end of summer to see if anything changed for this spring's class.

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Boning Up on Active Learning Exercises for Teaching Skeletal System Anatomy: Pre-Class Accountability is Key

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Abstract

Active learning has been shown to improve learning outcomes for students in a variety of courses, including anatomy and physiology. However, designing active learning exercises may be more challenging for certain topics than for others. For example, learning the anatomy of the skeletal system may be difficult for some students because of the relatively simplistic manner in which skeletal system structures are named and described. Despite this potential challenge, active learning exercises can easily be developed for the skeletal system (or any system) if students are held accountable for learning prior to class via a high structure or flipped course design. In this article, specific active learning exercises for teaching skeletal system anatomy are detailed and recommendations are made for how to implement similar active learning activities in other courses.

Key words: active learning, high structure, flipped classroom, skeletal system, anatomy

Introduction

Active learning, the process of teaching that engages students in the learning process as opposed to passively listening to a lecture, has gained popularity recently in all science, technology, engineering, and math (STEM) fields and anatomy and physiology is no exception. Not only is teaching with active learning more engaging, exciting, and fun, but also research has shown that active learning is an effective way to improve student performance and learning. In a meta-analysis of over 200 published scientific studies, Freeman *et al.* (2014) found that student performance on examinations was on average ~6% higher in a variety of STEM courses that used active learning as compared to courses taught using traditional lecturing. Moreover, they found that students in courses taught with traditional lecturing were one and a half times more likely to fail than those taught in courses that used active learning methods. As the dropout, failure, and withdrawal (DFW) rate can be high in anatomy and physiology courses (Harris *et al.* 2004, Sturges *et al.* 2016), active learning may be just what is needed to help students succeed.

Teaching with active learning can take a variety of forms including: having students solve case studies in small groups; polling the class with personal response system software (iClicker, Turning Point, Top Hat, Learning Catalytics, etc.); having students draw or complete hands-on projects; or simply having students talk to each other to quickly answer a question (Bonwell and Eison 1991, Allen and Tanner 2005). When I first began teaching an undergraduate human anatomy course, I wanted to employ as many active learning methods as possible. However, I thought that it might prove to be more difficult to use active learning methods for teaching some topics, or aspects of anatomy, compared to others. For example, I thought it would be relatively easy

to use active learning methods to teach the anatomy and physiology of the nervous system since students could be asked to draw concept maps to make connections between the nervous system and components of other systems of the body. In addition, students could be asked to solve clinical case studies concerning muscular innervation problems. Furthermore, drawing could be used to illustrate the paths that peripheral nerves travel through the body. It is easy to use active learning to teach anatomical parts of the cardiovascular system by asking students to draw the path of blood through the pulmonary and systemic circuits. In addition, teaching epithelial lining components of the digestive system can be done using compare and contrast tables. Finally, the muscular system lends itself to active learning as students can stand up to move their limbs and palpate various muscles to note their locations and actions.

However, I had a great deal of difficulty devising an active learning lesson plan for the skeletal system. I was not sure how to develop an engaging lesson for teaching bone names and markings. The use of anatomical models for hands-on active learning exercises would have been ideal, however, this was not feasible in a large class (>100 students). Knowing the benefits of active learning, however, I was committed to using active learning to teach my course, even for the skeletal system. Therefore, I designed some activities, tried them out, and refined them over the years.

I found that the key to making these active learning exercises effective is *holding students accountable for learning prior to class*. If students come to class without any prior preparation or exposure to the topic at hand, they will need to rely on the instructor to provide them with content to use for active learning exercises. However, if students prepare before class, either by reading their textbooks, watching videos, or

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completing pre-class assignments, class time can become a practice session. I can ask students a series of questions to test the knowledge they acquired prior to class or have them complete exercises on their own or in a group. Each of these strategies allows students to assess their own knowledge. This is valuable since frequent assessment and retrieval practice have been shown to improve learning (Roediger and Karpicke 2006, Butler and Roediger 2007, Karpicke and Blunt 2011). Therefore, not only does this method allow for an easier way to incorporate active learning exercises into lessons, it may also help students learn more than they would have done on their own.

Courses that include frequent assessment (e.g., pre-class content acquisition and graded assignments, in-class active learning, and weekly graded review assignments) are called high structure courses (Freeman *et al.* 2011, Haak *et al.* 2011, Eddy and Hogan 2014). These courses are referred to as “high structure” because there are many checkpoints built in for formative and summative assessment. In a similar vein, courses that include a pre-class learning component to facilitate the inclusion of in-class active learning exercises as well as formative assessments are referred to as flipped classes (O’Flaherty and Phillips 2015). In the case of my upper-division high structure undergraduate human anatomy course (Shaffer 2016), students acquire content prior to class through custom reading guides that are designed to help students read their textbook. To test what they learned from reading, students are assessed through graded on-line pre-class assignments. In class, students are engaged through individual and group active learning exercises. Finally, students complete graded on-line weekly review quizzes that allow them to study in smaller chunks each week to help them prepare for larger summative exams (Shaffer 2016). Through this high structure course design, students come to class prepared and are ready to further test their knowledge. The students have both in-class and out-of-class opportunities to practice applying what they have learned, and to better master the course content. While this course design requires a large amount of student work and preparation, student performance in my course has been exceptional with the pass rate typically greater than 90%. In addition, students rate the structure of the course components very positively and frequently describe this course as one of their favorite college courses (Shaffer 2016).

Below are some specific examples of active learning exercises that I have designed to help teach skeletal system anatomy. I use these activities in the lecture component of my large enrollment (~140 students), high structure, undergraduate human anatomy course (Shaffer 2016). Each of these activities is preceded by a pre-class assignment that holds students accountable for learning content before they come to class. These activities can be easily modified for different class sizes, and the basic design of the activities can be used as the basis for similar activities when teaching other organ systems.

Example 1: Labeling the Skull

This activity was designed to help students ease into gross skeletal anatomy. The learning objectives of this activity are for students to be able to identify skull bones and markings, as well as develop good study habits. This activity can be adapted for virtually any organ or structure in the body, but I especially like to use it for the skull since we cover the skull early on in our course, usually in the second or third week of class. Introduced at this time, the activity can promote good study habits that students can use throughout the course.

For this activity, you will need to make copies of a worksheet with various views of the skull. For example, you may include an anterior view and a lateral view on one side of the worksheet, and a posterior view and an inferior view on the back of the worksheet. You can use images that come with your textbook or atlas or find freely available images on the web. Label one side of the worksheet “A” and the other side “B”.

Ask your students to put their notes and books away and pass out one worksheet per student. Set a timer for two minutes and tell them to label everything that they can on side “A.” Once the time is up, tell them to flip it over to side “B” and again give them two minutes to label everything they can. Once the time is up, project a slide (or have written on the board) a list of all of the structures that students should be able to identify on the four views of the skull that they have on their worksheet. In my course, students should be able to identify 48 different structures (bones and markings). Give the students another two minutes to identify any structures that they may have not initially labeled. Finally, give students two minutes to trade worksheets with each other to check each other’s labeling. When the time is up, have the students return the worksheets to their owners and debrief them on the activity (see below). The entire activity should take about 10 minutes to complete.

This activity not only provides students with practice labeling the skull, but it also teaches good study habits for anatomy and physiology courses. Remind students that labeling blank images can be an excellent way to study and identify structures and that it may be more effective than simply looking at the labeled images in the textbook. Students can opt to print out or draw the various views of the skull and label the bones and markings from memory. I tell students that everything they need to know is in their textbook and thus they should check their work when class is over.

Example 2: Comparing and Contrasting Vertebral Characteristics

While most anatomy and physiology textbooks depict the typical structures of cervical, thoracic, and lumbar vertebrae, they may only show one representative vertebrae for each region e.g. C5, T6 or L2. This may lead students to believe that all vertebrae of a certain type are identical or very similar, which is not the case. The learning objectives for this

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activity are for students to be able to compare and contrast the characteristics of cervical, thoracic, and lumbar vertebrae and to be able to describe how the vertebral characteristics change along the length of the vertebral column.

For this activity, you will need a PowerPoint slide or a worksheet that contains several images of vertebrae. In my course, I show the following eight different images of vertebrae: left lateral views of C4, T6, T12, and L2, and superior views of C7, T2, T12, and L5. T12 is especially important to include as at first glance it appears to share more characteristics of a lumbar vertebra rather than thoracic. You can use images from your textbook or atlas or find freely available images on the web. I use images from the Thieme Atlas of Anatomy (Gilroy *et al.* 2012.) as they provide many views the vertebrae.

As a warm-up activity in class, give students two minutes to compare and contrast vertebrae characteristics with each other e.g. shape of the vertebral foramen, body shape, spinous process angle, movements allowed, etc. Then show the PowerPoint slide or pass out the handout of unlabeled vertebrae. Give students one minute to identify each vertebra as cervical, thoracic, or lumbar. Then ask the class using a personal response system or by show of fingers how many vertebrae are from the thoracic region. Then give students one minute to discuss their answer with their neighbors and re-poll the class. Usually at this point very few students identify all of the vertebrae correctly. Reveal the true number of thoracic vertebrae on the PowerPoint or handout and ask students to identify those vertebrae. After one more minute of discussion you can reveal the identities of each vertebrae and then lead a class discussion about vertebral characteristics and regional variations in structure. I usually compare the images of T2 and T12 to show how thoracic vertebrae differ from superior to inferior and then I compare T12 and L2 to show how inferior thoracic vertebrae begin to resemble lumbar vertebrae in size and shape. The entire activity should take about 10 minutes to complete.

Other Brief Examples

Below are some other examples of active learning exercises that you can use when teaching skeletal system anatomy. These activities should take two minutes or less in each case, but can be expanded as needed.

- Give students a list of bone markings and have them work together to identify what bones they belong to and what their functions are.
- Have students draw a superior view of a thoracic vertebrae from memory and label the structures.
- Show students an image of a bone (e.g. the humerus) with a few leader lines labeled A, B, C, D, and E and ask students to identify a specific marking using a classroom response system.
- Show students an image of the bones of the hand and ask them to determine if the image is an anterior or posterior view, and additionally if this is an image of the left or right hand. For example, show an anterior view of the right hand and after students work to determine left/right and anterior/posterior, you can have a discussion about how to determine bones and structures from different views.
- Provide a clinical vignette or case to add medical context and have students identify the bones involved. For example: "A 31-year-old female went to the ER with severe swelling and pain in the metatarsal and tarsal regions after a climbing accident. X-rays showed fractures in the most lateral metatarsal and the tarsal immediately proximal to it. What bones did she fracture?"

Conclusion

By holding students accountable before class it is possible to turn any class session and any topic into a practice lesson using active learning exercises. Not only will this enliven class and make it more engaging, but students will also be practicing the application of their knowledge thus enhancing their learning in the process. Developing and using these exercises has shown me that active learning can be incorporated into lessons about skeletal system anatomy and now I would not think of teaching it any other way. Indeed, I teach most of my lessons using a similar approach and each one is not only engaging but also fun. All of my course materials (syllabus, lessons, reading guides, exams, etc.) are available upon request.

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About the author

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From Conference to Classroom: Ultrasonography in Anatomical Education

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Abstract

Ultrasound provides a practical and clinically relevant learning experience for anatomy students. At the 4th Annual Ultrasound in Anatomy and Physiology Education Conference, I learned more about the role of ultrasound in medical training and how it could supplement traditional anatomical and physiological education. After the conference, I was witness to the introduction of ultrasound into an anatomy classroom. With the declining cost, ease-of-use and low-risk nature of the devices, ultrasound may prove to be a valuable teaching tool for future anatomical education.

Key words: anatomy education, ultrasound, technology

Introduction

We have entered a new age of technology in the classroom. With devices becoming smaller, less expensive, and easier to use, their presence in the classroom is becoming more and more likely. Combined with the push for vitalization in the medical sciences curriculum, there are an overwhelming abundance of possibilities for enhancing the new anatomy classroom. In the last few years, ultrasonography has found a place as a valuable teaching tool in the anatomy classroom. This “new” tool has found a niche in the intersection between the need of curriculum re-development and the increased presence of technology in the classroom. The factors leading to this rise include the lowered cost of ultrasonography devices, their ease of use, and their high relevance both clinically and academically.

The Conference

Funded by a HAPS student grant, I attended the 4th Annual Ultrasound in Anatomy and Physiology Education Conference hosted by the Society of Ultrasound in Medical Education (SUSME) at The Ohio State University in Columbus in March of 2016. The conference consisted of a mixture of talks presented by experienced educators and active hands-on experience for participants with ultrasound based protocols. The conference was highly skewed towards physician education since most of the conference organizers were involved in graduate medical education. Despite the primary discussion revolving around medical education, the benefits of ultrasonography for anatomical education are apparent.

Similar to other imaging technology used in anatomical education, ultrasonography provides students with an opportunity to apply their anatomical knowledge while simultaneously learning a clinically relevant skill. Participants at the conference were actively introduced to the possibilities of using ultrasound through multiple practice sessions

each day. Experienced sonographers and medical students led these practice sessions. Each session was focused on a different anatomical area including the abdomen, thorax, neck, and wrist. As conference attendees practiced with the ultrasound machines, the group leaders shared tips for finding structures and ways to scaffold learning about using the machine and applying anatomical knowledge. It was easy to see how ultrasonography could be a valuable activity in the classroom.

Conference speakers from more than five institutions across the country reported that they support the endeavor to integrate ultrasound into medical education and they detailed a number of ways in which they had integrated ultrasound into their programs. From Ohio State to North and South Carolina, the conference speakers detailed the ways they had integrated ultrasound into their programs. Assessments of the skills required by medical schools for ultrasonography varied from images as test questions to practical examinations that each student completed to assess their anatomical knowledge and clinical skills. Each institution has adapted their programs to best fit their curriculum and the needs of their students. For example, Ohio State has even turned to social media to reach a wide audience. Program directors often tweet an ultrasound challenge from a Twitter account, @EDUUltrasound, and tweet the answer later in the day. Social media is used extensively to reach ultrasound students at Ohio State and 81.5% of Twitter followers report finding the information useful (Bahner *et al.* 2012).

Overall, the conference provided a wonderful introduction to the role of ultrasound in anatomical and medical education. With the declining cost of ultrasound devices and as the devices themselves get smaller and smaller (one company has an ultrasound transducer that can be used with a smartphone), ultrasound is likely to become more prevalent in medical education. As the future of this technology

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changes, its role in the classroom can be expected to change. I was fortunate to be able to witness this emerging role a few months after the conference.

The Classroom

A few months after the conference at Ohio State, I moved to Indiana University-Bloomington to begin doctoral study in the Anatomy and Cell Biology program with a focus on Anatomy Education. This experience was exciting for many reasons. Indiana University had just re-structured its medical school curriculum and the new Human Structure course (Gross Anatomy and Histology) would be introducing ultrasound to the first-year class. This was a rare opportunity to witness the application of classroom protocols similar to those that were demonstrated at a conference.

The course was broken into blocks based on regional anatomy, with each block having a short session of lab time devoted to ultrasound practice and demonstration by instructors and teaching assistants. Students alternated from the gross laboratory session (typically a 2-3 hour session, 3 days a week) to attend a 20-30 minute ultrasound session. A demonstration of structures was done followed by time for students to practice. Emphasis was mostly placed on increasing familiarity with the machines, practicing professional methods of patient interaction and connecting anatomical knowledge. Students were later assessed by practical exam using a couple ultrasound images amid CT, MRI, radiological and histological images.

As a student in the course, I found these short sessions to be a reprieve from the fast-paced nature of dissection. This was an occasion to condense anatomical knowledge and apply it in a new setting. The medical students within the course jumped at the opportunity to practice clinical skills and witness their own living anatomy. As a graduate student, I enjoyed applying knowledge of tissues and predicting the different textures and colors that these tissues cause. From the different presentation of tissues to the visualized physiology of the cardiac system, it seemed as the ultrasound sessions had something for everyone. However, the sessions could be overwhelming for students who were unfamiliar with the targeted anatomy for that session. There was also a learning curve associated with understanding how structures are represented on the ultrasound screen. Students tended to struggle in the beginning with being able to orient the view seen on the ultrasound screen but they quickly caught on by identifying certain key structures.

Despite the overall positive learning experience, the educational scientist in me could not let a personal learning experience be enough to encourage others to adopt ultrasound in their anatomy classrooms. I turned to the research to see if ultrasound was providing a significant experience. While we are in the early stages of research into

ultrasound in medical education, the results are promising. No significant difference in knowledge was found between students taught with cadaveric prosection (n=55) and students taught cardiac anatomy with ultrasound (n=53), (independent t-test, $t = 0.065$, $P = 0.948$) (Griksaitis *et al.* 2012). Ultrasound has been shown to be just as effective teaching cardiac anatomy as cadaveric prosections (Griksaitis *et al.* 2012). Student perceptions of ultrasound have been favorable as well (Moscova *et al.* 2015, Sweetman *et al.* 2013). Royer (2016) found in a survey of United States Master's and Doctoral programs in Anatomy that 91% of anatomists surveyed believed that ultrasound reinforced anatomical concepts. However, only 15% of the programs surveyed offered hands-on training to graduate students (Royer, 2016). Jurjus *et al.* found that groups instructed in ultrasound by anatomists tested just as well as groups instructed by clinicians. Ultrasound education may become even more important in the coming years for non-medical graduate students as well.

Ultrasound is a safe and clinically relevant imaging modality that may serve as a valuable teaching tool. As class time is taken away due to provide a larger focus on clinically relevant experiences, ultrasound may serve as a method of getting students back into the gross anatomy lab. For more information on the Society of Ultrasound in Medical Education (SUSME) or ultrasound resources, check their website: <http://www.susme.org/>.

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About the Author

Theodore Smith, MS is a first-year Ph.D student in the Anatomy and Cell Biology-Education track program at Indiana University-Bloomington. He teaches undergraduate anatomy labs and is interested in classroom technology, spatial ability and student success, and curriculum re-design.

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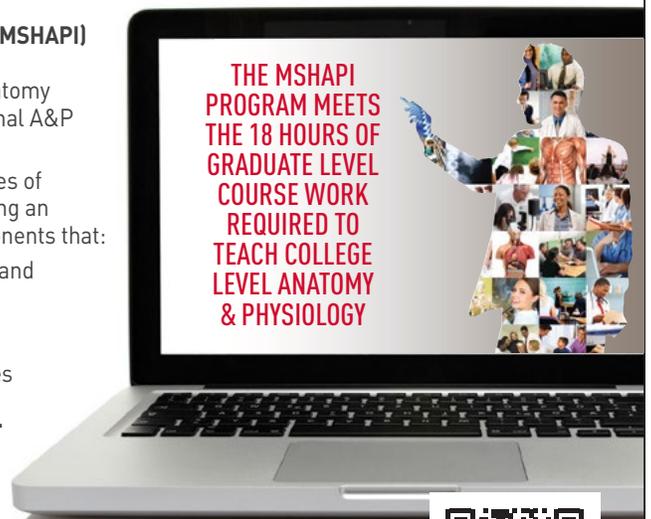
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The Benefits of Faculty-authored Course Materials for Students and Faculty

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Abstract

In the United States most of the discussion about textbook use by faculty tends to focus on whether it is ethical for faculty to require students to buy their published material because of the potential financial gain. We started to use our own course material a few years ago in our anatomy and physiology courses and examined how this change affected grades and passing rates for Anatomy and Physiology I courses. During the three-year reporting period our passing rate (students earning a final grade of A, B or C) climbed from 57.6% in Year 1 to 69.7% in Year 3 and more students earned a final grade of A or B. We were pleasantly surprised to find that we received better teaching evaluations by our students after introducing our own books in Year 2 and 3.

Key words: faculty authors, textbooks

Introduction

In the United States most of the discussion about textbook use by faculty over the last ten years or so has focused on whether it is ethical for faculty to require students to buy their published material. The 2004 statement titled *“On Professors Assigning Their Own Text to Students”* by the American Association of University Professors (AAUP 2004) addressed some of the key issues, especially the perception that faculty enrich themselves at the expense of their students and their parents. A search for articles related to the topic brings up articles that focus on this topic and most of the time the answer is “no”, faculty should not assign their own works to their course because of the potential for financial gain (Yale Daily News 2009, Study.com 2011, The Daily Illini 2013, Collegiate Times 2014, Psychology Today 2015).

Almost all states and most public American universities and colleges have policies regulating textbook adoption that include provisions on the role of faculty as textbook authors. For example, the Florida Board of Governors passed Regulation 8.003 Textbook Adoption in 2008 and our institution implemented FGCU-PR3.003 Textbook Adoption and Affordability in 2013.

We know from personal experience and discussions with colleagues that it is fairly common for faculty teaching in European countries to use their own textbooks in courses they teach. In fact, it is even encouraged by administrators and students. Faculty, who are not authors or co-authors of textbooks related to their course often publish or sell a printed version of extended lecture notes or other instructional resources to their students. It is also common at European universities for departments or programs to print lab manuals and to sell them at cost to students. However, countries such as Germany do not allow faculty to designate

required textbooks. Faculty may only give students a list of recommended books and a good portion of faculty will not include their own published works on that list. If the textbooks or manuals are published by one of the major publishers, students can ask for a written proof of enrollment in class, which enables them to purchase the books at a discounted price at bookstores. The discounts are subtracted from royalty payments to faculty so faculty will not benefit financially from their own students buying their books.

What seems to have gotten lost in the discussion here in the United States is the fact that faculty are highly educated professionals often with many years of teaching experience. If faculty are trusted to develop and teach courses based on their educational and professional background, they should also be trusted to develop written course content for their students. No doubt, textbook publishers go to great length to produce excellent books and additional support materials. We actually work in a college that is named after Elaine Nicpon Marieb, who has a long history of publishing anatomy and physiology textbooks. However, just like no one size fits all people, no one textbook fits all courses at all colleges. This may be especially true for anatomy and physiology courses as we prepare students for a rather wide variety of career options in the healthcare field. We felt that given our background in clinical medicine and medical illustration as well as our experience in teaching anatomy and physiology in private and public universities, we could develop course materials that would enhance the learning of our students. As we will lay out below, we found that there were tangible benefits for both our students and ourselves, which is why we decided to write this short article. Faculty can author or co-author course material for their classes in various ways,

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and we hope that our experience will encourage others to try their hand at it too.

Methods

Our anatomy and physiology course is a typical two-semester course sequence subdivided in two parts, Anatomy and Physiology I and II. Both courses are combined courses consisting of a lecture component and lab sessions. The lecture part is teacher-centered whereas the lab sessions are learner-centered and emphasize active learning strategies. Students receive one final grade based on their overall performance in lecture exams and the lab sessions.

We narrowed the data analysis down to Anatomy and Physiology I only, because a varying number of Anatomy and Physiology II students are transfer students from other institutions with different anatomy and physiology backgrounds, so they often have used or still use other textbooks. The percentage of students repeating Anatomy and Physiology I was almost constant, ranging from 3.5% for year 1 to 3.9% for years 2 and 3.

We decided to subdivide the three-year period we used for this article into Year 1, 2 and 3. During the first year the students were required to buy a textbook (Marieb and Hoehn, *Anatomy & Physiology*, 4th ed. Pearson) and a lab manual (Allen and Harper *Laboratory Manual for Anatomy and Physiology* 4th ed. Wiley).

The textbook stayed the same for the second year, but we replaced the lab manual with our own book (*Anatomy & Physiology I Course Companion and Lab Workbook*). The book was mainly designed and written by us with help and input from some of our adjunct lab instructors. The book was called a Course Companion because the modules were specifically designed for our course and our students. The text passages were short, often not much more than bulleted lists of definitions or short explanations. It was designed to be used along with the required textbook.

Things changed even more for Year 3. Students were now required to purchase the 2nd edition of our *Anatomy & Physiology Course Companion and Lab Workbook* as well as the newly created pocket book *Anatomy & Physiology Essentials*. The Course Companion and Lab Workbook consisted of two parts: a Course Companion with short chapters with integrated illustrations, and a Lab Workbook with lab modules, labeling exercises and activities. The *Anatomy & Physiology Essentials* was a cliff notes-style pocketbook with 212 pages. We decided to not require a textbook, because we had learned from the bookstore that only about 15-20% of our students had bought the required textbook the year before. Instead we prepared a list of suitable textbooks, but left the purchasing decision to our students. We discussed the limitations of our own books with our students and educated them on the benefits of having a standard textbook in

addition to our books.

The content and set up of lecture and lab sessions did not change over the three years. We also continued to use the same quizzes, lab practicals, and exams.

Currently we are in Year 6 of teaching the course with the latest editions of our books. However, too many variables changed after year 3 to include data from years 3-5 in this article. For example, the State of Florida switched from Student Assessment of Instruction (SAI) to Student Perception of Instruction (SPOI). We also started to offer hybrid courses with an online virtual lecture component and incorporated flipped classroom techniques in all courses offered.

Please note that this was not a preplanned study, otherwise we would have used survey tools other than SAI to get the student perceptions of the textbooks we used.

Analysis

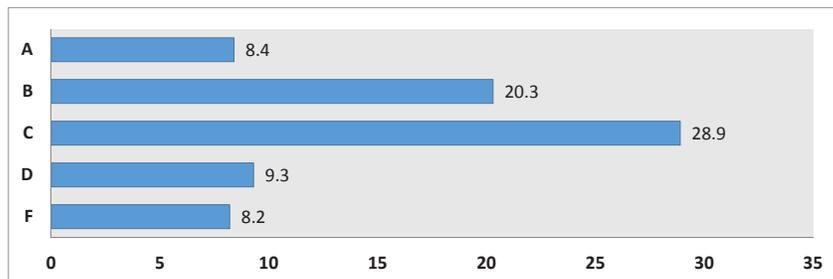
A Pearson Chi-Square test (used to test differences between sets of categorical data) was used to test whether the annual passing rate (the proportion of students that passed with a C-grade or higher out of the total number of students that initially enrolled in the course) changed across the three-year time period. A one-tailed Fisher's Exact Test was used to examine whether passing rates increased between years 1 and 2 and again between years 2 and 3. A Pearson Chi-Square test and one-tailed Fisher's Exact Tests were used to test:

- 1) whether the proportion of students earning an 'A' grade changed over the three-year time period and whether this change could be seen as an increase between years 1-2 and 2-3
- 2) whether the proportion of students withdrawing from the course changed over the three-year time period, and whether this change could be seen as a decrease between years 1-2 and 2-3.

Results

Overall 453 students were enrolled in Anatomy and Physiology I during Year 1. One hundred and thirteen students (24.9%) withdrew during the term and 340 students (75.1%) completed the course. Of those 340 students, 261 students (57.6 % overall) earned a passing final grade of A, B, or C.

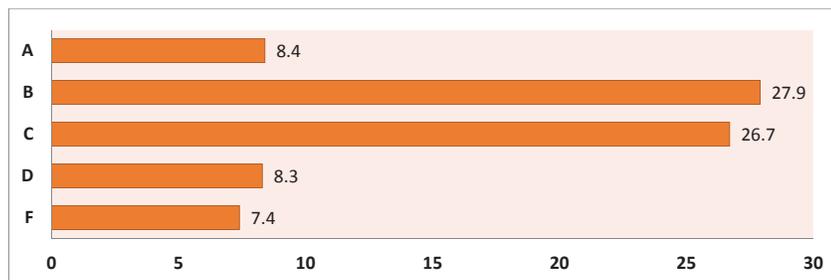
Diagram 1. Percentage of students earning a certain final grade for Year 1 (n = 453)



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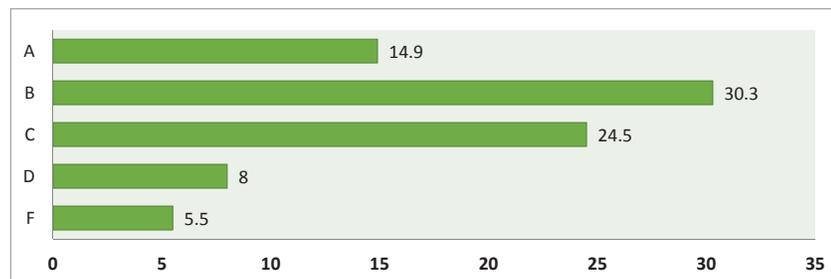
The number of students enrolled increased to 540 for Year 2. The percentage of students who withdrew during the term was 21.3% (n = 115), i.e. 425 students (78.7%) completed the course. The overall passing rate was 63.0% (n = 340) with 8.4% of students earning an A, 27.9% earning a B, and 26.7% earning a C as a final grade.

Diagram 2. Percentage of students earning a certain final grade for Year 2 (n = 540)



Enrollment rose again to 597 students for Year 3 with 497 students (83.2%) completing the course and 100 students (16.8%) withdrawing during the term. The overall passing rate increased again (69.7%) as did the percentage of students earning an A as a final grade (14.9%).

Diagram 3. Percentage of students earning a certain final grade for Year 3 (n = 597)



The proportion of students earning a grade of 'A' differed among the three years in which data were collected (Pearson Chi-Square Test, Chi-Square = 16.578, DF = 2, n = 1590, p < 0.0003). The proportion of students earning a grade of 'A' did not increase in year 2 compared to year 1 (Fisher's one-tailed exact test, DF = 1, n = 993, p = 0.5592). However, the proportion of students earning a grade of 'A' did increase in year 3 compared to year 2 (Fisher's one-tailed exact test, DF = 1, n = 1137, p = 0.0004).

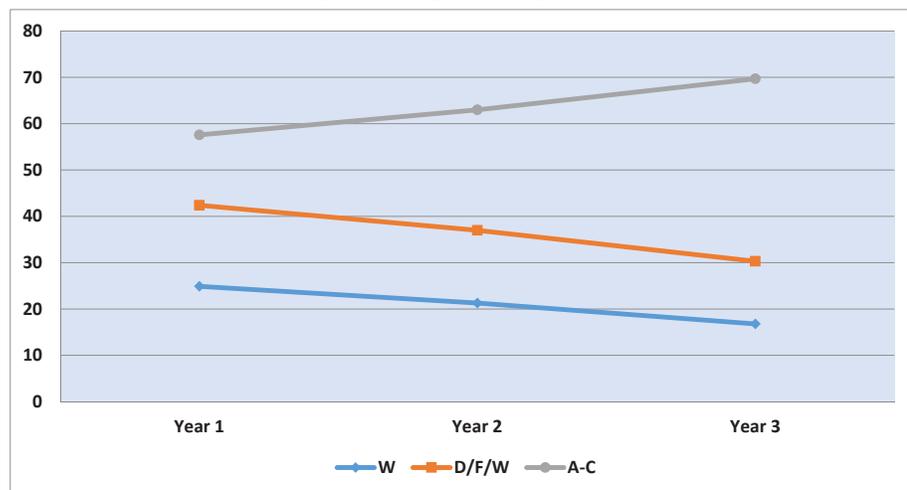
Table 1. Percentage of students earning a certain final grade for Year 1, 2 and 3

Grade	Year 1 (n = 453)	Year 2 (n = 540)	Year 3 (n = 597)
A	8.4%	8.4%	14.9%
B	20.3%	27.9%	30.3%
C	28.9%	26.7%	24.5%
D	9.3%	8.3%	8.0%
F	8.2%	7.4%	5.5%

The percentage of students withdrawing from class or failing to earn a passing grade (A, B or C) decreased and our passing rate climbed from 57.6% in Year 1 to 69.7% in Year 3.

Increasing the overall passing rates as well as the percentage of students excelling in class by achieving a final grade of A are positive outcomes for students, faculty and our

Diagram 4. Percentage of students earning a passing grade (green), withdrawing during the term (blue) and withdrawing or earning a failing grade (red) for Year 1, 2 and 3



institution. However, we also received improved teaching evaluations by our students. Until recently institutions in the Florida State University System used a standardized Student Assessment of Instruction (SAI) tool to get feedback from students about each course and its course faculty. The questionnaire had 20 questions overall. We chose four question, the answers to which could reasonably be influenced by the use of faculty-authored course material to look at. They were:

1. Overall assessment of instructor*
2. The instructor uses a variety of instructional materials/methods in the course**
3. I recommend the instructor**
4. I have learned a great deal about the subject**

The passing rate differed among the three years in which data were collected (Pearson Chi-Square Test, Chi-Square = 16.622, DF = 2, n = 1590, p < 0.0002). The proportion of students receiving a passing grade was higher in year 2 than in year 1 (Fisher's one-tailed exact test, DF = 1, n = 993, p < 0.0493). The proportion of students receiving a passing grade increased again from year 2 to year 3 (Fisher's one-tailed exact test, DF = 1, n = 1137, p = 0.0170).

The proportion of students withdrawing from the course differed among the three years in which data were collected (Pearson Chi-Square Test, Chi-Square = 10.785, DF = 2, n = 1590, p < 0.0046). The proportion of students withdrawing from the course did not decrease in year 2 compared to year 1 (Fisher's one-tailed exact test, DF = 1, n = 993, p = 0.0994). However, the proportion of students withdrawing from the course did decrease in year 3 compared to year 2 (Fisher's one-tailed exact test, DF = 1, n = 1137, p = 0.0302).

* Grading scale: Poor – Fair – Good – Very good – Excellent

** Grading scale: Strongly disagree – Disagree – Neither agree nor disagree – Agree – Strongly agree

We only looked at SAI scores for one of us (P.R.), as he was the lecturer for all A&P I courses during Year 1-3. The percentage of students competing SAIs was almost constant over the three year period. In year 1 79.1% of students enrolled in class in week 14 competed an SAI. For year 2 the percentage was 77.6% and for year 3 79.7%. The average scores for all four items went up from Year 1 to Year 3, with the biggest increases for items 1 and 2. While many factors contribute to student assessment of these items, it still is encouraging to see those increased numbers because they are part of the promotion portfolio.

Table 2. Average evaluation score for selected SAI items (see above) for Year 1, 2, and 3.

SAI Item	Year 1	Year 2	Year 3
1. Overall assessment of instructor	3.7/5	4.0/5	4.4/5
2. The instructor uses a variety of instructional materials/methods in the course	3.6/5	3.7/5	4.3/5
3. I recommend the instructor	4.0/5	4.2/5	4.6/5
4. I have learned a great deal about the subject	4.3/5	4.4/5	4.7/5

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Discussion

Many factors influence how well students perform in anatomy and physiology and other science classes. Faculty only have a limited number of tools available to positively influence overall passing rates, while holding the students to a high standard of achievement. Our short analysis shows that the use of faculty-authored course material can play an important role in increasing student success and in lowering D/F/W rates. This success is not only important for students, but also for college administrators at a time of increased performance-based (i.e., metrics-based) funding efforts.

A neglected or forgotten positive side-effect is the increased appreciation of faculty by students that leads to more positive feedback and evaluations in SAs (Student Assessment of Instruction) and SPoIs (Student Perception of Instruction), which are important for annual evaluations as well as promotion decisions.

About the Authors

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Valerie Weiss, MD, MS is an Adjunct Professor at Florida Gulf Coast University where she teaches undergraduate anatomy and physiology to students in the pre-health professions. She is also a medical illustrator, contributing to the course companion and lab workbook used in the course.

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