A double-blind atropine trial for active learning of autonomic function

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Fry JR, Burr SA. A double-blind atropine trial for active learning of autonomic function. Adv Physiol Educ 35: 438–444, 2011; doi:10.1152/advan.00075.2011.—Here, we describe a human physiology laboratory class measuring changes in autonomic function over time in response to atropine. Students use themselves as subjects, generating ownership and self-interest in the learning as well as directly experiencing the active link between physiology and pharmacology in people. The class is designed to concomitantly convey the importance of bias in experimentation by adopting a double-blind placebo-controlled approach. We have used this class effectively in various forms with ~600 students receiving atropine over the last 16 yr. This class has received favorable feedback from staff and students of medicine, pharmacy, and neuroscience, and we recommend it for such undergraduates. The learning objectives that students are expected to achieve are to be able to 1) know the ethical, safety, and hygiene requirements for using human volunteers as subjects; 2) implement and explain a double-blind placebo-controlled trial; 3) design, agree, and execute a protocol for making (and accurately recording) precise reproducible measurements of pulse rate, pupil diameter, and salivary flow; 4) evaluate the importance of predose periods and measurement consistency to detect effects (including any reversibility) after an intervention; 5) experience direct cause-and-effect relationships integrating physiology with pharmacology in people; 6) calculate appropriate summary statistics to describe the data and determine the data’s statistical significance; 7) recognize normal variability both within and between subjects in baseline physiological parameters and also recognize normal variability in response to pharmacological treatment; 8) infer the distribution and role of muscarinic receptors in the autonomic nervous system with respect to the heart, eye, and mouth; 9) identify and explain the clinical significance of differences in effect due to the route and formulation of atropine; 10) produce and deliver a concise oral presentation of experimental findings; and 11) produce a written report in the form of a short scientific research article. The results of a typical study are presented, which demonstrate that the administration of atropine by a subcutaneous injection elicited a significant increase in pulse rate and pupil diameter and a significant decrease in salivary flow, whereas administration of atropine in an oral liquid elicited significant effects on pulse rate and salivary flow, and an oral solid format elicited a significant alteration in salivary flow alone. More detailed analysis of the salivary flow data demonstrated clear differences between the routes of administration and formulation in the onset and magnitude of action of atropine.

human physiology; autonomic laboratory; placebo controlled

UNDERSTANDING the physiology and pharmacology of the autonomic nervous system is a key component of modern medical science. This is frequently taught ex cathedra, although useful adjuncts are provided at some institutions involving interactive computer programs based on predictive mathematical models (14), ex vivo isolated tissue models (3), either conscious (12) or unconscious (4) in vivo animal models, or problem solving of case studies (17). Here, we describe how to implement a laboratory class whereby students themselves receive a known anti-muscarinic drug or placebo treatment and make sequential measurements of their own parasympathetic responses. Atropine is known to act as a muscarinic receptor antagonist in humans, whether given by a subcutaneous injection or taken orally as either liquid or tablet (9). The anti-muscarinic effects include tachycardia, mydriasis, and xerostomia. All three effects occur earlier and with greater magnitude with injection than oral exposure and with liquid than solid ingestion, as would be expected due to a more rapid absorption and distribution. In addition, at total doses of between 0.5 and 2 mg atropine, bradycardia is known to precede tachycardia in adults (9). However, the expectations of investigators and subjects can bias measurements. Random anonymized allocation to either atropine treatment or equivalent placebo control ensures that the preconceptions of both students and staff do not unduly influence data collection. This enables a more accurate test of the importance of the route of administration and formulation for the physiological effects of atropine in humans.

In most scientific experiments, there is a need to avoid bias in the making of observations and measurements. With experiments involving drugs, this bias may arise from knowing the action of the drug and therefore what sort of change to expect and the direction (i.e., increase or decrease) in which it should occur. The need to minimize bias is particularly strong when observations are made of drug effects in humans. The double-blind clinical trial has evolved to allow unbiased comparisons to be made of drug effects in disease (7a), and the principles of the double-blind trial are used in this laboratory class to measure a drug effect in humans. To take account of spontaneous changes in the parameters that are measured, the response to an inactive substance (a placebo) is also investigated. Neither the subjects who receive the drug nor the observers who make the measurements will know whether they are studying the effects of the active drug or the placebo; the trial is thus “double blind.” The allocation of any particular subject to the test group (active drug) or to the control group (placebo) will not be done in any systematic manner but will be done randomly. In clinical trial practice, this eliminates one source of bias in deciding which patient will receive which treatment. The groups should be of equal size and demographic profile (age, weight, sex) to minimize the bias that would result from unbalanced groups.

Experiential learning involves the learner in a concrete experience (6). Achieving this through inquiry-based learning
is popular in empirical science as it relies on teachers creating problems for the students to solve. But how much guidance from the teacher is appropriate to maximize student learning? Discovery learning (1) espouses learning by doing, so as to learn to better apply oneself to solving problems, but learning from one’s mistakes, while engendering deep reinforcement, can be slow and demotivating. Active learning goes further, by focusing the responsibility for decision making onto the learners, to engage in problem solving by asking their own questions or questions of themselves. There is now a substantial body of published evidence to support the proposition that active learning works and should be more widely adopted (8). Unfortunately, limited resources often prohibit the implementation of classes based on active learning because they usually require small-group activities. However, the implicit benefits of active knowledge over passive belief (16) can still be achieved without the need for costly small problem-based learning groups, as is the case with the class described here. “Students making measurements on themselves” represents an alternative discrete subcategory of active learning that has previously lacked consideration. The clinical relevance and self-interest perceived in classes such as this attracts and holds the attention of students. Thus, maximizing realism while focusing the responsibility for decision making onto the learners can be slow and demotivating. Active learning goes further, by learning from one’s mistakes, while engendering deep reinforcement, can be slow and demotivating. Active learning goes further, by

**METHODS**

**Integrating the Class as a Coherent Course Component**

In its current incarnation, the class has required 2 short days to run comfortably according to the following timetable.

**Day 1.** Day 1 is composed of the following activities:
- 1 h: instructional briefing by staff and division of roles and responsibilities
- 1 h: practice measurements and design and agreement of the protocol
- 3.5 h: data collection

**Day 2.** Day 2 is composed of the following activities:
- 1.5 h: data analysis
- 1.5 h: oral presentation (seminar) preparation
- 1 h: delivery of seminars and summary discussion
- 2 h: individual report writing (can be as a remote learning exercise)

The nature and purpose of the ethical review process for this practical class was discussed at the initial briefing. It was also made clear that a clinically qualified colleague would be available at the start of the practical class to answer any queries that students might have as to their suitability to be subjects; this included any disease that the students may have or medications that they may be taking.

The importance of balancing groups by sex was also stressed at this briefing session.

**Protocol Design**

A key feature of this plan was that the students practiced the measurements (given some general initial guidance; see below) and then used this experience to produce the final protocol for each measurement, which was then used by the entire class. This activity was done in discussion with the staff and aimed to produce reliable and reproducible measurements, often across multiple laboratory work areas. The final agreed protocol was then copied and distributed for the whole class to adhere to. As an example, the students were informed that pulse rate was to be measured at the wrist, but they were expected to devise the best protocol that minimized error and bias in the measurements, so that timing of counting the number of pulses, the positioning of the wrist, etc. were considered.

**Ethical and Safety Considerations**

The protocol was approved in advance by the Medical School Ethics Committee of the University of Nottingham. A medically qualified member of the staff was needed to administer the injections and to be available in case of any adverse reactions; however, over 16 yr, a total of ~600 students have received atropine in this class or a variation of it without incident. Having read the supporting information sheets, students who wished to volunteer to be subjects signed the approved consent forms. Usually half of the class volunteered. Each volunteer joined one (or more) nonvolunteer, and the workload of making observations, recording data, and, most importantly, taking responsibility for the safety of the volunteer was charged to the nonvolunteer observers. Copies of the current information sheet for volunteers and of the consent forms are provided as Supplemental Material.¹

**Measurements**

Pulse rate was measured by counting the pulse rate at the wrist (expressed in beats/min), and pupil diameter was measured using a pinhole pupillometer under uniform artificial lighting conditions.

Salivary flow was stimulated with citric acid and measured using a variation of the method described by Murrin (10). The subject swallowed all resting saliva, and four drops of 4% citric acid were then placed on the tongue (using a disposable plastic pipette dropper) and swilled around the mouth for 30 s without swallowing. Next, 4 ml water was introduced into the mouth (using a 5-ml plastic syringe) and swilled around for 15 s without swallowing. At the end of this 15-s period, the mixture of water and saliva was ejected into a plastic funnel placed in a plastic 10-ml measuring cylinder. The measured volume minus 4 ml gave the volume (in ml) of saliva produced during the test.

**Placebo/atropine dosage.** This class experiment was first developed as one in which atropine was administered as a subcutaneous injection. For this, a dose of 12 µg/kg body wt was chosen based on previous literature evidence of a reproducible effect at this dose when atropine was administered intramuscularly (9). This dose translates to a dose of 0.84 mg for an “average” 70-kg person.

More recently, this practical has been developed further to allow investigation of the effect of a different route of administration (oral) in different formulations (liquid and solid). Under these conditions, it was considered that a dose of 1.2 mg/subject would be appropriate, again being comparable with doses reported in the literature (10). Conveniently, this dose corresponded to two ampoules of atropine sulphate or two tablets of atropine sulphate formulations available in the United Kingdom (as listed in the British National Formulary), thus enabling easy preparation of the dosages.

To ensure that the double-blind nature of the experiment was not compromised by any taste of the atropine solution, the atropine or

¹ Supplemental Material for this article is available at the *Advances in Physiology Education* website.
placebo was administered in 200 ml apple juice. Furthermore, because of the unavailability of placebo tablets, the atropine tablets were packaged in gelatin capsules (at the Nottingham University Hospital Pharmacy), whereas empty gelatin capsules were used as the placebo control.

Thus, atropine (as the sulphate) was administered subcutaneously at a dose of 12 μg/kg body wt, with the placebo being an injection of 0.9% saline. Atropine sulphate solution was administered orally at a dose of 1.2 mg in 200 ml apple juice, with the placebo being 2 ml of 0.9% saline in 200 ml apple juice. Solid atropine sulphate was administered orally as tablets held within a gelatin capsule taken with 200 ml apple juice, with the placebo being an empty gelatin capsule, also taken with 200 ml apple juice.

A single member of staff randomly divided the subjects between the placebo and atropine treatments but kept the key secret until after all data collection had finished. The same member of staff administered the doses at the appointed time in the schedule as indicated below.

Postdose measurements. After subcutaneous injection, the cycle of measurements was continued every 10 min for a further 70 min and then at 90, 120, and 150 min after the injection.

Similarly, pulse rate, pupil diameter, and salivation were measured at 15-min intervals for 150 min after oral administration.

Data Analysis

At the end of the first day, the data from all subjects were collated, and these were then available for further analysis at the start of the second day. Typically, time-course graphs were prepared, and these were used as the basis for the statistical analysis of the effects of atropine.

RESULTS

The results of a typical experiment (with a class of 120 students in October 2002) are presented in Figs. 1–3, for subcutaneous, oral liquid, and oral solid treatments, respectively. From these, students were expected to comment on the direction of any changes, time of peak effects, and the duration of responses and recovery and to calculate statistical significance, this in the context of comparing both the route and formulation with the three physiological measures. Groups were balanced for sex in each arm of the study, and all subjects were in the age range of 19–21 yr.

Description of the Effects of Atropine

The subcutaneous administration of atropine elicited an increase in pulse rate and pupil diameter, together with a reduction in salivary flow, each of which was maximal at 50–60 min after administration. In the control group, pupil diameter and salivary flow remained reasonably constant throughout the experiment, whereas pulse rate fell by 10 beats/min during the time of the experiment. Although the two groups were balanced for sex and the students were all of the same age (19–21 yr), the baseline values (“predose”) were not superimposable, with these values being noticeably different in the salivation data.

In the oral liquid experiment, the administration of the placebo had no observable effect on any of the variables measured, with each remaining relatively constant throughout the experiment, whereas pulse rate fell by 10 beats/min during the time of the experiment. Although the two groups were balanced for sex and the students were all of the same age (19–21 yr), the baseline values (“predose”) were not superimposable, with these values being noticeably different in the salivation data.

In the oral solid experiment, all three variables remained relatively constant in the placebo group throughout the experimental period, although there was a suggestion of a slight increase in salivary flow at the later stages of the experiment. Pulse rate and pupil diameter also remained relatively constant in the atropine group throughout the experiment, whereas there was a reduction in salivary flow throughout the postadministration period, with this reduction reaching a plateau at 150

![Fig. 1. Effect of a subcutaneous injection of atropine (12 μg/kg; ▲) or an equivalent volume of 0.9% saline (placebo; ◆) on pulse rate (A), salivation (B), and pupil diameter (C). Three baseline measurements were taken, after which the injections were administered, and measurements were continued for a further 150–155 min. Values are means ± SE of 8–9 subjects.](http://advan.physiology.org/10.1152/advan.00024.2011)
groups were similar in the oral solid experiment, so that the raw values at time of peak effect could be used directly. The times for peak effect and the $P$ values for the $t$-test are shown in Table 1.

The results of these analyses demonstrated that the subcutaneous injection of atropine elicited significant ($P < 0.05$) changes in all three variables measured. The oral administration of atropine in a liquid formulation also produced significant changes in pulse rate and salivary flow but with no significant effect on pupil diameter, whereas the oral administration in a solid formulation elicited a significant change in salivary flow alone.

Fig. 3. Effect of oral administration of atropine (1.2 mg in gelatin capsule; ▲) or empty gelatin capsule (placebo; ●), both taken with 200 ml apple juice, on pulse rate (A), salivation (B), and pupil diameter (C). Three baseline measurements were taken, after which atropine or placebo was administered, and measurements were continued for a further 150–155 min. Values are means ± SE of 9–10 subjects.

Statistical Analysis

The statistical test adopted for this class was an unpaired $t$-test, performed on data collected at the time of greatest difference between the two groups. As reported above, a feature of the data collected in the injection and oral liquid experiment was that the baseline values were different for the two treatment groups. This was corrected for in the statistical analysis by subtracting the value at peak effect from the middle baseline value in the two treatment groups and using this difference in the unpaired $t$-test. The baseline values of the two groups were similar in the oral solid experiment, so that the raw values at time of peak effect could be used directly. The times for peak effect and the $P$ values for the $t$-test are shown in Table 1.

The results of these analyses demonstrated that the subcutaneous injection of atropine elicited significant ($P < 0.05$) changes in all three variables measured. The oral administration of atropine in a liquid formulation also produced significant changes in pulse rate and salivary flow but with no significant effect on pupil diameter, whereas the oral administration in a solid formulation elicited a significant change in salivary flow alone.
Students should be able to design a protocol, facilitated by practice (i.e., experience through manipulation, observation, and evaluation), that enables them to make reproducible measurements and investigate basic principles in real time. Time organization and the management of group dynamics are crucial to success.

**Comparison of Time Course and Magnitude of Effect**

The statistical analyses demonstrated that salivary flow was the most sensitive variable out of those measured with which to assess the action of atropine. Accordingly, this allowed a reworking of the data to more clearly present differences in timing and magnitude of response, as shown in Fig. 4. From this, it is apparent that the order of speed of effect of atropine is subcutaneous > oral liquid > oral solid. It is also apparent that an oral dose of 1.2 mg atropine in a liquid formulation produced essentially the same magnitude of effect as atropine given subcutaneously at a dose equivalent to 0.84 mg for a 70-kg person, whereas an oral dose of 1.2 mg in a solid formulation produced a lesser effect compared with the equivalent dose given in liquid formulation.

**DISCUSSION**

We have experience in running this laboratory class in various forms for the past 16 yr. Approximately 600 students have received atropine without any adverse incidents. Consequently, we recommend use of this class model for medicine, pharmacy, or neuroscience students in either their first or second year of undergraduate study, as a method of efficiently conveying a complex set of interrelated core learning objectives.

**Learning Objectives**

*Know the ethical, safety, and hygiene requirements for using human volunteers as subjects.* Students should be able to recall the most important aspects of declarative knowledge for the class (i.e., what facts the student needs to know to act responsibly when conducting medical experiments).

*Implement and explain a double-blind placebo-controlled trial.* Students should have the procedural knowledge needed to run a trial while eliminating the effects of expectation based on prior mechanistic knowledge (i.e., how to do medical experiments with minimum bias).

*Design, agree, and execute a protocol for making (and accurately recording) precise reproducible measurements of pulse rate, pupil diameter, and salivary flow.* Students should be able to actively design a protocol, facilitated by practice (i.e., discovery through manipulation, observation, and evaluation), that enables them to make reproducible measurements and investigate basic principles in real time. Time organization and the management of group dynamics are crucial to success.

Evaluate the importance of predose periods and measurement consistency to detect effects (including any reversibility) after an intervention. Students should be able to interpret the time course of an experiment (i.e., the direction of any changes, time of peak effects, and the duration of responses and recovery).

Experience direct cause-and-effect relationships integrating physiology with pharmacology in people. Students should gain first-hand experience of modulating functional regulation by pharmacological intervention. This is discovery learning, encouraging active construction of knowledge's meaning (1). One of the key distinguishing features of this class is the use of one’s self as the subject, to foster a greater ownership and interest in the findings of the work. As a consequence, enhanced motivation, deeper understanding, and longer retention should occur, leading, in turn, to more meaningful learning.

Calculate appropriate statistics to describe the data and the data's statistical significance. Students should be able to apply statistical knowledge and skills covered previously in our course. This objective provides both reinforcement and an opportunity to practice in an alternative applied setting.

Recognize normal variability in baseline physiological parameters and also recognize normal variability in response to pharmacological treatment. Students should be building a mental model where concepts map onto each other (11). Here, this includes the ability to recognize normal from abnormal responses, to be able to effectively take account of predose differences between placebo- and atropine-treated groups, and consequently convey misconceptions about treatment effect sizes.

Infer the distribution and role of muscarinic receptors in the autonomic nervous system with respect to the heart, eye, and mouth. Students should be able to confirm the expected antiparasympathetic physiological effects of atropine mediated via antagonism of muscarinic receptors (i.e., appreciation of an otherwise abstract reductionist mechanism of action).

Identify and explain the clinical significance of differences in effect due to the route and formulation of atropine. Students should recognize that the experiment is a realistic application of direct clinical relevance. They should identify the parallels between their findings and the intended and unwanted effects of chemicals on the body in real life. In particular, the potential for route and formulation effects on the efficacy of any drug, the clinical indications for using atropine, and side effects due to various forms for the past 16 yr. Approximately 600 students have received atropine without any adverse incidents. Consequently, we recommend use of this class model for medicine, pharmacy, or neuroscience students in either their first or second year of undergraduate study, as a method of efficiently conveying a complex set of interrelated core learning objectives.

**Table 1. Times to peak difference and P values for statistical analysis of values at peak effect**

<table>
<thead>
<tr>
<th></th>
<th>Time to Peak Difference, min</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
<td>50</td>
<td>0.0013</td>
</tr>
<tr>
<td>Pupil diameter</td>
<td>62.5</td>
<td>0.0034</td>
</tr>
<tr>
<td>Salivary flow</td>
<td>55</td>
<td>0.0010</td>
</tr>
<tr>
<td>Oral liquid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate</td>
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<td>0.0321</td>
</tr>
<tr>
<td>Pupil diameter</td>
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<td>0.2453</td>
</tr>
<tr>
<td>Salivary flow</td>
<td>155</td>
<td>0.0067</td>
</tr>
<tr>
<td>Oral solid</td>
<td></td>
<td></td>
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<td>Pulse rate</td>
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</tr>
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<td>Pupil diameter</td>
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</tr>
<tr>
<td>Salivary flow</td>
<td>140</td>
<td>0.0325</td>
</tr>
</tbody>
</table>

Fig. 4. Comparison of the time course of action of atropine on salivary flow when administered by a subcutaneous injection (●), oral liquid (■), or oral solid (▲). Values are means of 8–10 subjects.
to other drugs and toxins with anti-muscarinic mechanisms of action.

Produce and deliver a concise oral presentation of the findings. Students should be able to convey to others their scientific findings, adopting the language and format of the discipline being learned (7). Producing and delivering an oral presentation with visual aids (seminar) are also transferable skills (13). Each group of students is allocated a 10-min presentation slot and a specific topic to cover. Example topics might include the following: experimental design, data analysis, results, background physiology and pharmacology, and comparison of different routes and formulation. The group of students then decide what to include and how to deliver the presentation between them. This provides the opportunity for students to debate their findings independently of staff. The small groups also often informally compete to generate the best presentation. This motivates active collaborative learning from peers (5), both within and between groups. In addition, the requirement to publicly articulate self-explanations encourages the students to ensure that they have a deep understanding (2).

Produce a written report in the form of a short scientific research article. Fulfilling this objective requires independent work, which is partly self-directed and partly remote learning. Each student should present their own experimental data within the context of the whole class data, perform their own analysis, and convey their own interpretations of the findings. A focus on hypotheses reinforces a foundation to learning through testing ideas about preconceived concepts, by doing, and by realizing the complementary nature of content and process (i.e., undertaking a process to gain content that will enable an evaluation of the process). This reinforces the basis of advances made by research and provides the student with an opportunity to demonstrate that they can critically evaluate evidence and present their findings in the conventional format for scientific communications.

Related Points for Discussion

The experiment described in this report represents the version currently used at our institution for a large (~150 students in 2011) group of second-year pharmacy students, which, by virtue of the laboratory space available to us, can be performed with the entire year in one teaching session. This expedites a ready comparison of the different routes and formulations of exposure. Clearly, however, a number of simpler versions of this could be run depending on local circumstances, which could then incorporate suitable modifications. For example, it is possible to run the oral solution component of the experiment alone, in which case it would be possible to dose subjects according to body weight at a dose of, say, 20 μg/kg.

The level of statistical analysis that is undertaken is determined by the statistical expertise of the student group performing the experiment. Thus, a full analysis might involve analysis of variance of all the data, whereas a more simplified analysis might involve a two-group comparison at a fixed time point, correcting for differing baseline (predose) values if necessary, as used in this report. Alternatively, the atropine- and placebo-treated groups may be compared using area under the curve data.

As indicated in METHODS, dosing is, in part, based on the availability of tablet and liquid preparations of atropine in the United Kingdom, but similar experimental formats could be set up using locally available preparations. In the United States, for example, the 1.2-mg oral solid dose could be achieved with the 0.4-mg tablets available locally, whereas the oral liquid dose could use the 0.4-mg/ml preparation available locally (data on United States formulations from http://www.drugs.com/monograph/atropine.html; accessed 24 August 2011).

Most recently, we have used a similar experimental design to investigate the action of atropine as part of final-year degree projects, maintaining the essential element of protocol design that is a feature of this experimental learning approach. Under such circumstances, the students are required to devise their own information sheet and consent form for volunteers, and this acts as an additional valuable teaching tool.

If a similar experimental design is run over a number of years, a large results database will be generated, which, in turn, may provide a valuable teaching resource for other student-led activities, such as classes on data analysis and discussions of variability in drug responses.

In performing this experiment over several years, it has become apparent that atropine produces clear statistically significant effects on pulse rate and salivation when given subcutaneously or orally, but that pupil diameter occasionally shows little change (as with the oral liquid results presented in this report), a finding that appears to be at odds with what the students might expect from reading of textbooks. We ascribe this to the relative insensitivity of the measurement device and/or relative insensitivity of the muscarinic receptors in the eye and/or the presence of a structural or functional barrier to entry of systemically delivered atropine to the muscarinic receptors in the eye. In an experiment our students undertake in their first year, they have established that a muscarinic antagonist dropped directly into the eye produces the expected mydriasis. This difference acts as a further discussion point when considering the importance of the route of administration, using the students own prior experiential learning.

Summary

The class proposed here has the potential drawback of requiring medical cover and the small (in our experience unrealized) risk of an adverse reaction to atropine in a student. Nevertheless, the class remains for us a concrete participatory induction to several concepts that are fundamental to medical science. As can be seen from the learning objectives, the class elegantly encompasses all of the phases of Kolb’s cycle for experiential learning (6), with student design of the protocol enabling some repeat cycling. The class especially aims to maximize student engagement and so also share many of the advantages of active learning as described by Gupta et al. (4). However, in contrast, this class uses the students themselves as subjects and consequently not only engages the students even more closely but also has a comparatively low cost for a laboratory class. Should this class be adopted elsewhere, then it would be possible to directly evaluate its impact by changes in measures of student feedback and improved learning.

ACKNOWLEDGMENTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

J. R. F. and S. A. B., conception and design of the research; J. R. F. and S. A. B., performed the experiments; J. R. F., analyzed the data; J. R. F. and S. A. B., interpreted the results of the experiments; J. R. F., prepared the figures; S. A. B., drafted the manuscript; J. R. F., edited and revised the manuscript; J. R. F. and S. A. B., approved the final version of the manuscript.

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