Flexner 2.0—Longitudinal Study of Student Participation in a Campus-Wide General Pathology Course for Graduate Students at The University of Arizona

Margaret M. Briehl, PhD1, Mark A. Nelson, PhD1, Elizabeth A. Krupinski, PhD2, Kristine A. Erps1, Michael J. Holcomb1, John B. Weinstein, PhD3, and Ronald S. Weinstein, MD1,4,5

Abstract
Faculty members from the Department of Pathology at The University of Arizona College of Medicine-Tucson have offered a 4-credit course on enhanced general pathology for graduate students since 1996. The course is titled, “Mechanisms of Human Disease.” Between 1997 and 2016, 270 graduate students completed Mechanisms of Human Disease. The students came from 21 programs of study. Analysis of Variance, using course grade as the dependent and degree, program, gender, and year (1997-2016) as independent variables, indicated that there was no significant difference in final grade ($F = 0.112; P = .8856$) as a function of degree (doctorate: mean = 89.60, standard deviation = 5.75; master’s: mean = 89.34, standard deviation = 6.00; certificate program: mean = 88.64, standard deviation = 8.25), specific type of degree program ($F = 2.066, P = .1316$; life sciences: mean = 89.95, standard deviation = 6.40; pharmaceutical sciences: mean = 90.71, standard deviation = 4.57; physical sciences: mean = 87.79, standard deviation = 5.17), or as a function of gender ($F = 2.96, P = .0865$; males: mean = 88.09, standard deviation = 8.36; females: mean = 89.58, standard deviation = 5.82). Students in the physical and life sciences performed equally well. Mechanisms of Human Disease is a popular course that provides students enrolled in a variety of graduate programs with a medical school-based course on mechanisms of diseases. The addition of 2 new medically oriented Master of Science degree programs has nearly tripled enrollment. This graduate level course also potentially expands the interdisciplinary diversity of participants in our interprofessional education and collaborative practice exercises.

Keywords
Flexner 1.0, Flexner 2.0, Flexner 3.0, Flexner X.0, Flexner Report, Medical Science, STEM

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Introduction
At The University of Arizona, “Flexner 2.0” medical science courses are defined as medical sciences courses (eg, pathobiology, pathology, pharmacology, clinical microbiology) that are adapted from medical school curriculum and taught elsewhere in the university curriculum, ranging from college students to Doctor of Philosophy (PhD) students in biomedical engineering and Master of Public Health (MPH) students in public health. Flexner 3.0 was defined previously as medical science courses taught in K-12 schools.1 Medical schools teach
“Flexner 1.0” courses. Flexner X.0 is a family of medical science courses that can be taught either in middle schools, high schools, colleges, or graduate schools.

In 1910, the Carnegie Foundation for Education in America published a seminal report, authored by Abraham Flexner (often referred to as the “1910 Flexner Report”), on medical education. This is credited with transforming the United States’ apprenticeship-based medical education industry into our current university-based medical education system by 1930. Flexner recommended that medical science coursework be designated “upper-level” university coursework. For all practical purposes, pathology coursework was reserved exclusively for medical students for the next hundred years. A century later, in anticipation of the 2010 Flexner Centennial celebrations, there was a crescendo of both interest and concern over what became known as the “collateral damages” of the 1910 Flexner Report. Calls for a reevaluation of US medical education, in general, and the restructuring of the entrance requirements for medical schools, in particular, grew louder. On the other hand, an unanticipated benefit of this reevaluation activity was the freeing up of traditional medical school pathology coursework for teaching in environments other than medical schools. Today, this is manifested by the migration of medical school coursework onto undergraduate college campuses and even into K-12 schools. Recently, we described the successful implementation of K-12 General Pathology in Arizona public district and public charter middle and high schools.

The University of Arizona’s innovative K-12 General Pathology course was derived from the same medical college General Pathology Course used to create our graduate school “Mechanisms of Human Disease” (PATH 515) course described in this article. The PATH 515 content is more expansive than the K-12 General Pathology course to take advantage of the larger numbers of contact hours allocated to this graduate-level course. Other significant differences were the inclusion of 10 systems pathology lectures and 12 two-hour pathology laboratories in the graduate student version of the course (Appendix A, Appendix B, and Appendix C).

In this article, we provide longitudinal data on this single-semester graduate student course (PATH 515) based on course enrollment and student performance data sets collected over 19 consecutive years. We describe enrollment data and compare the performance of Master of Science (MS) degree students with PhD degree students.

Materials and Methods

Background

Mechanisms of Human Disease, designed for students pursuing a health science-related, non-MD, postbaccalaureate degree, was introduced at The University of Arizona in 1996. The course directors followed the university’s established procedure for a new course. Two basic science faculty members in the Department of Pathology met with the Chairs of Departments that offered PhD degrees in the biomedical sciences to assess the need for the course. Having established a perceived need for instruction in pathology to complement existing coursework available to graduate students, the PATH 515 course was designed based on content primarily in the first quarter of the College of Medicine’s year-long second-year Pathology course. The menu of lecture and laboratory topics is provided as Appendix A. The Graduate College reviewed the syllabus and schedule of class topics and officially approved the new course. It was first offered in spring 1996 and held every spring semester thereafter. The course consisted of two 75-minute lectures and a 2-hour laboratory session per week for 15 weeks. During the laboratory sessions, the students viewed gross and microscopic pathology that reinforced the content presented in the lectures. Data presented in this article were collected starting in 1997.

Institutional Review Board

An evaluation was conducted by the Human Subjects Protection Program at the University of Arizona, which determined that the proposed course did not constitute human subjects research as defined by 45 CFR 46.102(f).

Student Recruitment

Since PATH 515 was offered initially as an elective course, students were recruited by disseminating information about the course through relevant graduate programs. The program coordinators served as points of contact. The course directors created a flyer with the course title, meeting times, contact information for the course directors, and a course description. The flyer included the course objectives, which were stated as providing graduate-level instruction in pathobiology—the study of structural, functional, genetic, and biochemical changes in cells, tissues, and organs which cause or are caused by disease. The flyer/e-mail was delivered/distributed only once each year but was timed a few days before course registration began for the spring semester. The same flyer/e-mail was distributed to all recipients. We estimate that there were 75 to 100 students receiving the notice each year. With an average class size of 10 to 11, this represents 10% to 15% enrollment of the targeted graduate students.

General Information

From 1997 to 2003, the PATH 515 closely paralleled General Pathology, a course given by the Department of Pathology faculty in the first quarter of The University of Arizona medical students’ second year. The latter course was discontinued in 2003, in favor of a newly created, problem-based learning, organ-centric curriculum for medical students. It is noteworthy that, prior to 2003, the General Pathology course had received “Course-of-the-Year” honors, as selected by the medical students, 13 of the previous 16 years. The majority of “Basic Science Lifetime Teaching Awards” had gone to pathology...
faculty members as well. The graduate students’ Mechanisms of Human Disease course remains essentially intact today. As a practical matter, it has provided a venue for award-winning faculty members to continue teaching in a traditional, general pathology course format to graduate students who are interested in this content.

**Curriculum**

The topics covered in PATH 515 included cell injury, inflammation and repair, hemostasis and thrombosis, diseases of the immune system, neoplasia, genetic diseases, and infectious diseases. The PATH 515 was further enhanced by the inclusion of selected topics from the systems pathology course including, heart disease, hematopathology, renal diseases, oral and gastrointestinal diseases, liver diseases, diabetes, neuropathology, molecular diagnostics, and forensic pathology20 (Appendix A). The decisions on course topics were based on—(1) building an understanding of general pathological processes (eg, cell death, inflammation, neoplasia, and genetics), (2) showing how these processes manifest as diseases in different organ systems, (3) emphasizing diseases that cause the greatest number of deaths in the United States, and (4) capitalizing on the particular expertise of the Department of Pathology faculty. Adjustments to the course topics were made as new faculty were recruited either to replace departing faculty or expand the department’s expertise.

**Laboratories**

A weekly, 2-hour laboratory session reinforced the lecture content by giving the students the opportunity to study gross and microscopic specimens of normal and relevant diseased organs and tissues. Normal anatomy and histology were reviewed in the first laboratory session and prior to the presentation of diseased tissues, as instruction for students lacking a strong background in these subjects. Between 1996 and 2008, students studied tissue histopathology sections and cytopathology specimens through light microscopes. Each student was given a slide set of 95 specimens; 23 represented normal histology and the remainder illustrated the disease processes covered in the course. Starting in 2009, digital microscopic images (whole slide images) were introduced (Figure 1).21

In each whole slide imaging laboratory, 10 tables accommodating 6 students each were arranged around a central instructor’s station, when the laboratory was used for medical students. A large format screen for viewing images was mounted on the wall adjacent to each student table. During the laboratory session, a faculty instructor “drove” the virtual microscope image to point out the key features of each tissue specimen for the laboratory. The virtual microscope control was then given over to the students in each group to allow for group study. The PATH 515 occupied 1 part of a medical student laboratory while the medical students were involved with other activities elsewhere. The medical students and the PATH 515 graduate students did not commingle in the laboratory.

**Course Resources**

The textbook, *Basic Pathology*, edited by Kumar, Cotran, and Robbins was recommended as a course resource.20 A copy of the textbook was kept on reserve in the Arizona Health Sciences Library for students to check out in 2-hour blocks. A course Web site provided general information, including the syllabus, contact information for all faculty involved with the course, and the schedule of lectures, laboratory sessions, quizzes, and examinations. Students enrolled in the course were given access to the PowerPoint files used for the lectures, the laboratory session handouts, and the library of digital slides and gross specimen images used in the laboratory sessions. Additional support for the students that was provided through the course Web site included practice examinations and PowerPoint review files showing images of the microscopic and gross specimens covered in the laboratory.

**Faculty**

Two basic science faculty members, both PhDs, in the Department of Pathology currently serve as co-course directors and teach the first part of the course covering general pathological
processes. Clinical faculty members in the department provide instruction in their particular area of organ or system-specific expertise (e.g., cardiovascular, gastrointestinal, hematopoietic, renal, and neuropathological diseases). When the course enrollment increased substantially in 2013, a graduate student was recruited to work as a teaching assistant. Typically, this student had taken PATH 515 in a prior year and excelled in the course. The teaching assistant drafted the quizzes and examinations, graded these, and assisted with the laboratory sessions by circulating among the students and answering questions as the students studied whole slide images.

Data
At the end of the semester, the students were given a survey to complete regarding their perceptions of the course. Basic demographic data were acquired during course enrollment.

Statistics
The data were analyzed with an analysis of variance (ANOVA) using grade as the dependent and year, degree, program, and gender as independent variables. \( \chi^2 \) analysis was used to determine whether responses to questions on the student’s course evaluations were significantly different from year-to-year.

Results

Programs of Study for Mechanisms of Human Disease Students
Table 1 lists the 21 programs of graduate school study (plus nondegree seeking students) for the 270 students who enrolled in and completed PATH 515 between 1997 and 2016.

Enrollment in the Course
For the first 7 years, 5 to 15 MS or PhD students enrolled in PATH 515 per year, with an average enrollment of 11 students per year. A large spike in enrollment, going from 14 students to up to 35 students per year took place between 2012 and 2014 (Figure 2). Postspike enrollment levels of approximately 30 student per year continue to the present time.

Figure 3 shows the increased percentage of MS students enrolled in PATH 515 after 2012, following the designation of PATH 515 as a recommended course for MS degree programs in Cellular and Molecular Medicine, and in Applied Biosciences. Currently, well over half of the enrollees are in MS degree programs.

Academic Performance
Among the 270 students who completed the course, 268 passed; a score of 70% or greater was required to pass the course. Graduate students at The University of Arizona must maintain a GPA above 3.0. They can get a C in 1 graduate course, as long as they balance this with an equal number of credit hours with a grade of A in another course. The ANOVA using course grade as the dependent and degree, program, gender, and year (1997-2016)
as independent variables showed that there was no significant difference in final grade ($F = 0.112, P = .8856$) as a function of degree (PhD: mean = 89.60, standard deviation [SD] = 5.75; MS: mean = 89.34, SD = 6.00; certificate program: mean = 88.64, SD = 8.25), specific PhD degree programs ($F = 2.066, P = 0.1316$; life sciences: mean = 89.95, SD = 6.40; pharmaceutical sciences: mean = 90.71, SD = 4.57; physical sciences: mean = 87.79, SD = 5.17), or as a function of gender ($F = 2.96, P = .0865$; males: mean = 88.09, SD = 8.36; females: mean = 89.58, SD = 5.82). Students in the physical sciences and the life sciences performed equally well.

**Student Evaluations of Mechanisms of Human Disease (1997-2016)**

The percentage of students completing the evaluation survey per year is shown in Table 2. Overall, 160 responded. In 2015, we tried using an online system, with the students being asked to complete it on their own time. Given the low percentage of returns that year, we went back to the paper format.

Responses to questions on the student’s course evaluations were not significantly different from year-to-year (Table 3), despite changes in the composition of the classes and changes in the faculty over time. $\chi^2$ results for course survey questions showed no significant differences as a function of year for any of the questions (Table 3). Course ratings and the ratings for individual components of the course (ie, outside help, course textbook, etc) received nearly all “outstanding” or “satisfactory” ratings. A “poor” rating was given only 5 times over the 19-year period (2 times for the textbook, 1 time for “outside help,” 1 time for the Web site, and 1 time for laboratory presentations). Over the 19-year period, there were no differences in trends for the way individuals responded to the survey questions. Results from student course evaluations demonstrated a high level of student satisfaction with the course.

The comments ($n = 172$) from the students were analyzed to categorize them into themes. An initial review revealed 4 themes—(1) the variety and breadth of topics covered, (2) connecting what happens at a gross level in the tissue to underlying cellular processes, (3) the format of providing general

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**Table 2. Percent Students (Number in Parentheses) Responding to Survey Each Year.**

<table>
<thead>
<tr>
<th>Year</th>
<th>% Survey Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>73 (11)</td>
</tr>
<tr>
<td>2008</td>
<td>80 (8)</td>
</tr>
<tr>
<td>2009</td>
<td>92 (11)</td>
</tr>
<tr>
<td>2010</td>
<td>100 (8)</td>
</tr>
<tr>
<td>2011</td>
<td>92 (12)</td>
</tr>
<tr>
<td>2012</td>
<td>86 (12)</td>
</tr>
<tr>
<td>2013</td>
<td>92 (25)</td>
</tr>
<tr>
<td>2014</td>
<td>86 (30)</td>
</tr>
<tr>
<td>2015</td>
<td>50 (12)</td>
</tr>
<tr>
<td>2016</td>
<td>97 (31)</td>
</tr>
</tbody>
</table>

* In 2015, we tried using an online system, with the students being asked to complete it on their own time. Given the low percentage of returns that year, we went back to the paper format.

**Table 3. Student Evaluations of PATH 515.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>$\chi^2$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality of the course</td>
<td>1.24 (0.43)*</td>
<td>1.0 (0.0)</td>
<td>0.567</td>
<td>.9038</td>
</tr>
<tr>
<td>Contribution to my education</td>
<td>1.24 (0.43)</td>
<td>1.0 (0.0)</td>
<td>1.290</td>
<td>.7315</td>
</tr>
<tr>
<td>Outside help (2014 and 2013 only)</td>
<td>1.40 (0.53)</td>
<td>1.0 (1.0)</td>
<td>5.397</td>
<td>.2489</td>
</tr>
<tr>
<td>Course Web site</td>
<td>1.52 (0.55)</td>
<td>1.0 (1.0)</td>
<td>1.982</td>
<td>.7391</td>
</tr>
<tr>
<td>Course textbook</td>
<td>1.62 (0.54)</td>
<td>2.0 (1.0)</td>
<td>2.275</td>
<td>.8927</td>
</tr>
<tr>
<td>Laboratory organization</td>
<td>1.41 (0.49)</td>
<td>1.0 (1.0)</td>
<td>4.831</td>
<td>.1846</td>
</tr>
<tr>
<td>Laboratory content</td>
<td>1.41 (0.51)</td>
<td>1.0 (1.0)</td>
<td>3.819</td>
<td>.7012</td>
</tr>
<tr>
<td>Laboratory handouts</td>
<td>1.33 (0.47)</td>
<td>1.0 (1.0)</td>
<td>4.035</td>
<td>.2577</td>
</tr>
</tbody>
</table>

Abbreviation: PATH 515, Mechanisms of Human Disease.

* Rating scale: 1 = excellent; 2 = good; 3 = poor; and 4 = unsatisfactory.
pathology concepts followed by lectures on specific pathology taught by experts, and (4) a hands-on experience in the laboratory to reinforce the content taught in the lecture. Two authors (M.M.B. and M.A.N.) then independently reviewed each comment and placed it in one of the categories, using category 5 if it did not fit in any of the 4. Discrepancies in scores (131 of 172) were resolved by a third independent reviewer (E.A.K.). Overall, 67 (39%) were classified as category 1, 26 (15%) as category 2, 27 (16%) as category 3, 29 (17%) as category 4, and 23 (13%) as category 5.

Some typical examples of comments from each category are:

Category 1: “The variety of material covered and that the class is useful to a variety of majors rather than aimed at a particular set of programs.” “Breath (sic) of information was great.”

Category 2: “Seeing gross specimens and then observing what happens on a cellular level.” “Gross specimens and microscopic images in laboratory.”

Category 3: “Multiple different professors give richer material.” “Each discipline was taught by someone who specialized in the area.”

Category 4: “I liked the ‘hands-on’ training in the laboratory and being able to explore the micrographs on a digital eyepiece.” “The ‘hands on’ aspect of this course is absolutely amazing and a very valuable asset. I truly believe more graduate programs should require students to take this course.”

Category 5: “Easy learning environment, good presentations.” “The information was very interesting.”

Discussion

The PATH 515 represents an addition to the growing list of “Pathology for Non-Pathologists” courses offered in the United States. Such courses circumvent the Flexnerian “virtual monopoly” of pathology courses by medical schools. Our 20-year experience with the PATH 515 course has proven its popularity and utility for postbaccalaureate students who are pursuing biomedical science careers that require advanced degrees other than an MD.

Arguably, the first Pathology for Non-Pathologists course was pioneered a half century ago at Harvard Medical School (HMS), in the mid-1960s. Two distinguished HMS Pathology professors, Ramzi Cotran, MD, and Morris Karnovsky, MBBS, applied for and received a grant from the Commonwealth Fund to create a Boston city-wide course for graduate school students called Pathology for Non-Pathologists. Graduate students from more than 6 local universities enrolled. These annual courses accommodated 100 to 150 students each year and were given on the HMS campus. The primary focus was on mechanisms of diseases. The course mirrored the General Pathology course being taught to medical students at HMS in the late 1960s. This year-long course met once a week from 4:30 to 6:00 PM. Some lectures had a greater research focus than the HMS student lectures on the same topic (Weinstein, 1968, unpublished observations). In 1966, an author of this article (R.S.W.) had recently been promoted to a dual role as a pathology resident at the Massachusetts General Hospital (MGH) and director of the NIH-funded Mixter Laboratory for Electron Microscopy of the MGH Neurosurgical Service. Dr Cotran, a mentor of Dr Weinstein, invited him to audit the Pathology for Non-Pathologists Course and provide the course directors with a critique of the course. This led to career-long collaborations between Drs Cotran and Weinstein on developing innovative pathology courses for medical students, residents, and faculty members.

In the late 1970s and early 1980s, Dr Cotran and Dr Weinstein were co-course directors for a “spin-off” series of half-day Pathology for Non-Pathologist short courses, given annually at meetings of the United States and Canadian Academy of Pathology (USCAP). Their target audiences for these courses were Pathology Department PhDs and Doctors of Veterinary Medicine (DVMs) who served as faculty members for their institution’s general pathology courses. Many of the USCAP short course presentations were then expanded on, and published in, an annual series entitled “Advances in Pathology and Laboratory Medicine.” Today, a Google search shows that the course descriptor Pathology for Non-Pathologists is in common usage elsewhere.

This article documents The University of Arizona’s Department of Pathology’s experience teaching Pathology for Non-Pathologists coursework to 270 graduate students based on a wide variety of MS and PhD graduate programs at The University of Arizona, over a 19-year period. The data for the first year of the 20-year program, to date, was incomplete and is not included. Three levels of postbaccalaureate programs are available at the University of Arizona—certificate, MS, and PhD. All 3 were represented in enrollment for PATH 515. The course has also attracted a number of nondegree seeking, postbaccalaureate students. Programs that have brought in the greatest numbers of MS degree students to the PATH 515 course are Cellular and Molecular Medicine and Applied Biosciences (Table 1). The former degree is used as foundation for additional graduate studies (eg, MD or PhD) or for positions in basic and translational clinical research. Applied Biosciences is a 2-year course of study designed to prepare students to competitively enter the scientific workforce, applying the biological sciences to solve problems faced by public institutions and private industry. In the group of students pursuing PhD, the PATH 515 course attracts the largest numbers of students from programs in Biomedical Engineering, Pharmacology and Toxicology, Cancer Biology, and Physiological Sciences.

The PATH 515 faculty members found that weekly, 2-hour, pathology laboratories could be taught to a diverse student body, including students coming into the course with little knowledge of biology, chemistry, and histology. We avoided creating any course prerequisites. The assumption was that the standard "premedical science courses, including biology, inorganic and organic chemistry, and physics, were nonessential for the subsequent mastery of medical science courses in
graduate school, an increasingly popular notion in many circles today. Incorporating the minimum of premedical science into the PATH 515 course enabled students from very diverse disciplines to achieve high scores on the PATH 515 quizzes and examinations. As an example, we reviewed the gross morphology of the heart in relation to the pulmonary and systemic circulations. Therefore, the absence of traditionally required preparatory coursework was not an impediment to performing well in the course.

Some revisions to the PATH 515 course were made over the years in response to advances in medical science, in education technologies, and to changes in department faculty composition. As an example of advances in medical sciences, a lecture on genetics was revised to cover present methodologies in molecular medicine and discoveries made as the result of subtyping lymphomas based on gene signatures. Major changes in response to advances in teaching technologies were the replacement of light microscope histopathology slides with whole slide images and gross pathology specimens with 3-dimensional photography images. In 2009, the University of Arizona’s College of Medicine implemented whole slide images for teaching pathology to medical students. The PATH 515 course is taught in College of Medicine classrooms and began using digital pathology technology shortly after it was implemented for medical students. In their PATH 515 course evaluations, the graduate students commented favorably on the effectiveness and convenience of using whole slide images. The students noted that having access to the images outside of the laboratory, through Web-based programs, was particularly useful.

In their course surveys, students were asked to comment, in the free-text portion, on what they “liked best about the course.” Common themes were—(1) the variety and breath of topics covered; (2) connecting what happens, at a gross level in the tissue, to underlying cellular processes; (3) the format of providing general pathology concepts followed by lectures on systems pathology taught by experts; and (4) a hands-on experience in the laboratory to reinforce the content taught in the course. In response to the question of what they “liked least,” a handful of students noted that having a panel of 5 to 7 teachers was a drawback. In response to this comment, we reduced the total number of instructors in the course. This was achieved by having the general pathology part of the course taught entirely by just 2 faculty with new faculty coming in assigned to systems pathology lectures. Furthermore, when faculty who had taught system pathology lectures moved away, these lectures were reassigned to the 2 faculty members who gave the general pathology lectures. Our goal was to have the number of faculty reduced to just 3 or 4. For this introductory course, our surgical pathologists and autopsy pathologists were prepared to give lectures on several organ systems each.

As an interesting twist of fate, the 1910 Flexner Report’s recommendations that pathology be upper level university coursework inadvertently reserved the teaching of much of pathology exclusively for medical students. This resulted in a large segment of the population having no exposure to pathology education. The pervasive lack of exposure to pathology education among nonmedical students provides an excellent opportunity to observe what, if any, course prerequisites significantly impact a person’s ability to learn pathology.

It is noteworthy that the 1910 Flexner Report was published at a time when medical doctors represented nearly half of the health-care workforce. The other half consisted mainly of licensed practical nurses. Registered nursing programs were barely on the radar screen. Flexner’s recommending that medical science be upper level coursework at US universities reflected what had been established at the German university-based medical schools as their preferred way of educating future medical doctors. This became the aspirational model for United States’ medical schools following the publication of the Carnegie Foundation’s Flexner Report in 1910. The German university model had been successfully implemented at only a handful of US medical schools before that time, a century ago.

Flexner 2.0 is relevant to current workforce issues. Today, the makeup of the health-care workforce is very different than it was a century ago. The needle has barely moved with respect to numbers of physicians per 100 000 population in the United States, since 1850, according to DC Baldwin, MD, a Scholar-in-Residence at the Accreditation Council for Graduate Medical Education. (DC Baldwin, personal communication, 2013). The 20-fold expansion of the US health-care workforce over the past century has gradually reduced physicians’ representation in the workforce to less than 8% of the total workforce today. This translates into an ever-increasing proportion of the health-care workforce lacking exposure to pathology coursework on mechanisms of diseases. This may directly impact on the scope of team training in clinical practice. Conversely, by broadening the base of students who have prior knowledge of mechanisms of diseases, the range of topics suitable for interdisciplinary team training is expanded as well.

Today, the 1910 Flexner Report recommendations can be linked to the underrepresentation of pathology coursework on mechanisms of diseases in nursing schools and pharmacy schools as well as many other categories of health education programs such as the allied health sciences. In addition, the restriction of pathology coursework to medical schools has severely limited the potential exposure of college students, as well as K-12 students, to what academic pathologists still define as “general pathology.” The impact of the maldistribution of pathology coursework throughout the US education system on the low level of health literacy in the general population in the United States is a matter for future investigation.

On the other hand, what is now becoming apparent is that the century-long exclusion of pathology as coursework for the vast majority of US students, at all levels in the education system, inadvertently created a level playing field for the introduction of pathology to large segments of the population today, a previously unanticipated opportunity from the perspective of health education research. Now, having been partially freed of the Flexnerian premedical science coursework requirements, biology, inorganic and organic chemistry, and physics, which were in place for a century but are now beginning to fade in popularity, greater flexibility exists for curriculum planners.
with regard to identifying and justifying their preferred grade levels for the inclusion of pathology courses in a broad spectrum of science curriculums. As reported previously, we showed that pathology coursework can be adapted for use by motivated students in public district and public charter K-12 schools.

In this study, we have now tested the feasibility of introducing pathology coursework at the upper end of the education spectrum, by teaching such coursework to MS and PhD students drawn from 21 different graduate programs, in the physical and biological sciences at a research university. Having shown that medical science can be taught at multiple levels throughout the education system, without prior student exposure to the traditional premedical sciences, serious thought should be given to preferentially introducing such pathology coursework at grade levels on which it would have the greatest positive impact on the health and welfare of the general population. Our finding that PATH 515 was especially attractive to MS students is noteworthy given that MS degree programs are rapidly proliferating on university campuses today. Academic pathologists interested in public policy should be encouraged to become involved in creating an inclusive national vision for medical science education for nonphysicians in order to increase public awareness concerning the broadening of opportunities in the health-care industry and the benefits of personal knowledge about the nature of diseases as active participants in their own health care.

Appendix A

Table A1. Mechanisms of Human Disease Course Topics.

<table>
<thead>
<tr>
<th>Topic</th>
<th>No. of Lectures</th>
<th>No. of Laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>General pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell injury</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inflammation and repair</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hemodynamic disorders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diseases of the immune system</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Genetic diseases</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Systems pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematopathology</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Renal diseases</td>
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<tr>
<td>Oral and gastrointestinal</td>
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<td>1</td>
</tr>
<tr>
<td>diseases</td>
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<td></td>
</tr>
<tr>
<td>Liver diseases</td>
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<tr>
<td>Endocrine disorder—diabetes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathology</td>
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<td>1</td>
</tr>
<tr>
<td>Molecular diagnostics</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Forensic pathology</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>12</td>
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</table>

*Normal histology was the topic of the first laboratory session for a total of 13 sessions.

Appendix B

Mechanisms of Human Disease (PATH 515): Syllabus (Example)

The objective of this course is to provide graduate-level instruction in pathobiology: the study of biochemical, structural, and functional changes in cells, tissues, and organs, which cause or are caused by diseases. The course is designed for graduate student training for a career in biomedical research. The goal of the course will be to expand and extend the student’s knowledge of normal structure and function into the realm of disease processes. The course also provides a foundation for understanding the medical science literature.

Introduction. Modern pathology is practiced as both a clinical and an investigative science. Clinical pathology assists in disease diagnoses based on the observed changes in tissue structure or biochemistry, whereas the focus of investigative pathology is the elucidation of the underlying mechanisms related to tissue injury and disease processes. PATH 515 is a 4-unit, graduate-level course providing students with the necessary foundation to incorporate investigative pathology into research programs relevant to human disease. Basic principles of tissue injury and disease processes will be presented in the course lectures. Laboratory sessions will be used to illustrate material presented in the lectures. Prerequisites for PATH 515 include basic courses in biology and biochemistry.

General course objectives. Students are expected to work toward meeting the following objectives:

1. To become familiar with pathology nomenclature. By the end of the course, the students are expected to be able to communicate an understanding of tissue injury and diseases processes using appropriate vocabulary.
2. To recognize morphological and functional differences between normal and injured or diseased tissue. The first goal of the course is to learn to distinguish pathological lesions from normal tissue. The second goal is to understand, from a structural, functional, and biochemical perspective, the different types of pathological lesions and provide scenarios for how they each arise.
3. To integrate pathological findings with clinical manifestations of disease. As this course is designed for graduate student training for research in the medical field, the students are expected to develop an understanding of the clinical features for certain disease processes. Particular emphasis will be placed on clinical aspects of cancer and heart disease. These features may impact on detection, treatment, or outcome of the disease or injury.
4. To integrate the principles and information presented in this course with that from related disciplines. Material presented in the course is expected to contribute to the
body of knowledge that students will carry with them into a research career. This should be a “working” body of knowledge that the student can apply, in a problem-solving manner, to understanding mechanisms of disease.

5. In working toward a current understanding of the pathologic basis of disease, the student should develop a sense of which questions in pathology remain to be resolved.

**Recommended text.** Basic Pathology, 9th ed., V. Kumar, A. K. Abbas, J. C. Aster (eds.) Saunders/Elsevier, 2013. The textbook can be checked out, for 2 hours at a time, from the information desk at the AHSL library. The textbook is also available as an e-book.

**Additional reference material and learning resources.** PATH 515 course information can be found on the UA D2L website. The site provides contact information for faculty teaching the course, the course description, the course syllabus, a listing of course topics, and additional course resources including copies of lecture presentations and laboratory study guides. Course handouts, quizzes, and grades will also be available.

The UA College of Medicine Virtual Slides are available at the PATH course website.

**Course format.** The format of PATH 515 will consist of two 1¼ hour lectures per week and one 2-hour laboratory session. General mechanisms of disease will be emphasized in the first part of the course. Knowledge about how these mechanisms manifest in specific organ systems will be the focus of the second part of the course. The laboratory will serve to illustrate and clarify material presented in the lectures and will focus on the consequences of disease processes in cells, tissues, and organs.

**Laboratory activities.** The goal of the laboratory exercises will be to teach students a system for examining biological samples and making a pathologic diagnosis. This “hands-on” training is aimed at enabling graduate students to incorporate pathology into their research programs.

Laboratory exercises will include the following:

1. **Virtual microscopic (whole slide images) examinations—tissue sections.** For every disease process presented in the laboratory, students will first be introduced to normal cellular and tissue structure. With the normal structure as a frame of reference, students will then be asked to observe tissue sections representing a disease state and describe the changes they observe.
2. **Macroscopic examinations—gross specimens.** Gross specimens of the disease processes under study will be presented along with the tissue sections. Students will be asked to describe the changes they see in the diseased tissue or organ.

The exercises will help students relate the gross appearance of diseased tissues to changes in cellular structure. From the integration of this information with the lecture material, students should be able to describe structural, functional, and biochemical changes that occur in cells, tissues, and organs, as the result of specific disease processes.

**Appendix C**

*Pathology 515 (Example): Neoplasia I—General Concepts and Tumor Nomenclature*

**Reading assignment:** Basic Pathology, 9th ed.: 161-214

**Learning objectives**

1. Define neoplasia and its related terms: tumor, cancer, and oncology.
2. Be able to distinguish between carcinomas and sarcomas and their tissues of origin and describe their benign equivalents.
3. Distinguish between “benign tumors” and “malignant tumors” by their gross and microscopic appearances and their behaviors. Understand the significance of the terms “well differentiated” and “poorly differentiated” as they relate to tumors. How do benign tumors cause problems?
4. List the 3 most common cancers in men and women in the United States as well as the 3 most lethal cancers.
5. Given a tumor name, be able to determine the cell of origin and describe its behavior. Given the cell of origin, name the tumor.

I. **Overview of cancer: why is it important?”**

A. One out of every 5 persons in the United States who die this year will die of tumors (approximately 500,000 cases).
B. Cancer is the second most common cause of death in the United States.
C. Cancer is the leading disease-related cause of death in children and young adults.

II. **Definitions**

Cancer (L., crab)—means any malignant tumor. Hippocrates bestowed the name karkinoma after karkinos, Greek for “crab” to denote the invasive nature of malignant cells (cancer is the Latin term for “crab”).

Tumor (L.)—a nonspecific term that literally means any lump or swelling. In current usage, it is a synonym for neoplasm.

Neoplasm (G., neos, new; plasma, anything formed, a growth)—means new growth; a disease of cells characterized by alteration in normal growth regulatory mechanisms.

Oncology—the study of tumors. In current usage, an oncologist is an internist or surgeon who is specialized in treating neoplasms.

Carcinoma—malignant tumor of epithelial origin.

Sarcoma—malignant tumor of mesenchymal origin.
III. Tumor nomenclature

1. To assign a name to a tumor, begin by using the suffix “-oma.” Most tumor names end this way (unfortunately, the suffix simply means “swelling” and some nonneoplasms also use this suffix [see #6 below]).

2. If the tumor is malignant, write the root “carcin-” if the tumor is epithelial in origin or “sarc-” if it is mesenchymal in origin, before -oma.

3. Further classify according to the cell of origin.
   - If the tumor originated in glandular epithelium, use the root “adeno-.”
   - If the tumor originated in squamous or transitional epithelium, is benign, and protrudes from the epithelial surface, use the root “papillo-.”
   - For tumors derived from cartilage, use the root “chondro-,” while those derived from bone, use “osteo-,” and so on.

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Cell/Tissue of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibro</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td>Chondro-</td>
<td>Cartilage</td>
</tr>
<tr>
<td>Osteo-</td>
<td>Bone</td>
</tr>
<tr>
<td>Lipo-</td>
<td>Fat</td>
</tr>
<tr>
<td>Lieomyo-</td>
<td>Smooth muscle</td>
</tr>
<tr>
<td>Rhabdomyo-</td>
<td>Striated muscle</td>
</tr>
<tr>
<td>Hemangio-</td>
<td>Blood vessel</td>
</tr>
<tr>
<td>Lymphangio-</td>
<td>Lymphatics</td>
</tr>
<tr>
<td>Mesothelio-</td>
<td>Mesothelium</td>
</tr>
<tr>
<td>Meningio-</td>
<td>Arachnoid</td>
</tr>
</tbody>
</table>

4. If needed, add an adjective to further describe the tumor. For example:
   - well differentiated
   - moderately differentiated
   - poorly differentiated
   - papillary (fond-like)
   - schirrous (dense fibers)
   - medullary (soft, cellular with less stroma)

5. A handful of tumors are malignant but have “benign” sounding names. Unfortunately, there are no rules to follow, these simply have to be learned.
   - lymphoma
   - mesothelioma
   - myeloma
   - astrocytoma
   - melanoma
   - seminoma
   - hepatoma
   - leukemia

6. Several “-omas” are not tumors and should be learned as exceptions. A hamartoma is not a tumor but a developmental abnormality that contains the same tissues as the organ in which it is found, but in the wrong proportions. A choristoma is a mass of normal tissue in an abnormal location. Aspergilloma and tuberculoma are masses caused by infections. Granulomas are masses due to a chronic inflammatory process and hematoma is a collection of blood in an organ or tissue resulting from a ruptured blood vessel.

7. Eponyms—tumors named after people who discovered, defined, or described them.
   - Hodgkin disease: A type of lymphoma
   - Ewing sarcoma: A malignant childhood tumor usually arising in bone
   - Kaposi sarcoma: A malignant tumor of vascular cells

8. Mixed and compound neoplasms
   - Mixed—more than 1 neoplastic cell derived from 1 germ layer. For example, mixed tumor of salivary gland origin, Wilms tumor
   - Compound—more than 1 neoplastic cell type derived from more than 1 germ layer. For example, teratoma, teratocarcinoma

IV. Characteristics of benign and malignant tumors

- Tumors are similar to organs
  1. All have parenchyma and stroma.
  2. Cells usually look similar to cells in the organ where the tumor arises.
  3. Cells will continue to perform some of the specific functions of the parent organ.

- Tumors are different from organs
  1. They don’t contribute to the homeostasis of the body.
  2. They usually grow more rapidly than surrounding tissues.
  3. Some benign and all malignant tumors never cease growing.
  4. Most tumors show some derangement of histological architecture.
  5. Malignant tumors are locally invasive and have metastatic potential.

A. Benign tumors
   1. Cells resemble normal cells and tumor architecture resembles that of the parent organ (ie, it is well differentiated).
   2. Usually spherical and compress the surrounding tissues (giving rise to the appearance of a capsule).
   3. Grow slowly and have few mitotic figures.

B. Malignant tumors
   1. Generally grow more rapidly than benign tumors.
   2. Cells differ morphologically and functionally from normal cells and tumor architecture is less organized than that of parental tissue.
   3. Tumor cells are locally invasive—the tumor grows into the surrounding tissue and destroys it.
   4. Many tumors will eventually metastasize and spread to other sites within the body remote from the original site of the tumor.
   5. Altered nuclear features include increased amount of nuclear DNA, increased nuclear-to-cytoplasmic ratio, hyperchromatic nucleus, coarsening of chromatin, wrinkled nuclear edges, multinucleation, and macronucleoli.
6. Numerous and bizarre mitotic figures.
7. Failure to mature along normal functional lines.
8. Cells of widely varying sizes.
9. Loss of orientation of cells to one another.

C. Differentiation
1. Tumor cells will almost always biochemically and morphologically mimic one cell type of a normal organ, usually the one in which they arose (i.e., cells may continue to elaborate keratin, mucus, hormones, immune globulin, etc).
2. The degree of differentiation is a reflection of the extent to which the neoplastic cell resembles its cell of origin both morphologically and functionally. The resemblance will be better or worse depending on the degree of differentiation that the tumor displays. The well-differentiated tumors display many features (morphological and biochemical) of the tissue of origin whereas poorly differentiated tumors differ morphologically and biochemically from the tissue of origin. At the extreme end of the spectrum are anaplastic (“without form”) tumors in which it is almost impossible to determine the tissue of origin through morphological techniques.

Worth knowing:
Squamous cell carcinomas may arise in any stratified squamous epithelium, either healthy (skin, esophagus, mouth, and others) or in the setting of squamous metaplasia (bronchi, endocervix).

Look for:
keratin (will stain orange-red on H&E)
pearls (whorling structures composed of keratin)
desmosomes (“intracellular bridges”, “prickles”)

The better these features show, the better differentiated the tumor!

Adenocarcinomas may arise anywhere there are glands, even single-celled glands (i.e., goblet cells).

Look for:
lumens (intracellular, intercellular)
glands within glands (“Swiss cheese”)
mucin (intracellular “lakes, intracellular; mucicarmine” stain will identify these)
cells forming cohesive nests, or at least sticking to one another
signet-ring cells containing mucin, alone or in clusters

Note that adenomas may exhibit most of the same features (though not glands-within-glands or signet-ring cells).

D. Rate of growth
• It is fundamentally wrong to think of cancer cells as “cells growing more rapidly than other cells.” Rather, they are less subject to normal controls, and are reproducing faster than they are dying off.
• Benign tumors generally are progressive and slow growing; they contain few mitotic figures.
• Malignant tumors exhibit erratic growth which may be slow or rapid and display numerous and often bizarre mitotic figures.

<table>
<thead>
<tr>
<th>Table C2. Comparison of Benign and Malignant Tumors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>Differentiation</td>
</tr>
<tr>
<td>Nuclear-to-cytoplasmic ratio</td>
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<tr>
<td>Rate of growth</td>
</tr>
<tr>
<td>Local invasion</td>
</tr>
<tr>
<td>Metastasis</td>
</tr>
</tbody>
</table>

E. Local invasion
• For an unknown reason, cartilage, tendon, and elastic tissue are rarely invaded
• Intraepithelial spread is possible and may take the form of single cells or of carcinoma in situ, in which an epithelial surface is replaced by a layer of several cells deep of malignant tumor that has not yet penetrated the basement membrane.

F. Metastatic spread.
There are 4 routes:
1. Seeding of the serosal surface (body cavity)
   a. Peritoneal spread of colon or ovarian cancers
   b. Pleural cavity spread of lung cancer
   c. Cerebrospinal fluid spread in CNS cancer
2. Via lymphatics (traditional route for carcinomas)
   a. Lung to bronchial nodes to tracheobronchial and hilar nodes
   b. Breast to axillary lymph nodes
   c. Prostate to pelvic lymph nodes
3. Via blood vessels (traditional route for sarcomas)
   a. Venous invasion
   b. Portal blood flow to liver (colon to liver)
   c. Caval blood flow to lungs (renal carcinoma to lungs)
   d. Paravertebral plexus (thyroid and prostate to bone)
4. Mechanical transplantation
   a. Rare
   b. Typically iatrogenic
Cancer epidemiology

A. Incidence

1.5 million new cases of cancer occurred in 2011, and 569,000 people in the United States died of cancer that year.

The most common cancers in the United States (in descending order):

Males: prostate, lung and bronchus, colon, and rectum

Females: breast, lung and bronchus, colon, and rectum

The most commonly fatal cancers in the United States (in descending order):

Males: lung and bronchus, prostate, colon, and rectum

Females: lung and bronchus, breast, colon, and rectum

Under age 15—leukemia, the most common cancer followed by brain and CNS

B. Geographic factors

Death rate for gastric cancer is 8 times higher in Japan than in the United States; Japanese born in the United States—incidence is much lower

Skin cancer deaths—6 times greater in New Zealand than in Iceland

Worldwide, cancer of the cervix is the great killer of women. The other great third-world killer is hepatocellular carcinoma, which is primarily a disease in males (associated with hepatitis B infection)

C. Age

Largest risk factor for cancers: older people—higher incidences of the most common cancers

D. Environment

Includes exposure to drugs, chemical, etc—for specific associations.

Influence of societal factors

a. Smoking

b. Sun exposure

E. Heredity

1. Inherited cancer syndromes—autosomal dominant (eg, familial adenomatous polyposis coli [APC gene defect]); heredity nonpolyposis colorectal cancer (HNPPC); retinoblastoma

2. Familial cancers (family cluster, mechanisms, eg. Li-Fraumeni syndrome, breast cancers [BCRA1 and BCRA2], ovarian cancer)

3. Defective DNA repair—autosomal recessive (eg, xeroderma pigmentosum; ataxia-telangiectasia)

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