Biology 102, Tuberculosis

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Course catalog description. A first-year seminar covering tuberculosis from several perspectives: the molecular biology and chemosensitivity of *Mycobacterium tuberculosis*, the pathology and epidemiology of tuberculosis, social and historical perspectives on the disease, and public policy issues.

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Preceptor: Matt Fragale: email, ma_fragale@acad.fandm.edu. Mr. Fragale's responsibilities in this course will include reading and commenting upon your papers, participating in class discussions, sometimes leading class discussions, and helping me help you with your projects.

Texts:

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Why Study Tuberculosis in 2000?

Abbreviations used in the following essay:

BCG, bacillus Calmette-Guérin; CDC, Centers for Disease Control and Prevention; DOTS, directly observed therapy, short-course; HIV, human immunodeficiency virus; INH, isoniazid; MDR, multi-drug resistant; TB, tuberculosis; WHO, World Health Organization

I.A. Introduction

> "TB is a communicable disease caused by *Mycobacterium tuberculosis*, or the tubercle bacillus. It is spread primarily by tiny airborne particles (droplet nuclei) expelled by a person who has infectious TB. If another

> person inhales air containing these droplet nuclei, transmission may occur. Some bacilli reach the alveoli, where they are ingested by macrophages. Infection begins with the multiplication of tubercle bacilli within these alveolar macrophages. Some of the bacilli spread through the bloodstream when the macrophages die; however, the immune system response usually contains the bacilli and prevents the development of disease. Persons who are infected but who do not have TB disease are asymptomatic and not infectious; such persons usually have a positive reaction to the tuberculin skin test. About 10% of infected persons will develop TB disease at some time in life, but the risk is considerably higher for persons who are immunosuppressed, especially those with HIV infection. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease. " (CDC, 2000, p. 5)

The disseminated form of the disease occurs in 15% of TB patients and affects bone, skin, the meninges, and several other sites (Bloom and Murray, 1992).

The summary above is from the CDC's *Core Curriculum on Tuberculosis* (2000), which was written to present basic information about TB for health care professionals. Why did the CDC write an update on a disease that was in decline for much of the 20th century? Your grandparents and great-grandparents can probably tell you about TB, but you and your parents probably have had very little contact with it. Why, then, are we devoting an entire course to TB? Why not study cancer or cardiovascular disease or arthritis—all of which affect millions of persons worldwide, including individuals whom you all know personally?

In fact, infectious diseases—not cancer or chronic diseases such as cardiovascular disease—cause the largest number of deaths worldwide; and the leading cause of death from a single infectious agent is TB, which kills 2 million persons each year (WHO, 2000). About 1/3 of the world's population, or about 1.7 billion persons, are infected with *M. tuberculosis*; about 4 million of them are contagious (Bloom and Murray, 1992; National Jewish Medical and Research Center, 2000). At least 10 million Americans are thought to be infected with *M. tuberculosis* (National Jewish Medical and Research Center, 2000). Moreover, because TB is much more communicable than HIV—non intimate contact suffices—it poses a greater threat to public health than HIV.

I.B. The incidence of TB declined in the early part of the 20th century

As you will read in *The White Plague*, TB has been a major cause of death in humans for centuries. As recently as the 1940s, TB was so common among health-care workers that urban medical schools routinely admitted 6 extra students, expecting to lose that many to TB (Rosenthal, 1992c). The impact of TB can be seen in the fact that it provided the stimulus for several medical breakthroughs during the 19th and 20th centuries (Rieder, 1998; Young and Robertson, 1998):

- Identification of *M. tuberculosis* as the causative agent of TB in 1882 was a key element in the formulation of Robert Koch's principles for the study of microbial infection.

- Calmette and Guérin were pioneers in the field of vaccination with the development of bacillus Calmette-Guérin (BCG), an attenuated form of the bovine tubercle bacillus.

- Selman Waksman was awarded the Nobel Prize in 1952 for discovering an effective antibiotic treatment for tuberculosis.

- The first randomized controlled trial in medicine was conducted to test the effectiveness of the antibiotic streptomycin in treating TB.

The control of infectious disease, including TB, is regarded as one of the 10 great public health achievements in the United States in the 20th century (CDC, 1999b).

Several factors contributed to the decline of TB in the 20th century. Koch's discovery of the causative agent led to the development of the BCG vaccine and to the understanding that TB was a communicable disease. When the mode of transmission of the disease was understood, infected persons were quarantined or isolated to reduce transmission of the disease. Improvements in housing and sanitation were also important in reducing transmission of TB (Altman, 1992). The development of antibiotics, streptomycin at first and then others, was critical to the decline of TB after the 1940s. In 1972, Dr. Jesse L. Steinfeld, M.D, the Surgeon General of the United States, speaking on Capitol Hill, said it was "time to close the book on infectious disease." (Specter, 1992a). By 1985, TB had been in decline for 35 years (Brown, 1992).

I.C. The recent and ongoing crisis

Dr. Steinfeld's optimistic declaration was soon followed by the AIDS epidemic and newspaper headlines about other infectious diseases, for example Ebola virus and dengue fever. In 1992, the *New York Times* published a series of 5 front-page articles on the re-emergence of TB as a threat to the public health of the United States. In 1998, more people died from TB than in any previous year in history (Iseman, 1999).

The articles in the *New York Times* were largely a reaction to outbreaks of multidrug resistant (MDR) strains of *M. tuberculosis* in the United States, but they also drew attention to a much larger problem worldwide (Brown, 1992). By definition, MDR strains of the tubercle bacillus have patterns of drug resistance that include 2 key drugs, isoniazid (INH) and rifampin (Young and Robertson, 1998). In 1990 and 1991, 13 outbreaks of drug-resistant TB had been reported to the CDC (Rosenthal, 1992b). Moreover, a large number of health care workers at urban hospitals had become infected. In a survey at Cook County Hospital, 46% of a sample group of doctors training to be internists had become infected with the TB germ (Rosenthal, 1992c). By 1999, MDR-TB had been reported in 100 countries (Miller, 1999; Farmer et al., 1999)

Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease (and thus the top federal AIDS scientist), was quoted as saying that TB might become as serious a health threat as AIDS unless a major new research effort was begun (Altman, 1992). In that same year, a substantial paper on the reemergence of TB was published in *Science* magazine, a leading international journal of science (Bloom and Murray, 1992). This paper described the context for the reemergence of TB, identified the major scientific problems that needed to be addressed in order to combat the disease, and estimated the economic cost of failure to address the problem. In 1993, to heighten public and political awareness of the problem, the World Health Organization (WHO) declared TB to be a global health emergency (Raviglione et al., 1995). The WHO now estimates that between the years 2000 and 2020, nearly 1 billion people will be newly infected with the tubercle bacillus, 200 million will get sick, and 35 million will die from TB if control is not further strengthened (WHO, 2000).

I.D. Causes of the current crisis

Experts disagree on the relative importance of the several causes of the current crisis, but they all agree on what those factors are (Bloom and Murray, 1992; Brown, 1992; Belkin, 1999; Farmer, 1999). Indeed, the causal factors themselves are intertwined. For example, the emergence of MDR-TB is clearly an important factor in the current epidemic. Infection with MDR strains of the tubercle bacillus increases the length and cost of treatment and threatens healthcare workers and others, for example prison guards, who come into contact with infectious persons. However, the emergence of MDR strains has been caused, in turn, by the misuse of antibiotics. The causes for this misuse include the over-the-counter availability of antibiotics in some countries, the failure of patients to complete antibiotic drug regimes, and errors in treatment (Rao et al., 2000). A study of patients with multidrug-resistant pulmonary TB referred to the National Jewish Center in Denver, Colorado, found errors of treatment in 28 of 35 patients, with a mean of 3.9 errors per patient (Mahmoudi and Iseman, 1993).

Recent changes in the social conditions in American cities and throughout the developing world have also contributed to the current TB epidemic. Homelessness, poverty, and crowding in jails and prisons have all facilitated the spread of this communicable disease. As a result of crowding and malnutrition in jails and prisons—ideal conditions for the spread of TB—in Russia and other former members of the Soviet Union, the disease is "out of control" and an "epidemiological catastrophe" (Farmer, 1999).

Another contributing factor has been the lack of trained personnel familiar with TB who can develop and test new antibiotics and vaccines, study the immunological response to the TB bacillus, treat patients, etc. (Bloom and Murray, 1992; Brown, 1992). Moreover, until recently there were no standard protocols for treating MDR-TB (Rosenthal, 1992b). Physicians of the current generation were taught little about TB (Altman, 1992), so even diagnosis is sometimes faulty. Recent articles in leading medical journals have begun to address the latter problem (Elad et al., 1998; Leung, 1999; Jerant et al., 2000; Lauzardo and Ashkin, 2000). (See also the excellent series of papers published in the *Canadian Medical Association Journal* in 1999 and 2000)

The HIV epidemic has also contributed to the TB crisis, because immuno-compromised patients are particularly susceptible to *M. tuberculosis* and other microbes. The highest prevalence of TB infection and estimated annual risk of TB infection are in sub-Saharan Africa and Southeast Asia, in part as a result of HIV (Raviglione et al., 1995). Other contributing factors to the crisis include the ongoing use of an inadequate vaccine (BCG) and, at least in the United States, immigration (Brown, 1992). In 1998, for example, 40% of patients with TB came to the United States from other countries (Geiter, 2000).

Many of the problems identified above were in turn the result of, or were exacerbated by, inadequate funding—for basic research, drug and vaccine development, public health programs, adequate housing, isolation rooms in hospitals and prisons, etc. (Bloom and Murray, 1992; (Specter, 1992a). But the biggest culprit has been our neglect of the problem (Geiter, 2000). In 1992, Lee Reichman—then President of the American Lung Association, currently the executive director of the New Jersey Medical School National Tuberculosis Center—said of our failure to prevent and cure TB, "We should be ashamed." (Specter, 1992a).

II.A. Where do we go from here? TB in the 21st century

It is unlikely that any fundamentally new way(s) will emerge to combat TB in the next decade. Instead, refinements of existing techniques—new antibiotics; new and better vaccines; better diagnostic tests; an understanding, in molecular terms, of drug resistance; and standard public health measures—will be used (Altman, 1992; Rieder, 1998). Above all, we need to know much more about the basic biology of *M. tuberculosis*, e.g., how it causes TB, the virulence factors it produces, and how it lives within macrophages (Bloom and Murray, 1992; Cole et al., 1998; Young and Robertson, 1998). Thus, an important goal for the next decade is to learn more about the tubercle bacillus.

A big step toward a better understanding of the tubercle bacillus was the elucidation of the complete genome sequence for *M. tuberculosis* (Cole et al., 1998). Sequencing identified two new families of proteins and discovered genes that code for enzymes involved in polyketide synthesis; polyketides act as toxins responsible for the virulence of other species of *Mycobacterium* (George et al., 1999). Sequencing may also identify potential protein targets for the development of a vaccine, identify possible sites of variation in antigens at the surface of the bacterium that may explain the persistent nature of TB infection, and explain the genetic basis of human pre-disposition to TB infection (Cole et al., 1998; George et al., 1999). The tools of molecular genetics are also being used to perform molecular epidemiology (Bifani et al., 1999) and to study drug-induced changes in gene expression in the tubercle bacillus (Wilson et al., 1999).

M. tuberculosis is naturally resistant to many antibiotics, primarily but not solely because it has enzymes that can metabolize and thus inactivate these antibiotics (Cole et al., 1998). Sequencing will facilitate the identification of these enzymes and the design and synthesis of novel antibiotics that inhibit these enzymes. For example, although INH is widely used to treat TB, its molecular target has remained elusive. Recently, however, availability of the genome sequence enabled Mduli et al. (1998) to show that a protein whose level changed in response to low-level INH treatment is an acyl-carrier protein.

Identification of this protein led them to a metabolically related protein, Kas A (□-ketoacyl carrier protein synthase) that is mutated in INH-resistant patients (Mduli et al., 1998).

TB is a social disease—a disease associated with poverty that accompanies alcoholism, HIV, homelessness, and substance abuse—and economic and social conditions are therefore critical factors in its transmission (Dubos and Dubos, 1987; Specter, 1992a; Campion, 1999; Farmer, 1999). Thus, addressing the TB epidemic will require not only antibiotics and vaccines but public policy initiatives that address poverty worldwide. In short, we will need a comprehensive, integrated approach to solve the problem.

II.B. Preventing TB

It is far better to prevent TB than to treat it after infection. Prevention is cheaper, and it avoids the terrible human cost of infection and drug treatment. Vaccines—"harmless variants or derivatives of pathogenic microbes that stimulate the immune system to mount defenses against the actual pathogen" (Campbell, 1996, p. 333)—have been effective tools for preventing some infectious diseases. The only TB vaccine currently available is BCG, an attenuated strain of *M. bovis*. Though it has been used since 1921, its effectiveness is still debated (Colditz et al., 1994; Young and Robertson, 1998). There is a lack of consistency in its protection (Rieder, 1998), and it induces a positive skin test for TB (Huygen, 1998). Recent evidence suggests that differences in the efficiency of BCG in different trials are the result of genetic changes in the vaccine strains over the past 70+ years (Behr et al., 1999; Young and Robertson, 1999). The recent rise in TB cases, especially those caused by MDR, have prompted a re-examination of the efficiency of BCG vaccine. Meta-analysis of data from 14 prospective trials and separately from 12 case-control studies found that BCG vaccination does significantly reduce the risk of active TB cases and deaths (Colditz et al., 1994). Thus, although vaccination with BCG does not provide 100% protection, it remains a useful tool in preventing TB (Colditz et al., 1994).

DNA vaccines may offer several advantages over BCG (Young and Robertson, 1998; Tanghe et al. 1999). A DNA vaccine is one in which DNA encoding a microbial antigen is used instead of the microbe itself to induce an immune response. The gene, as part of a plasmid, is injected into a host (e.g., a mouse), infects cells there, and causes the host to express the microbial antigens. An immune response ensues, giving, perhaps, immunity to the microbe itself (Huygen, 1998). Several such vaccines are under development (CDC, 1998; Huygen, 1998).

However, even if an effective vaccine were to become available tomorrow, it would likely be useless for the 1.7 billion persons already infected with the tubercle bacillus. Thus, the early detection and treatment of TB patients must be the objective of efforts aimed at controlling TB (Enarson, 2000). In other words, for the foreseeable future the prevention strategy against TB will be based on case management.

II.C. Treating TB

Several approaches—rest and relaxation, surgery, antibiotics—have been used to treat TB. I will discuss only the use of antibiotics here. Several strategies are available, depending on whether treatment is prophylactic (exposure but not infection), preventive (infection but not clinically active), or chemotherapy against an active infection (Rieder, 1998).

Streptomycin, the first anti-TB drug, was licensed in 1952 (Brown, 1992). Since then more than a dozen other drugs and their derivatives have been developed (Davidson and Le, 1992). Nevertheless, important gaps exist in our knowledge of how the drugs used to treat TB work (Mitchison, 1992). The minimally required duration of treatment, defined in 1982, is 6 months and involves four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol (or streptomycin) for 8 weeks and then isoniazid and rifampin for an additional 16 weeks (CDC, 2000). A less expensive eight month regime is also available (Rieder, 1998). Many of the drugs have severe side effects, from nausea to hearing loss (CDC, 2000).

Compliance with drug regimes that last up to a year has long been a concern of physicians. Even the six month "short course" raises problems with compliance (Mitchison, 1992). Problems with compliance are even more severe with the treatment of MDR-TB, which may require up to two years (Farmer, 1999). Thus, even having an effective therapy does not ensure that it will be used (Rieder, 1998).

To address the problem of noncompliance, New York City began in 1979 to send health-care workers into the field to watch people take their medicine every day. This practice is known as "directly observed therapy, shortcourse," or DOTS. DOTS, with incentives including cash payment, has had considerable success in treating infectious TB patients and thus controlling the spread of TB (Specter, 1992b). The use of DOTS was crucial for decreasing the number of TB cases in New York City and Miami in the early 1990s (Frieden et al., 1995; Havlir and Barnes, 1999) and more recently in parts of India (Dugger, 2000). The use of DOTS has been so successful that some have argued for the increased use of DOTS with all TB patients throughout the world (Iseman et al., 1993; New York Times, 1999).

II.D. Public policy and TB

Communicable, infectious diseases like TB reside at the intersection of science and the public interest. In the case of a contagious disease like TB, which can be spread by airborne microbes, how does a society protect its healthy members from those who are infected with TB (Specter, 1992b)? How do we, as a society, balance the principle of individual freedom, guaranteed under the U.S. constitution, against protecting the public health (Gostin, 1993; Campion, 1999; Gostin, 2000)? Is TB an example of a medical condition in which the basic human right to refuse treatment may not hold and in which the public health may require a person to be treated (Campion, 1999)?

In 1992, at least 40 states had laws that permitted public health officers to detain infectious TB patients (Specter, 1992b). A recent survey of TB laws in 50 states led Gostin (1993) to conclude that many of these laws are antiquated and in need of reform.

Public health officers have a range of restrictive interventions at their disposal, including DOTS and detention. In practice, however, such restrictive interventions are used in only a minority of cases. For example, a recent survey of TB cases in New York City showed that restrictive measures were used with only 304/8000 persons and that less restrictive measures were often effective (Gasner et al., 1999). Nevertheless, because detention and even DOTS are restrictive measures, we need to know the extent to which they are being used and the consequences of the more restrictive measures and of less restrictive ones (Gasner et al., 1999).

Public policy is also relevant to the cost of preventing and treating TB. The cost of treating a single physician who contracts MDR TB can exceed $25,000 (Gibbons, 1992). The cost of bringing the New York City crisis under control in the early 1990s was $1 billion, and the problems in the prisons in the former Soviet Union are far greater (Farmer, 1999). Thus, while prevention is expensive, the cost of treatment is much higher.

The first TB control program in the United States was created by New York City in 1892 (Specter, 1992a), and cities and states—not the federal government—continue to bear a large share of the burden of the cost of public health programs. Perhaps it is time to reassess this situation and ask whether the federal government can do more (Gibbons, 1992). This might mean extra dollars for the federal budget for the public health, or it might mean the re-allocation of funds now targeted at other infectious diseases. Some of the shortfalls in funding for TB research have been blamed on the huge amount of money put into AIDS research and treatment (Specter, 1992a).

It takes years and about $200 million to bring a drug to the market in the United States (Gibbons, 1992). This imposing figure places practical constraints on the companies that develop new drugs, because they must be able to envision an appropriate market before they embark on a project. The decline of TB in industrialized nations has removed the financial burden incentive for the pharmaceutical industry to develop new anti-TB drugs. Thus, the cost and time required for drug (and vaccine) development must be built into planning models (Rieder, 1998).

In the prisons and jails of the former Soviet Union, we can see another way in which public policy is affecting the spread of TB (Remnick, 1999). According to Farmer (1999), many persons being held in these detention facilities—under ideal conditions for the spread of TB—are there for no good reason.

Lee Reichman (1997) has argued that the United States should view the battle against TB as a defense program. His position is supported by a recent report from the National Intelligence Council (2000) recommending that the United States place global disease prevention at the center of its national security agenda. The Council reached this conclusion not only because the diseases, including TB, could infect U.S. citizens but also because they weaken the global economy. More than 70% of the nearly 15 million people sick with TB today are in their most economically productive years of life (WHO, 1996). Economic decline in high burden countries poses a national security threat to the

U.S., to the extent that these countries are U.S. trading partners. The economic significance of the TB epidemic can be seen in the very title of the recent ministerial conference in Amsterdam: "Tuberculosis and Sustainable Development.". Because the prevention and treatment of TB are among the most cost-effective of any health care intervention in low income countries, support for TB programs should be among the highest priority for any government, including that of the United States (WHO, 1996; Enarson, 2000).

III. Conclusion

The goal of U.S. anti-TB efforts since 1989 has been to eliminate TB from the United States, defined as fewer than 1 case per million population (CDC, 1989). As of 1998, however, the case rate for the U.S.A. was 6.8 cases per 100,000 population, far above the goal of elimination (CDC, 1999a). At the current rate of decline, the case rate of TB in the U.S. will not reach the stated goal for another 60 years (Geiter, 2000). Globally the TB problem is likely to get worse, not better, in the next decade (Raviglione et al., 1995). We will need an integrated approach, from basic research to changes in the public health infrastructure (Binder et al., 1999), to fight it. TB is a global issue, affecting both low-income and industrialized nations alike. The resources available to combat TB are very different in these two groups of nations; and the choices they make, from diagnosis to treatment, will probably differ (Rieder, 1998). Public health officers will need a full, graded range of options to protect the public health, not only coercive measures but also provisions of funds for treatment. Better epidemiological modeling will be needed to predict the impact of vaccination and treatment so that we, as a society, can decide how best to combat TB (Anderson, 1998).

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Evaluation

Class participation and attendance. Your individual contributions to the class—making and responding to oral presentations and participating in class discussions—will be an important part of this course. Thus, your participation in class will be the basis for 20% of your course grade. Moreover, you will fail the course if you have more than two unexcused absences from class.

Writing assignments, general comments. You will write 6 papers (described below), beginning with a short one (a memorandum) and ending with a project report. Mr. Fragale and I will describe each assignment in class, and for most assignments, there will be assigned reading in Pechenik. I will also give you an evaluation form for each assignment. (Click here for forms). These forms will function as a check list (Did you format the document properly, submit the appropriate documents, etc.?) and will also describe the criteria by which Mr. Fragale and I will grade your papers.

Except for the pre-proposal and final project report, you will submit each paper twice, first to Mr. Fragale and then to me. Mr. Fragale, using the evaluation form as a guide,

will read and mark your paper and return it to you with suggestions for revision. You will then revise the paper along the lines suggested and submit the paper to me, along with the version you submitted to Mr. Fragale and his comments. I will then read and grade your revised paper. Neither Mr. Fragale nor I will mark every mistake, every infelicity, every poorly cast sentence in your papers. Rather we will try to identify, on the basis of the paper you have given us, your strengths as a writer; and we will give you a few pointers on how you can become a better writer. If we believe it appropriate, we will refer you to the Writing Center (KEI-316; ext. 3866) to work on specific aspects of your writing. At the Writing Center you will also find a number of books and useful (and free) handouts on punctuation (e.g., the semicolon, the colon), grammar (e.g., idioms, passive voice, parallelism), and writing papers (e.g., writing introductions). The Center also publishes a book, *Model Student Essays*, that you may find useful for this and other courses. The Writing Center tutors are very busy, so you should make an appointment if you wish to work with one.

Papers are due at the beginning of class on the dates listed in the Schedule of Classes (see below). For some assignments, I will also ask you to submit a digital version of your paper. You can do this by dropping a copy of it in the Submissions folder for this course on the Curriculum Server. Having access to these digital files will make it easier for me to combine the reviews into a single document for you. For example, I will use such electronic documents to combine all of your book reviews into a single document, which I will then make available to you via the Distribution folder for this course on the Curriculum Server.

On the dates on which most papers are due to me, you will also make an oral presentation to the class in which you summarize—not read—your paper. These presentations will serve at least two functions. First, they will give you opportunities to develop and practice an important skill. Second, they will enable you to tell the rest of us about your project, which will be of general interest to all of us as we work to understand tuberculosis and which may be of specific interest to students working on other projects.

Every paper must have an Acknowledgments section in which you identify the individuals who helped you prepare the paper and the specific ways in which they helped you, for example, discussing ideas, proofreading, editing, helping in the library, etc. The College holds its students to the highest standards of intellectual honesty and prescribes harsh penalties for academic dishonesty, including plagiarism. It is your responsibility to be sure that work you submit conforms to the College's guidelines, as described in *The Catalog*.

Memo. In your memo, you will list the five available projects in your order of preference, with #1 being your first choice; describe the reasons for your choices; and tell me what strengths (language skills, database knowledge, organizational skills, related prior experience, etc.) and interests (interest in the topic, career goal, etc.), that you will bring to the project. The choices for projects are:

- TB in children

- DOTS Plus in the treatment of MDR-TB
- TB in migrant workers (This project will include a modest field component in Lancaster County.)
- TB education needs among community health organizations in Lancaster (This project will be primarily, though not exclusively, a field project in Lancaster City.)
- Anti-TB vaccines

Book review. On Sept. 14, you will choose a book related to this course in the F&M Library. On that date, you will also learn about writing book reviews. You will then write a review of the book you have chosen. In addition to submitting the usual paper copies of your review on Oct. 5, you should also place a copy in the Submissions folder for this course on the Curriculum Server. I will combine the reviews and distribute them to the entire class. One of your goals in writing this review is to tell the rest of us about the potential value of the book for the class projects, in particular which project(s) it might be most useful for.

Web site review. On Oct. 5, you will choose a web site related to this course and then become familiar with the site. On Oct. 17, each of you will describe your site in a brief presentation (less than 5 minutes) to the class. One of your goals in giving this review is to tell the rest of us about the potential value of this web site for the class projects, in particular which project(s) it might be most useful for.

Project. Working in teams of three (or four), you will prepare four documents on the topic to which you have been assigned.

The first will be a **pre-proposal**. This document, which is due to both Mr. Fragale and me on Sept. 28, should have a title page, about 2 pages of text (this and all other documents should be double-spaced), and a Literature Cited section. The text should include an introduction, a thesis statement or a statement of your objectives, and your plans for developing the thesis statement or meeting your objectives.

The second document will be a **proposal** for your project. The proposal will include an Introduction and background, in which you will describe the general topic that your team is addressing; the specific topics that you will address; the resources (books, papers in the literature, web sites) that you have identified; a Literature Cited section; a timetable for your work; and a plan for how you will meet your objectives. The last item should include a description of how you will divide responsibilities among the members of your team, how often and when you will meet to work on your project, and how the actual document will be written. The text of this paper (excluding Literature Cited) should be 6-8 pages. On the due date, your team will make a 15 minute oral presentation. An additional 10 minutes will be allotted for questions and discussion. Among other things, the oral presentations should inform the rest of us about your progress and help the other four teams better understand the place of your and their projects in the overall scheme of the course.

The third document will be a **progress report** for your project. The progress report, which you should consider as representing 50–75% of your final paper, will include an Introduction and background; supporting text; a description of what remains to be done (read, summarized, written); your plan for how you will finish the project; and a Literature Cited section. The text of this paper (excluding Literature Cited) should be 10-14 pages. On the due date, your team will make a 15 minute oral presentation. An additional 10 minutes will be allotted for questions and discussion. Among other things, the Q&A following your presentation should help you clarify what remains to be done on your project.

The fourth document, your **project report**, will include and Introduction and background, supporting text; a conclusion; and a Literature Cited section. The text of this paper (excluding Literature Cited) should be 14-18 pages. On the due date, your team will make a 25 minute oral presentation. An additional 15 minutes will be allotted for questions and discussion. For the oral presentations, I will invite a discussant to participate in the response to your paper. The discussants will be F&M faculty, physicians, or public health officers.

Evaluation of team members. By Sunday, December 3, you should send me an email in which you succinctly evaluate the contributions of your collaborators to the project.

Summary of evaluation:

Memo	25 points
Book review	50 points
URL review	20 points
Project	
Pre-proposal	40 points
Proposal	50 points
Progress report	90 points
Project report	125 points
Class participation	100 points
TOTAL	500 points

Schedule of Classes, Due Dates for Assignment, and Readings

Date	Topic	Assignment Due	Reading
R, Aug. 31	• Introduction to course: working hypothesis, description of projects • Lecture: Introduction to tuberculosis • Writing memos		• Syllabus • Dubos and Dubos
T, Sept. 5	• Video and discussion: "Tuberculosis in America: The People's Plague, Part I. The Captain of All These Men of Death"		
R, Sept. 7	• Video and discussion: "Tuberculosis in America: The People's Plague, Part II. The Gospel of Health"	Memo to Fragale	
T, Sept. 12	• Lecture: TB in the 21st century • Discussion		Bloom & Murray
R, Sept. 14	• Dale Riordan, Science Librarian (ext. 3843), and Tom Karel, Associate Librarian for Reference and Instruction (ext. 3103), Shadek-Fackenthal Library computer classroom (SFL207): the F&M catalog, search strategies, book reviews • Choose a book to review	Memo to Fluck	

T, Sept. 19	• Project assignments, getting started on your projects • Writing your proposals • Keeping track of information; use of notebooks, journals, files, vocabulary, lists of questions, databases, etc. • Preparing oral presentations		• Pechenik: --Ch. 2, "General advice on reading and note-taking" --Ch. 5, "Writing essays and term papers" --Ch. 6, "Writing research proposals" --Ch. 8, "Preparing oral presentations"
R, Sept. 21	• Shadek-Fackenthal Library computer classroom (SFL207): periodical indexes • Journals at F&M that will be useful to you this semester • Using other libraries	Book review to Fragale	• Pechenik: pp. 95-98, "Citing sources," pp. 120-123, "Preparing the literature cited section"
T, Sept. 26	• Videotape, "Revising Prose," by Richard Lanham • Revising your book review; in-class workshop		• Pechenik: Ch. 10, "Revising"; Appendix D and Appendix E
R, Sept. 28	• Oral presentations of pre-proposals	Pre-proposals to Fragale and Fluck	
T, Oct. 3	• Historical trends in the epidemiology of TB • Class will be led by Fragale		• To be announced
R, Oct. 5	• Shadek-Fackenthal Library computer classroom (SFL207): internet sources, government documents • Choose a URL to review	Book review to Fluck. Submit the usual paper copies and, also, place a copy in the Submissions folder for this course on the Curriculum Server.	

R, Oct. 12	• Lecture and discussion: Molecular biology of *Mycobacterium tuberculosis*		Cole et al.
T, Oct. 17	• Oral presentations of URL reviews		
R., Oct. 19	Epidemiology of TB	Project proposal to Fragale	Raviglione et al.
T, Oct. 24	• Questions for Dr. Reichman • Sign up for meetings with Dr. Reichman • Sign up for conferences with Fragale to discuss your progress reports and final project reports		
R, Oct. 26	Oral presentations of project proposals	Project proposal to Fluck	
T, Oct. 31	Oral presentations of project proposals		
W, Nov. 1 8 p.m. Stahr Aud. (Stager 102)	Lecture by Dr. Lee Reichman (MD, MPH, FACP, FCCP), Professor of Medicine, Professor of Preventive Medicine and Community Health, and Executive Director of the New Jersey Medical School National Tuberculosis Center, Newark, New Jersey. speak on "Defusing the TB Timebomb"		
R, Nov. 2	• Dr. Reichman meets with the class. • Dr. Reichman meets with project teams during the late morning and afternoon.		

T, Nov. 7	• Registration for spring semester • Chemotherapy and antibiotic resistance, cont'd.	Progress report to Fragale	Rouhi
R, Nov. 9	• Chemotherapy and antibiotic resistance		Rouhi
T, Nov. 14	Public policy and TB		Gasner et al.; Gostin
R, Nov. 16	Oral presentations of progress reports	Progress report to Fluck	
T., Nov. 21	Oral presentations of progress reports		

T, Nov. 28	• Project report **Discussant(s)**: • Project report **Discussant(s)**:		
R, Nov. 30	• Project report **Discussant(s)**: • Project report **Discussant(s)**:		
T, Dec. 5	Project report **Discussant(s)**:		
R, Dec. 7	Semester wrap-up, course evaluation	Project reports to Fluck	