AN ORIENTATION TO BIOMEDICINE

1. Introduction. On September 5, 1976, a man named Mabalo Lokela was admitted to the Yambuku Mission Hospital in what is now the Democratic Republic of the Congo [4, Ch. 5].[1] He was gravely ill, suffering an intense fever, headache, chest pain and nausea. He vomited blood, and had bloody diarrhea. The medical workers at the hospital recognized the signs of a hemorrhagic fever, but that still left them largely in the dark. Many different pathogens can cause hemorrhagic fever. But whatever the cause, Lokela was in trouble. He was dying, despite the best efforts of the hospital staff. Their level of frustration grew as every attempt to treat Lokela failed. They simply could not figure out what was going on. They also missed something else—Lokela had put them, and many others, in desperate jeopardy.

Lokela's tissues were essentially melting away. Internal bleeding became worse and worse as his organs, including his skin, slowly disintegrated. After a few days he began "bleeding out" as the clotting factors in his blood were finally exhausted. By then, the hospital staff could do little more than watch him die in what may be the most horrible manner possible.

But the story did not end there. Shortly after Lokela's burial, a number of his friends and family started feeling similar symptoms. Eventually, 20 of them contracted the disease. Only two survived. While these 20 people suffered, the hospital in Yambuku started admitting case after case with the same presentation. Workers at the hospital also began to fall ill. The epidemic spread like wildfire. Within weeks of the outbreak, astonished, and frankly terrified, scientists and medical professionals around the world began trying to get a handle on what was happening in Yambuku. Their initial efforts focused on two questions: what was the pathogen, and how did it pass from person to person? Surprisingly quickly they discovered that the pathogen was unknown to the science and medicine of the time, and that it jumped between hosts via body fluids. Unaware of this latter point early in the outbreak, many Yambuku medical workers contracted the disease because they failed to protect themselves from their patients' blood. In fact, the hospital became an amplifier of the epidemic as the pathogen spread from patient to patient within the hospital, carried at times by the medical workers themselves. Quickly, however, hospitals throughout sub-saharan Africa were made aware of the disease and taught how to handle it. The epidemic died out nearly as rapidly as it flared.

One might think that this tragedy in Yambuku highlights a medical failure. Nothing could be further from the truth—in fact, it shows medicine at its best. Here we use the word *medicine* in its most general sense—it means 'the art of preventing or curing disease" and "the science concerned with disease in all its relations" [5].[2] In Yambuku, the two "arms" of medicine—**curative health care** and **public health care**—complemented each other beautifully. As its name implies, curative medicine focuses on cures or treatments for diseases—the Yambuku Mission Hospital staff trying to keep Mabalo Lokela alive, for example. In contrast, the goal of public health is to prevent disease. In Yambuku, public health professionals slowed the epidemic by identifying the pathogen and recommending techniques to prevent infection among hospitals in the region. When these two arms work together, the effectiveness of

[1] This story is report in Laurie Garrett's excellent book, *The Coming Plague*, chapter 5.
[2] In addition to meaning "a drug," the word "medicine" also refers to health care not associated with surgery.

medicine is maximized. In this country we tend to focus on curative medicine. But public health is primary. As the developing world shows us daily, inadequate public health care makes curative health care superfluous. The number of cases simply swamps efforts to treat the sick and dying.

The definition of medicine points to another dichotomy along another axis. In particular, medicine is both **art** and **science**. The "art" of medicine typically refers to clinical practice.[3] In the clinic, medical professionals work with individual patients out of necessity—each patient presents a unique case. In contrast, medical *science* looks in the opposite direction. It seeks broad patterns and causative relationships within the chaos of individual cases. These patterns exist both within and among patients.

As the Yambuku example shows, medical *science* informs, or should inform, the practice of the medical *art*. Health professionals in the clinic rely on discoveries made by their scientific colleagues. At least, they should. When they do, we refer to the practice as **evidence-based medicine**. Our goal in this course is to explore how mathematics, dynamical models in particular, have in the past and can in the future advance the practice of evidence-based medicine.

2. Disease. Central to all of medicine, and its founding scientific discipline of physiology (see below), is the concept of **homeostasis**. Surprisingly, given its ubiquity in biology texts from high school to graduate school, the concept is frequently misinterpreted as equilibrium in living systems. In fact, the correct definition includes both equilibrium and *disequilibrium*. For example, it is well know that mammals maintain a constant body temperature. But that is not necessarily an example of homeostasis. We say that mammals homeostatically regulate body temperature because they maintain a constant body temperature *in disequilibrium with the environment*. A dead mammal could maintain a constant body temperature, but only in equilibrium with the environment. Therefore, death obliterates the possibility of homeostasis.

Antithetical to homeostasis is the concept of **disease**. By the standard definition [5], disease is "an interruption, cessation, or disorder of body function, system or organ." Almost all body functions, organs and systems work to maintain homeostasis. Therefore, one might describe disease as an inability to maintain homeostasis. Unfortunately, that definition fails for one organ system—the reproductive system. It functions not to maintain homeostasis, but to perpetuate the genes. However, homeostatic mechanisms exist, ultimately, in support of the reproductive system.

Like the word medicine, "disease" can be used with subtly different meanings. The word also applies to a sickness with "at least two of these criteria: recognized [causative] agent(s), identifiable group of signs and symptoms, or consistent anatomic alterations" [5]. A symptom is something a patient feels that indicates disease, whereas a sign is an outward, objective manifestation of disease. For example, sore throat is a common *symptom* of a cold, whereas fever is a common *sign* of bacterial infection. A collection of signs and symptoms characteristic of disease is called a **syndrome**. For example, HIV infection is a disease characterized by acquired immunodeficiency syndrome (AIDS), signs of which include loss of certain types of immune cells and the presence of various opportunistic infections and cancers, like *Pneumocystis carinii* pneumonia and lymphoma, among others.

[3] The word "clinic" here refers generally to areas where medical doctors work—hospitals, private offices, and actual clinics, among others.

3. The Scientific Basis of Medicine. Modern curative medicine is founded on the scientific disciplines of **anatomy** and **physiology**, the study of form and function, respectively, of living systems.[4] However, emphases are shifting. As a direct result of the molecular biology revolution, the scale of focus continues to become finer and finer. Traditionally, disease processes were understood at the organ system level. With the advance of microscopy, including improved instruments and staining techniques, tissue- and cell-level processes were added to our descriptions and explanations of disease. Now, new medical insights arise mostly from molecular biology. Modern medical practice requires competence at all levels of biological organization from organ systems to DNA.

For example, consider the leading cause of death in the world, coronary artery disease (CAD). At the organ system level we think of the disease as being confined largely to the cardiovascular system (heart, blood and blood vessels). We describe its cause as **atherosclerosis**, a narrowing of coronary (heart) arteries caused by plaque development within the vessels. Eventually, blood flow to the heart becomes blocked, most often by thrombosis (a blood clot forming in a blood vessel), causing infarction (tissue death caused by lack of blood flow) of a portion of the myocardium (muscular wall of the heart)—hence, myocardial infarction, or MI. At the tissue level, the arterial plaques, deposits of lipid and calcium carbonate mixed with smooth muscle cells, originate from inflammation of the artery wall, roughly speaking. So, researchers are now studying antiinflammatory drugs as potential preventative treatments for CAD. At the molecular level, it appears that low density lipoproteins (LDLs) somehow cause the inflammation. Not only does that observation explain why high blood LDL levels correlate positively with CAD, it led to lifestyle recommendations that have helped people in developed nations avoid premature deaths. How the body handles LDLs is in part determined genetically, so we recognize the DNA as a potential target for therapy.

This CAD example, although greatly abbreviated, already exhibits many of the basic biology disciplines related to curative medicine—anatomy, physiology, **histology** (study of tissues), cytology, more commonly called **cell biology**, **molecular biology** and **genomics** (roughly, the study of all genes and DNA sequences in an organism). In addition, a competent medical researcher must have proficiency in basic chemistry, biochemistry biophysics and classical physics. (Hemodynamics, the study of blood flow dynamics, requires plenty of fluid physics, for example). In mathematical medicine, we add the powerful tools of dynamical systems and stochastic processes, among others.

4. Aspects of the Medical Art. On its clinical side, medicine's primary concerns include **diagnosis**, **prognosis** and **treatment**. Diagnosis refers to the identification of disease processes and their causes. For example, in Mabalo Lokela's case, the disease process was hemorrhagic fever and the cause was Ebola virus infection. Prognosis, one of the most difficult aspects of medicine, involves estimation of the likely course of a disease. A person infected with the same strain of Ebola virus that killed Mabalo Lokela faces a grim prognosis, for example—the probability of survival is less than 10%, and death usually occurs within two weeks of the onset of symptoms.

Treatment, of course, means an attempt to alleviate symptoms. One way to do that is to effect a **cure**, or permanent reversal of the disease process, usually by

[4] In this course we largely ignore public health, founded on the science of **epidemiology**. Although fascinating, this topic is well treated in numerous other texts. See [1] and [3] for introductions to this field.

eliminating its cause. However, the goal of treatment is not always a cure. In many cases, a disease cannot be cured. In such situations, treatment may simply manage the disease so that it no longer progresses or presents a threat to health and survival. The Highly Active Antiretroviral Treatment (HAART) applied to HIV patients works in this way. Although it cannot cure HIV disease, in most cases HAART allows HIV patients to live, if not a normal life, one close to it. In extreme cases, like terminal cancer, for example, it is not even possible to manage the disease. In these cases, standard practice calls for **palliative** treatment—an attempt to alleviate symptoms to make the patient as comfortable as possible.

5. Pathology–where art and science meet. All beginning medical students take a battery of basic science courses in their first two years of medical school. When asked what she saw as the main value of this portion of her education, one young medical doctor told one of us (JDN) that she needed it to understand her pathology course.[5] Indeed, pathology and epidemiology are the main conduits by which basic and medical science inform the medical art.

Pathology refers, literally, to the study of suffering and "is devoted to the study of the structural and functional changes in cells, tissues and organs that underlie disease" [2, pg. 1]. Cotran et al. [2], in their classic pathology text, recognize four "core areas" within pathology: **etiology**, **pathogenesis**, **morphology** and **clinical significance**. Etiology refers to the cause of a disease, pathogenesis to its biological course, morphology to the structural changes it causes to organs, tissues and cells, and clinical significance includes the disease's signs and symptoms, clinical course (characteristic sequence of appearance of signs, symptoms and morphological changes) and prognosis.

For those interested in mathematical medicine, pathology is a key science. In fact, an alternate title for this course could be "Mathematical Pathology." Most applications of mathematical models to medicine that do not focus on epidemiology are overtly part of pathology. Examples abound in tumor biology, perhaps the most well developed field in mathematical medicine. The greatest contributions of mathematics to medicine include the discovery that malignant transformation of cells requires multiple mutations. This turned the accepted etiology of cancer on its head, because at the time most oncologists believed that cancer formation required only one mutation in a single cell. Models of cell movement, including chemo- and haptotaxis, are yielding insight into tumor formation, and other models of tumor growth and angiogenesis are advancing our understanding of tumor necrosis, a morphological change characteristic of many tumors. More recent modeling efforts are helping to explain cachexia, a syndrome in which the body wastes away that represents the most common immediate cause of death among cancer patients. These are just a few examples, and many, many more will arise in the next few years as this young field blossoms.

REFERENCES

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[2] Cotran, R. S., V. Kumar and T. Collins. 1999. *Pathologic Basis of Disease.* W. B. Sanders Co.

[3] Diekmann, O. and J. A. P. Heesterbeek. 2000. *Mathematical epidemiology of infectious diseases: Model building, analysis and interpretation.* John Wiley and Sons, New York.

[4] Garrett, L. 1994. *The Coming Plague: Newly Emerging Diseases in a World out of Balance.* Penguin, New York.

[5] The person in question had recently graduated from Midwestern University's medical program.

[5] Pugh, M. B. [ed.] 2000. *Steadman's Medical Dictionary.* [27th ed.]. Lippincott Williams and Wilkins, Philadelphia.