At first glance, the inaugural 1812 issue of the New England Journal of Medicine and Surgery, and the Collateral Branches of Science seems reassuringly familiar: a review of angina pectoris, articles on infant diarrhea and burns. The apparent similarity to today's Journal, however, obscures a fundamental discontinuity (1812a, b, c; see box). Disease has changed since 1812. People have different diseases, doctors hold different ideas about those diseases, and diseases carry different meanings in society. To understand the material and conceptual transformations of disease over the past 200 years, one must explore the incontrovertibly social nature of disease.

Disease is always generated, experienced, defined, and ameliorated within a social world. Patients need notions of disease that explicate their suffering. Doctors need theories of etiology and pathophysiology that account for the burden of disease and inform therapeutic practice. Policymakers need realistic understandings of determinants of disease and medicine's impact in order to design systems that foster health. The history of disease offers crucial insights into the intersections of these interests and the ways they can inform medical practice and health policy.

Epidemiologic Transitions

In addition to angina, diarrhea, and burns, early Journal issues examined gunshot wounds, spina bifida, tetralogy of Fallot, diabetes, hernia, epilepsy, osteomyelitis, syphilis, cancer, croup, asthma, rabies, and urethral stones. Although some case reports describe patients who might walk into a clinic today, others are nearly unrecognizable. Apoplexy, a syndrome of fainting spells that might mean stroke, seizure, or syncope today, was understood to arise from a "nervous sympathy" by which the stomach influenced the head (1812d). Doctors agreed that even a near miss by a cannonball — without contact — could shatter bones, blind people, or even kill them (1812f). Reports of spontaneous combustion, especially of "brandy-drinking men and women," received serious, if skeptical, consideration (1812g). And physicians were obsessed with fevers — puerperal, petechial, catarrhal, and even an outbreak of "spotted fever" in which some patients were neither spotted nor febrile (1812e). The bill of mortality from 1811 (see figure) contains both the familiar and the exotic (1812h). Consumption, diarrhea, and pneumonia dominated the mortality data, but teething, worms, and drinking cold water apparently killed as well.
A century later, the infections that filled the Journal had been redefined according to specific microbial causes. The Journal ran reviews of tuberculosis (1912b), gonorrhea (1912e), and syphilis (1912i). Diphtheria, measles, pneumonia, scarlet fever, and typhoid made frequent cameos, and Massachusetts still maintained a leper colony on Penikese Island (1912d). Tropical infections also fascinated authors, whether worms in immigrants or outbreaks of plague, yellow fever, and malaria in the nation’s new tropical empire.

Doctors in 1912 did have some reasons to celebrate. By any account, the previous year had been “the healthiest of which there is any record” (1912a). Nearly every Journal issue that year mentioned another centenarian, and coverage of the “overwhelming success” of U.S. athletes at the Stockholm Olympics celebrated American racial vigor (1912f). One editorial, describing progress made since the Journal’s early years, rhapsodized about what another century of medical discovery might bring: “Perhaps in 1993, when all the preventable diseases have been eradicated, when the nature and cure of cancer have been discovered, and when eugenics has superseded evolution in the elimination of the unfit, our successors will look back at these pages with an even greater measure of superiority” (1912c).

Such paeans to progress, however, were accompanied by fear of the diseases of modernization. One article described a new problem, “automobile knee,” and decried the prevalence of “persons of extremely indolent habits of life” who no longer walked more “than the few steps that are needed from the chamber to the elevator, from the elevator to the dining-room, or lounging-room, and then to the automobile” (1912j). Long-standing concern about epilepsy, alcoholism, and feeblemindedness took on new relevance in a society increasingly preoccupied by fears of race suicide and the promise of eugenics (1912g, 1912h). Doctors struggled with cancer, eclampsia, impotence, heart disease (chiefly atherosclerotic), and arthritis.

During the 20th century, heart disease, cancer, and other chronic conditions assumed more dominant roles (see bar graph), although outbreaks of infectious disease — from eastern equine encephalitis (1938) and kuru...
(1957) to legionnaires’ disease (1977), AIDS (1981), and multi-drug-resistant tuberculosis (1993) — necessitated ongoing vigilance against microbes. New concerns also came to medical attention, from the terrifying consequences of thermonuclear war (1962) to the indolent but devastating effects of environmental pollution (1966) and climate change (1989). Optimism about prospects for the health of future populations persisted but remained tempered by concern about the pathologies of civilization. An obesity epidemic, feared in 1912, has come to pass. Our previously steady increase in life expectancy has stalled and may even be reversed (2005).

DEFINITIONS AND CONSEQUENCES

The material and conceptual dynamism of disease poses challenges: how do we define disease meaningfully, and how do we measure our burden of disease and set health policy priorities? These are deceptively simple questions. The definition of disease in Merriam-Webster’s Medical Dictionary as “an impairment of the normal state of the living animal or plant body” raises questions: What is normal? What is impaired? We cannot answer by referencing biology alone; the line between the normal and the pathological requires value judgments. As physicians know, not every symptom constitutes a disease. Nor, as anthropologists have shown, is it feasible simply to contrast “disease,” as diagnosed by doctors, with “illness,” as experienced by patients. As contemporary disputes over the definitions of alcoholism, chronic fatigue syndrome, and attention-deficit disorder make clear, physicians are never the sole arbiters of disease.

Any responsible attempt to define disease must account for the phenomenon’s complexity. A disease has characteristic signs and symptoms, afflicts particular groups of people, and follows a characteristic course. Doctors name diseases and work to identify their causes and develop ways to prevent and treat them. But patients also ascribe meaning to their suffering and assign responsibility for what went wrong. And diseases have utility, with concrete consequences for patients, doctors, and their institutions. They mediate patients’ claims to the sick role and adjudicate access to health care resources. Disease definitions structure the practice of health care, its reimbursement systems, and our debates about health policies and priorities. These political and economic stakes explain the fierce debates that erupt over the definition of such conditions as chronic fatigue syndrome and Gulf War syndrome. Disease is a deeply social process. Its distribution lays bare society’s structures of wealth and power, and the responses it elicits illuminate strongly held values.

The complexities and consequences of disease extend to its measurement. Even after a disease has been clearly defined, measuring its frequency, intensity, and relevance is not simple. Since the 17th century, polities have compiled causes of death into annual bills of mortality. Successive generations of demographers and epidemiologists have transformed such statistics into age-adjusted measures of disease-specific mortality and developed...
measures of morbid-
ity and of the impact
disease has on peo-
ple's ability to lead
meaningful, produc-
tive lives. But such measures, in-
cluding disability- and quality-
adjusted life-years, reduce the
complex experience of disease to
a single coefficient.

A population's disease status
can also be gauged by lists of
common diagnoses at clinics or
hospitals, but no single measure
definitively characterizes a popu-
lation's burden of disease. Choos-
ing among metrics is as much
about values and priorities as
about science, and it directly af-
facts health policy. Whereas ad-
vocates of clinical and research
funding for cardiovascular dis-
ease might use mortality data to
support their claims, mental
health advocates can cite morbid-
ity measures in seeking greater
resources. Data on causes of child-
hood mortality would justify cer-
tain priorities; analyses of health
care spending would justify others.

An ideal, sophisticated health pol-
icy would integrate all measures
to form a holistic map of the
burden of disease, but in practice
competing interests use different
representations of disease burden
to recommend particular policies.

ACCOUNTING FOR THE BURDEN
OF DISEASE

Regardless of the metric chosen,
any map of the burden of disease
exposes disparities within and
among populations. Two as-
pects of the burden of disease have
remained particularly vexing: chan-
ges over time in the prevailing
diseases and the persistence of
health inequalities.

By examining the many new
diseases that have appeared over
the past two centuries, historians
have categorized the ways in which
diseases emerge. New causes (e.g.,
severe acute respiratory syndrome,
motor vehicle accidents, radiation
poisoning), new behaviors (ciga-
rette smoking, intravenous drug
use), and even the consequences
of new therapies (insulin trans-
forming the course and manifes-
tations of diabetes) can produce
new diseases. Changing environ-
mental and social conditions can
increase the prevalence of once-
obscure ailments (myocardial in-
farction, lung cancer, kuru, and
“mad cow” disease). New diagno-
sis technologies and therapeutic
capacity can unmask previously
unrecognized conditions (hyper-
tension). New diagnostic criteria
can expand a disease's boundar-
ies (hypercholesterolemia, depres-
sion). Changing social mores can
redefine what is or is not a dis-
ease (homosexuality, alcoholism,
masturbation). New diseases can
emerge as the result of conscious
advocacy by interested parties
(chronic fatigue syndrome, sick
building syndrome). HIV–AIDS
alone demonstrates many of these
modes of emergence. The emer-
gence, recognition, and impact of
disease are never just a biosci-
centific process; the advent of a new
disease always involves social,
economic, and political processes
that shape its epidemiology and
influence our understanding and
response.

The interaction between the
biologic and the social is equally
apparent in the decline of a dis-
ease. Cannonball injuries, a fre-
cent cause of concern in 1812,
disappeared from the Journal,
only to be replaced by a new and
more terrible litany of war-related
injuries. Neurasthenia, a wide-
spread phenomenon of depleted
nervous energy in the late 19th
century, has disappeared, but
traces of it have remained recog-
nizable in other diagnoses
throughout the past century. In
some cases, a disease’s decline
clearly resulted from medical ac-
tion. Immunizations eradicated
smallpox and may someday erad-
icate polio. Genetic screening
has led to dramatic reductions in
Tay–Sachs disease, thalassemia,
and familial dysautonomia (2009). But often the potential for eradication has been incompletely realized — witness the continued prevalence of AIDS and tuberculosis in low-income countries and of atherosclerotic heart disease globally.

Even as prevailing diseases have changed, health disparities have endured. Inequalities in health status have always existed, regardless of how health has been measured or populations defined. When Europeans arrived in the Americas, they witnessed stark disparities in the fates of European, American, and African populations. During the ravages of 19th-century industrialization, physicians grew familiar with health disparities between rich and poor. Health inequalities remain ubiquitous, not just among races and ethnic groups but also according to geography, sex, educational level, occupation, income, and other gradients of wealth and power.5

The persistence of health inequalities challenges our scientific knowledge and political will. Can we explain them and alleviate them? Genetic variations don't explain why mortality rates double as you cross Boston Harbor from Back Bay to Charlestown or walk up Fifth Avenue from midtown Manhattan into Harlem. Nor do they explain why Asian-American women in Bergen County, New Jersey, live 50% longer than Native American men in South Dakota.6 Although we know something about the relationships among poverty, stress, allostatic load, and the hypothalamic–pituitary–adrenal axis, doctors and epidemiologists need more precise models that sketch in the steps between social exposure, disease, and death.

Accounting for the history of disease also requires us to examine why some disparities in disease are seen as proof of a natural order while others are considered evidence of injustice. The 4.3-year life-expectancy gap between blacks and whites in the United States provokes outrage, but the 4.9-year gap between men and women does not. It is tempting to assume that differences between the sexes are natural and those between races are not. But a 19th-century Journal reader might be skeptical of this explanation: men then lived at least as long as women. The survival advantage of women that appeared in the 20th century owed as much to changes in childbearing, improvements in obstetrical practice, and a new epidemic of heart disease disproportionately affecting men as to differences between the X and Y chromosomes. Disparities in health and disease are outcomes that are contingent on the ways society structures the lives and risks of individuals.

Recognition of the contingency of health inequalities should make them a target for intervention, yet the opposite has frequently happened: the ill health of impoverished or marginalized groups has been used against them — as evidence of their inferiority or as an argument that they're unworthy of assistance. In the late 19th and early 20th centuries such sentiments produced government policies with tragic outcomes for blacks and Native Americans. They may underlie current policies that would limit health care access for mentally ill, impoverished, and immigrant populations.

**THE ROLES OF MEDICINE**

Medical practice and health policy rely on the assumption that the solution to the problem of disease is to be found in physicians and their therapies. Physicians tend to credit biomedical science with 20th-century improvements in health and longevity. The history, however, is complex and contested.

For example, after Robert Koch's 1882 discovery of *Mycobacterium tuberculosis* and the advent of antibiotics in the 1940s, physicians claimed responsibility for the decline of tuberculosis in Europe and North America. But closer examination revealed that this decline had begun before Koch's discovery and had substantially run its course before effective antibiotics became available. Medicine's critics instead credited improvements in the standard of living, especially diet. A similar debate has emerged about coronary artery disease. Heart disease, like tuberculosis, followed a century-long epidemic wave, peaking in the United States in the 1960s before beginning 50 years of decline. Researchers have struggled to determine how much credit should be given to health care providers and how much to risk-factor reduction (2007). This debate has now been complicated by recent increases in coronary disease elsewhere, notably Russia and China, and by signs of a plateau and possible reversal of decline in the United States, Australia, and Western Europe (2005). The stakes of this debate are substantial, with implications for the allocation of contested health care resources.

Is there a best health policy? Our goal should be an integrated policy under which health care and public health programs together fully address the disease burden. But the details depend on how we conceptualize and mea-
In recent decades, biomarkers have become essential in diagnosing disease and assessing patients’ responses to therapy. The increasing quantitative rigor and efficiency of these tests have led to the possibility of “personalized medicine.” Despite such progress, the way in which a physician uses biomarkers recapitulates an enduring practice of medicine: measure the patient, think about the result, and make a decision.

With these advancements, U.S. researchers and companies have also claimed patents on their biomarker discoveries. These patents have generated controversy over whether they hinder the practice of medicine and research by covering not just the actual test but also the use of the biomarker generally in making diagnoses and discovering new applications. This year, a lawsuit over one such patent reached the Supreme Court.

The controversy originated in the mid-1990s, when researchers discovered that blood levels of azathioprine metabolites could guide the treatment of inflammatory bowel disease. Their patents on their discoveries covered, among other similar claims, administering azathioprine and measuring the level of a metabolite of the drug (see diagram): a level below 230 pmol per 8×10⁸ red cells suggested the need to increase the dose, while a level above 400 pmol per 8×10⁸ red cells suggested the need to reduce it. The researchers licensed their patents, including the one covering this dose-adjustment method, exclusively to Prometheus Laboratories to use in commercializing a diagnostic test.

Mayo Medical Laboratories initially sent out its specimens to Prometheus for analysis and recommendations that used the patented correlations. After some time, however, Mayo’s researchers created what they believed was a more accurate assay that employed