whom breast cancer developed, only 8 had a *BRCA1* mutation and 11 had a *BRCA2* mutation.[9] Since so few carriers were identified, the 95 percent confidence intervals for the effect of tamoxifen on the risk of breast cancer in this group were very wide. Thus, firm conclusions about the efficacy of tamoxifen as a preventive agent in women with *BRCA1* and *BRCA2* mutations cannot be drawn from these data. However, virtually all relevant studies suggest that reducing the number of ovulatory cycles, exposure to endogenous estrogen, or both has the same protective effect in women with *BRCA1* and *BRCA2* mutations as in large population-based series.

In contrast to screening for breast cancer, the limitations of screening for ovarian cancer lead us strongly to recommend prophylactic bilateral oophorectomy for women with *BRCA1* and *BRCA2* mutations after childbearing has been completed. Typically, surveillance for breast cancer in women with *BRCA1* and *BRCA2* mutations consists of annual mammography beginning at the age of 25 years, clinical breast examination and breast self-examination, and breast MRI as an investigational screening tool. However, in the Dutch study, the limitations of this strategy were evident in the eight cancers diagnosed during the study period.[10] Although breast MRI correctly diagnosed cancer in all six of the women in whom it was performed, six of the eight cancers were said to be palpable, and four of the eight were found to have spread to the ipsilateral axillary lymph nodes, an adverse prognostic feature. Remarkably, half the cancers in this group were detected in the interval between mammographic or MRI examinations.

Given the imperfect surveillance tools and difficult surgical choices, what should we recommend to women with *BRCA1* and *BRCA2* mutations? At present, prophylactic mastectomy is clearly the right choice for some women. For the remainder, oophorectomy and tamoxifen in conjunction with intensive screening that includes MRI is a viable alternative. Most important, ongoing and novel prospective studies to define the role of prophylactic surgery, new chemopreventive agents, and optimal screening strategies must be supported, and women at very high risk should be encouraged to participate.

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THE MAJOR INFECTIOUS DISEASES IN THE WORLD — TO TREAT OR NOT TO TREAT?

IN this issue of the *Journal,* Tahaoğlu and coworkers report on their experience in treating a cohort of patients infected with strains of *Mycobacterium tuberculosis* that are resistant to powerful antituberculosis drugs. Tuberculosis caused by strains that are resistant to at least isoniazid and rifampin is, by convention, termed "multidrug-resistant tuberculosis."[1] The authors of this report work in a referral center in Turkey that has available a full complement of clinical, laboratory, and surgical services, including multidrug treatment regimens given for 18 to 24 months, resources for the management of side effects, adjuvant surgery when necessary, and full financial and nutritional support. Tahaoğlu et al. show that with a high standard of care, the treatment of multidrug-resistant tuberculosis can have excellent results, especially among younger patients without serious coexisting conditions.

This study is important for several reasons. It has already been documented that multidrug-resistant tuberculosis is a pandemic. Drug-resistant cases of tuberculosis have been reported in every country surveyed.[2-4] *M. tuberculosis* is an airborne pathogen, and persons with active, pulmonary tuberculosis caused by a multidrug-resistant strain can transmit the disease to others as long as they are alive and coughing. For the hundreds of thousands who are sick with multidrug-resistant tuberculosis, the report by Tahaoğlu et al.

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should come as welcome news. Throughout the world, most patients with multidrug-resistant tuberculosis are like the majority of those in the Turkish study: young and middle-aged adults who are not infected with the human immunodeficiency virus (HIV) and who do not have serious coexisting conditions. Almost none of these patients, however, are receiving effective therapy, and most remain infectious.

Some *Journal* readers may be surprised to learn that the great majority of patients with multidrug-resistant tuberculosis throughout the world are not receiving effective therapy. The need for such therapy in "resource-poor settings" — the latest euphemism for poverty — is disputed in international tuberculosis-control circles, and it is argued that multidrug-resistant tuberculosis is too expensive and too difficult to treat. The authors of the current study take note of the debate about "whether to consider multidrug-resistant tuberculosis treatable or untreatable, given the often limited resources available." Some have claimed that multidrug-resistant tuberculosis can be treated with a short course of chemotherapy (i.e., treatment based on isoniazid and rifampin, the very drugs to which multidrug-resistant strains of *M. tuberculosis* are, by definition, resistant). It was not until last year that this misconception was put to rest. In a six-country study, the cure rates among patients with laboratory-documented, multidrug-resistant tuberculosis were well under 50 percent in most settings.[5] In a study in Ivanovo Oblast, Russia, only 5 percent of patients with multidrug-resistant tuberculosis were cured by short-course chemotherapy.[6]

It is not surprising that patients infected with multidrug-resistant strains of *M. tuberculosis* are not cured by treatment with the drugs to which the strains are resistant. Moreover, delays in establishing the diagnosis and initiating effective therapy are associated with poor outcomes, even when patients do finally receive effective therapy. In accordance with the current public health convention, all patients in Turkey who have smear-positive pulmonary tuberculosis receive empirical short-course chemotherapy based on isoniazid and rifampin. In the study by Tahaoğlu et al., drug-susceptibility testing was performed on specimens obtained from patients at the outset of therapy, and the results were then ignored. The delay in initiating effective therapy might have been reduced if the results of these tests had been taken into account.

It is not standard practice in North America or in Europe to perform such laboratory tests and then disregard the results. Why would such a procedure be followed? In most resource-poor settings, all patients receive empirical, standardized short-course chemotherapy, and it is assumed that drug-susceptibility testing is not available. Turkey is not a resource-poor country but geopolitically a part of Europe. At the facility described in this report, although it is perhaps not as handsomely equipped as a referral center in the United States, doctors have far more resources at hand than do the beleaguered doctors trying to battle tuberculosis in Latin America, the former Soviet Union, and other regions where multidrug-resistant tuberculosis is a major problem. The report by Tahaoğlu et al. shows that multidrug-resistant tuberculosis is treatable, at least where there are centers of excellence to deal with the problem.

What about countries where there are no centers of excellence? In a squatter settlement in Haiti and in a slum in Peru, my colleagues and I have obtained similar cure rates in treating patients with chronic multidrug-resistant tuberculosis.[7,8] Many communicable diseases can now be cured. Others, although still uncurable, can be suppressed effectively with therapy. That patients with multidrug-resistant tuberculosis are going untreated raises the general question of the standards of care for patients with chronic infectious diseases who have the misfortune to live in impoverished countries. The assumption that these diseases are treatable in some places and not in others is widely accepted. A lack of infrastructure is commonly cited as the justification for lower standards of care in some countries, but the real issue is cost. It has been argued that the high cost of "second-line" antituberculosis medications makes the treatment of multidrug-resistant tuberculosis problematic in poor countries. However, the prices of these medications, which have long been off patent, are exorbitant because there has not been a concerted effort to treat patients who have tuberculosis and who live in poverty.[9] The destitute sick generate no perceptible demand in the medical marketplace.

The most important question facing modern medicine involves human rights. We are witnessing a growing "outcome gap." Some populations have access to increasingly effective interventions; others are left out in the cold. The more effective the treatment, the greater the injustice meted out to those who do not have access to care.

The question of global injustice applies directly to AIDS, which has recently overtaken tuberculosis as the world's leading infectious cause of death among adults. Over the past five years, deaths from AIDS in the United States have dropped sharply, as have admissions related to HIV infection in U.S. hospitals, because of widespread use of highly active therapy against the virus. But these advances, like those in the treatment of multidrug-resistant tuberculosis, have served only a tiny minority of persons throughout the world who could benefit from them. For most HIV-infected persons, these lifesaving drugs are unavailable. We hear all kinds of excuses. Efforts to treat AIDS and multidrug-resistant tuberculosis in areas such as Africa and Haiti, which lack a health care infrastructure, are dismissed as "unsustainable" or "not appropriate technology." Antiviral therapy and complex antituberculosis therapies are not considered cost effective in an era in

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which money is worshipped so ardently that it is difficult to attack market logic without being called misguided or irresponsible.

In too many policy discussions, the argument that treatment is not cost effective is largely a means of ending unwelcome discussions about the destitute sick. A high-ranking official in the U.S. Department of the Treasury recently objected to a strategy that would make anti-HIV drugs available on the continent where they are most needed. He is quoted as saying that Africans lack the necessary "concept of time," implying that the drugs would be ineffective because of the required schedule of administration.[10] Despite the absence of data that support these claims — and much experience to the contrary — they are persuasive within the elite circles where decisions are made that affect the health and fates of millions of the world's sick.

Prevention is, of course, always preferable to treatment. But epidemics of treatable infectious diseases should remind us that although science has revolutionized medicine, we still need a plan for ensuring equal access to care. As study after study shows the power of effective therapies to alter the course of infectious disease, we should be increasingly reluctant to reserve these therapies for the affluent, low-incidence regions of the world where most medical resources are concentrated. Excellence without equity looms as the chief human-rights dilemma of health care in the 21st century.

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