sites include centers for treating substance abuse and human immunodeficiency virus infection, shelters, soup kitchens, parole programs, community health centers, and hospitals.

The structure of directly observed therapy must also vary with site and circumstance. Some patients in methadone-maintenance programs attend a clinic five days a week, others three days a week, and others once a week. Programs of intermittent therapy should be devised around such varying schedules and use existing routines. The Denver model presumes that all 62 doses of antituberculosis medication will be provided by a registered nurse. The nursing staff will never exist to provide this level of care to the more than 4500 patients with new cases of active tuberculosis reported in 1992 in New York State. Trained nonmedical personnel can provide most of the required services, with oversight to ensure an acceptable quality of care. Community outreach workers from the populations being served can most effectively establish the trust and rapport necessary to maintain the lengthy course of treatment for drug-resistant tuberculosis. . . .

GEORGE T. DIFERDINANDO, JR., M.D., M.P.H.
SUSAN J. KLEIN, M.S.
LLOYD F. NOVICK, M.D., M.P.H.
New York State Department of Health
Albany, NY 12237

To the Editor: The overlap of the epidemics of tuberculosis and drug use offers an opportunity to treat tuberculosis through drug-treatment facilities. Of 361 patients with tuberculosis seen at our institution over a four-year period, 165 (46 percent) had a history of using injectable drugs and 68 (19 percent) were enrolled in methadone-maintenance programs.* The use of these programs to provide directly observed therapy to patients with chemical dependency who have tuberculosis would be an efficient means of increasing available tuberculosis-treatment services while subjecting patients to minimal additional restrictions or inconvenience. Patients enrolled in methadone-maintenance programs who are found to have tuberculosis should receive antituberculous therapy when they receive their methadone, and opiate users with tuberculosis should be fast-tracked into methadone programs. . . .

DAVID C. PERLMAN, M.D.
NADIM SALOMON, M.D.
Beth Israel Medical Center
New York, NY 10003

*Chew D, Pumerantz A, Perlman DC, DePalo VA, Wilets I, Salomon N. A continued surveillance of tuberculosis in a New York City hospital: factors associated with drug resistance and outcome of therapy. Presented at the World Congress on Tuberculosis, Bethesda, Md., November 16–19, 1992.

The authors reply:

To the Editor: Although some perceive directly observed therapy as a draconian measure, we submit that its adverse effects on the individual and society are substantially less than the effects of two years of treatment of tuberculosis at a sanitarium, which was prevalent just three decades ago.

Two of us consulted with authorities in Mississippi as they were developing their program of directly observed therapy. We are most gratified to see it come to fruition. Although other elements presumably had a role in the reduction in the number of cases of tuberculosis in Mississippi, we believe that supervised treatment contributed greatly to this trend.

Dr. DiFerdinando and colleagues raise salient issues about the applicability of the Denver model to other settings. We agree wholeheartedly that there are many variations on this theme. We encourage local authorities and clinicians to devise programs and methods suited to their needs and assets.[1] With respect to the oversight of treatment, we calculated costs with the use of data on nurses, to produce a high-range estimate of expenses. In fact, we have employed lay community workers for much of the outreach efforts throughout the 25-year history of directly observed treatment in Denver. Not only is this approach more economical, but it is also more feasible (in terms of the number of nurses required). The use of lay community workers is potentially more effective (in terms of finding persons who have more flexibility and comfort in moving about local communities) and affords the indirect benefit of creating meaningful jobs in financially distressed areas. The recent initiation of a National Institutes of Health–sponsored nationwide trial of tuberculosis treatment that emphasizes intermittent, directly observed therapy is also helpful.

Drs. Perlman and Salomon identify a vital issue in tuberculosis treatment: the concordance of substance abuse and tuberculosis. Given the aspects of human nature that beget noncompliance with tuberculosis therapy, asking patients to visit multiple sites to receive methadone for opiate abuse or disulfiram for alcoholism, as well as medication for tuberculosis, poses a high risk that one or more programs will fail. Tuberculosis treatment should be integrated into substance-abuse programs. Some patients may be at high risk for the acquisition of tuberculosis in these settings, however. Thus, great care must be taken that patients with tuberculosis are screened carefully and their disorder is determined to be noncontagious. In addition, environmental controls[2] must be in place (ventilation and ultraviolet germicidal irradiation) in case patients with infectious disease do slip through.

MICHAEL D. ISEMAN, M.D.
National Jewish Center for Immunology and Respiratory Medicine
Denver, CO 80206

DAVID L. COHN, M.D.
Denver Department of Health and Hospitals
Denver, CO 80204

JOHN A. SBARBARO, M.D., M.P.H.
University of Colorado Health Sciences Center
Denver, CO 80262

1. Prevention and control of tuberculosis in U.S. communities with at-risk minority populations and prevention and control of tuberculosis among homeless persons: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR Morb Mortal Wkly Rep 1992;41:RR-5.
2. Iseman MD. A leap of faith: what can we do to curtail intrainstitutional transmission of tuberculosis? Ann Intern Med 1992;117:251-3.

THE LAW AND CONTROL OF TUBERCULOSIS

To the Editor: In his discussion of the law and tuberculosis control (Feb. 25 issue),[1] Annas concludes that interventions short of confinement are preferred and that it is "appropriate to use monetary and other inducements to encourage compliance with outpatient therapy." Although we agree that confinement should be a last resort, we recommend against direct payments to drug abusers (who are at high risk for drug-resistant tuberculosis) because there may be a substantial risk of relapse or overdose when cash is given directly to addicts. Physicians who treat substance abusers

are familiar with the detrimental effects of cash on their patients' compliance with treatment.

We recommend that officials responsible for tuberculosis control review the definitions of disability prepared by the Social Security Administration to apply to drug abusers.[2] When a patient is addicted to alcohol or illicit drugs, current law requires that there be a third-party payee for social security disability payments, to disburse the funds for the benefit of the addict. We suggest that the local tuberculosis program seek to act as the payee for adults with tuberculosis. This would enable the program to provide housing, food, and other needed services, as well as tuberculosis treatment. In addition, a determination of disability by the Social Security Administration almost always ensures eligibility for Medicaid.

Social Security officials have stated that their goal is to "assure that every drug addict and alcoholic who needs treatment will be identified and encouraged to file for disability benefits."[3] They stated further that "Currently, about 24,000 persons are receiving benefits because of a disability based on addiction. The number of people who should be receiving benefits is surely 10 times that many, possibly 20 times as many."[3]

ALAN I. TRACHTENBERG, M.D., M.P.H.
LURA ORAVEC, M.S.
Rockville, MD 20857 National Institute on Drug Abuse

1. Annas GJ. Control of tuberculosis — the law and the public's health. N Engl J Med 1993;328:585-8.
2. Social Security Administration. Disability evaluation under Social Security. Washington, D.C.: Department of Health and Human Services, 1986.
3. Office for Treatment Improvement (OTI). Supplemental security income for individuals disabled by alcohol and other drug abuse: workshop report (ADM 270-90-001). Rockville, Md.: Alcohol, Drug Abuse and Mental Health Administration, 1990.

To the Editor: Annas is appropriately concerned about the rights of the disempowered and homeless. It is this same group, however, that will be harmed by an inadequate tuberculosis policy. When a homeless patient with tuberculosis goes untreated, it is not the rich and privileged who suffer, but the other residents of the shelter. Striving to protect the rights of one innocent person with a communicable disease may rob many other innocent people of their health and safety.

I share in feeling outrage that society has chosen to ignore the health needs of the homeless, the addicted, and the HIV-infected. Unfortunately, there is currently neither public desire nor political will to address these needs meaningfully. Therefore, we must deal with the situation that exists.

By the time patients have demonstrated inability or unwillingness to comply with tuberculosis therapy, they have in all likelihood infected others. Requiring "clear and convincing" evidence of noncooperation before treatment is enforced is a prescription for exponential disaster. The fact that it is primarily the indigent and disempowered who would have their civil liberties curtailed should not obscure the fact that it is primarily the (as yet uninfected) indigent and disempowered whom mandatory treatment would protect.

It is not appropriate to compare patients with multidrug-resistant tuberculosis with psychotic patients who are of doubtful danger to society; instead, they should be compared with patients with smallpox. If we knew of patients with smallpox, would we accept their promise to stay at home as adequate protection for society? The risk of transmission of tuberculosis is proved, the consequences are often lethal,[1,2] and the fact of infection should itself be considered clear and convincing evidence of risk to the public health. Every patient should receive mandatory treatment, whether it is provided under direct observation, in confinement, or in confinement alone for those who refuse treatment. Infected people should bear the burden of proof of compliance before they are switched to voluntary treatment.

DAVID W. ROBERSON, M.D.
Seattle, WA 98195 University of Washington

1. Frieden TR, Sterling T, Pablos-Mendez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City. N Engl J Med 1993;328:521-6.
2. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993;328:527-32.

To the Editor: Annas suggests that in tuberculosis control there is

an understandable egalitarian desire to try to treat everyone in the same way by subjecting everyone to directly observed therapy. There is, however, insufficient justification for requiring this annoying and inconvenient method of treatment for patients who are virtually certain to take their antituberculosis medications. . . .

How is Annas going to predict just who these patients might be? Perhaps he will exclude all African Americans, homeless people, injection-drug users, or the socially disaffiliated. Perhaps he will include all physicians, lawyers, and whites.

Medical science knows that 33 percent to 100 percent of people do not take their medication properly.[1,2] Unfortunately, medical science has no way to predict who these people are. There is no correlation of age, race, sex, or socioeconomic status with compliance with a medical regimen.[3,4] This problem has led to our disastrous tuberculosis epidemic.

Physicians who treat tuberculosis have patients who are lawyers and physicians who are terrible at compliance, just as we have injection-drug users and alcoholics who are excellent at compliance. That is why the statement on tuberculosis treatment by the Advisory Council for the Elimination of Tuberculosis and the joint statement by the American Thoracic Society and the Centers for Disease Control and Prevention emphasize "strong consideration" of directly observed therapy for everyone, until compliance with medication has been demonstrated.

LEE B. REICHMAN, M.D., M.P.H.
BONITA T. MANGURA, M.D.
New Jersey Medical School
Newark, NJ 07103 National Tuberculosis Center

1. Brenner E, Poszik C. Case holding. In: Reichman LB, Hershfield E, eds. Tuberculosis: a comprehensive international approach. New York: Marcel Dekker, 1993:185-285.
2. Rudd P. In search of the gold standard for compliance measurement. Arch Intern Med 1979;139:627-8.
3. Roth HP, Caron HS, Hsi BP. Estimating a patient's cooperation with his regimen. Am J Med Sci 1971;262:269-73.
4. Mushlin AI, Appel FA. Diagnosing potential noncompliance: physicians' ability in a behavioral dimension of medical care. Arch Intern Med 1977; 137:318-21.

Professor Annas replies:

To the Editor: All the writers and I share the goal of reducing the incidence of tuberculosis and preventing the spread of multidrug-resistant tuberculosis. How can this goal be

most efficiently and fairly accomplished? I disagree with the statement of Trachtenberg and Oravec that addicts should never be paid for adhering to tuberculosis-treatment regimens. If this argument is correct, it would also seem that addicts should never be employed because we are concerned about how they will spend their salaries.

Contrary to Roberson's statements, the standard of clear and convincing evidence is required only for involuntary confinement, not for mandatory directly observed therapy. Second, it should be possible to discern noncooperation well before multidrug-resistant tuberculosis develops and certainly before it is spread. "The fact of infection itself" is no more a sufficient reason to confine patients with tuberculosis than it is to confine people with HIV infection. Likewise, whether we accept "voluntary" quarantine at home of a hypothetical patient with smallpox should depend on an individualized assessment of the patient.

Reichman and Mangura join Roberson in support of universal directly observed therapy. I support voluntary directly observed therapy. The statistics I cited suggest that over the past 15 years more than 80 percent of Americans with tuberculosis successfully completed 6 to 12 months of continuous chemotherapy.[1] Therefore, making directly observed therapy mandatory for everyone is a "wasteful, inefficient, and gratuitously annoying" overreaction.[2] Moreover, this strategy improperly assumes that no patient can be trusted and simultaneously redefines the tuberculosis problem in the United States as one of noncompliant patients, rather than as the complex multifactorial social problem that it is. We should try to make compliance with treatment easier, not harder.

Reichman and Mangura ask how I am "going to predict just who [the compliant] patients might be?" The short answer is that I am not; the treating physicians must make this assessment. This assessment will be more accurate if the focus is on "individualized case-management strategies and monitoring" rather than disease-based stereotyping.[3] For any outpatient treatment to be successful, the patients must be actively involved and the meaning of disease understood from their perspective.[4] Since "much patient nonadherence can be traced to difficulties of understanding and communication in the doctor–patient interaction,"[3] it seems reasonable to focus attention on this interaction. This is preferable to abandoning the individualized doctor–patient treatment model in favor of a standardized and mandatory model of public health prevention that assumes all patients with tuberculosis are untrustworthy.

GEORGE J. ANNAS, J.D., M.P.H.
Boston University Schools
Boston, MA 02118 of Medicine and Public Health

1. Bloom BR, Murray CJL. Tuberculosis: commentary on a reemergent killer. Science 1992;257:1055-64.
2. Annas GJ. Control of tuberculosis — the law and the public's health. N Engl J Med 1993;328:585-8.
3. Freund PES, McGuire MB. Health, illness, and the social body: a critical sociology. Englewood Cliffs, N.J.: Prentice-Hall, 1991:200.

SERUM CHOLESTEROL IN YOUNG MEN AND CARDIOVASCULAR DISEASE

To the Editor: Klag et al. (Feb. 4 issue)[1] report a strong correlation between the serum cholesterol level measured early in adult life in men and the incidence of cardiovascular disease in midlife. In contrast to other investigators,[2-4] they did not find a "J-shaped" relation between total mortality and the serum cholesterol level. Such a relation has been attributed to an excess of deaths from noncardiovascular causes among patients with low levels of serum cholesterol — for example, from cancer, accidents, or suicide. From the authors' Table 2, we calculated death from noncardiovascular causes. This was consistent with a positive relation between the serum cholesterol level and mortality from noncardiovascular causes, in contrast to studies that have found an inverse relation between serum cholesterol and mortality from noncardiovascular causes. Could the authors comment on their findings in the context of the other studies?

B. CORVILAIN, M.D.
J. MATTE, M.D.
C. LEVINE, M.D.
Erasme Hospital
B-1070 Brussels, Belgium Free University of Brussels

1. Klag MJ, Ford DE, Mead LA, et al. Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med 1993;328:313-8.
2. Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Arch Intern Med 1992;152:1490-500.
3. Stemmermann GN, Chyou PH, Kagan A, Nomura AMY, Yano K. Serum cholesterol and mortality among Japanese-American men. Arch Intern Med 1991;151:969-72.
4. Jacobs D, Blackburn H, Higgins M, et al. Report of the Conference on Low Blood Cholesterol: mortality associations. Circulation 1992;86:1046-60.

The authors reply:

To the Editor: The J-shaped relation between serum cholesterol and total mortality seen in midlife studies is due in part to lower serum cholesterol levels in people with subclinical cancer and other chronic diseases. Our study differed in that the men were enrolled at a relatively young average age (22 years) and, because of the entrance requirements for medical school, were likely to be healthy. Such a bias is therefore unlikely because our population was young and healthy at the time of serum cholesterol determination.

The incidence rates in Table 2 of our paper were calculated with Kaplan–Meier analysis. This takes into account withdrawals from the study. Because withdrawal times may vary for different end points, the subtraction of one cumulative incidence rate from another may not yield accurate estimates. In our data, there was no relation between serum cholesterol and mortality from noncardiovascular causes ($P = 0.6$). We are currently investigating the relation between serum cholesterol and cause-specific mortality in this cohort.

MICHAEL J. KLAG, M.D., M.P.H.
LUCY A. MEAD, Sc.M.
DAVID M. LEVINE, M.D., M.P.H., Sc.D.
Johns Hopkins University
Baltimore, MD 21205 School of Medicine

THROMBOXANE SYNTHASE AND ORGAN PREFERENCE FOR METASTASES

To the Editor: Studies of the metastatic behavior of cancer suggest that one of the factors influencing the site at which tumor cells lodge is the presence of a special "soil" that favors the survival and growth of these tumor cells. A variety of hormonal and growth factors have been shown to influence the expansion of a metastatic colony.