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- 1 Chenet L, McKee M, Leon D, Shkolnikov V, Vassin S. Alcohol and cardiovascular mortality in Moscow; new evidence of a causal association. *J Epidemiol Community Health* 1998;52:772-4.
- 2 Willich SN, Lowel H, Lewis M, Hormann A, Arntz H-R, Keil U. Weekly variation of acute myocardial infarction. Increased Monday risk in the working population. *Circulation* 1994;90:87-93.
- 3 McKee M, Britton A. The positive relationship between alcohol and heart disease in eastern Europe: potential physiological mechanisms. *J R Soc Med* 1998;91:402-7.
- 4 Peters RW. Circadian patterns and triggers of sudden cardiac death. *Cardiol Clin* 1996;14:185-94.

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Drug points

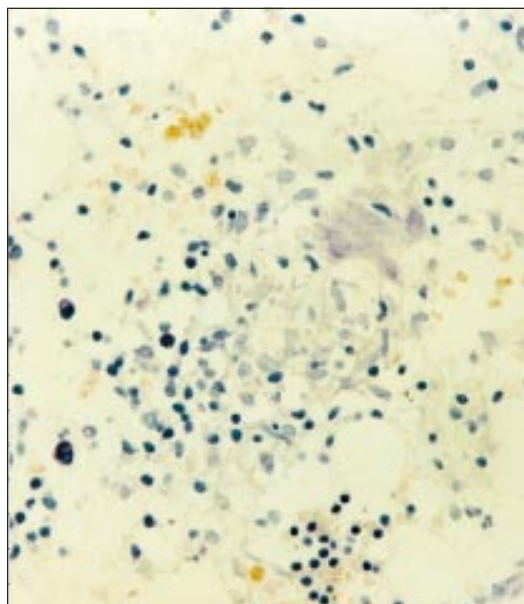
Systemic granulomatous disease after intravesical BCG instillation

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Vaccination with BCG, an attenuated strain of bovine tubercle bacilli, has been used for most of this century to protect against tuberculosis.¹ Recently the cell mediated immune response that follows inoculation with this organism was found to be an effective treatment for different types of cancer.² We report a patient in whom application of BCG into the urinary bladder was quite effective in controlling a superficial vesical carcinoma but who developed granulomatous disease of multiple organ systems.

A 75 year old man was admitted because of a two month history of recurrent fever up to 40°C. His history was unremarkable except that eight months earlier a transitional cell carcinoma of the urinary bladder (pT1) had been endoscopically resected and treatment with monthly intravesical instillations of BCG was begun.³ The last instillation had been given one month before the present admission. Laboratory studies on admission revealed thrombocytopenia ($82 \times 10^9/l$) and abnormal levels of aspartate aminotransferase (40 U/l, normal <18), γ -glutamyltransferase (254 U/l, normal <28), alkaline phosphatase (566 U/l, normal <180), cholinesterase (1534 U/l, normal >3000), and pancreatic lipase (720 U/l, normal <190). Computed tomography of the chest revealed a "ground glass" infiltration and micronodular pattern near the pleural space, and both a liver biopsy and a bone marrow sample (figure) revealed numerous non-caseating granulomas with epithelioid and giant cells. An attempt to cultivate mycobacteria from these specimens was unsuccessful. Although repeated cultures of blood, sputum, and gastric juice were also negative, *Mycobacterium bovis* was found in urine samples. After treatment with isoniazid, rifampicin, and ethambutol, clinical recovery was prompt: the fever quickly resolved, and within a week laboratory studies showed normal values. When tuberculostatic treatment was discontinued five months later no relapse occurred.

Since its development in 1910, more than 1.5 billion people have received BCG vaccine as a prophylaxis against tuberculosis, and its administration is generally considered safe.³ More recently BCG instillation into the bladder has become an established and highly effective treatment for in situ and recurrent low grade bladder cancer.² Although complications from intravesical appli-



Sarcoid-like granuloma in an otherwise normal bone marrow sample

cation of BCG have occasionally been observed,⁴ such extensive systemic complications as we describe have not previously been reported. This patient's clinical course suggests that systemic granulomatous disease, and bone marrow involvement in particular, should be considered when a patient develops symptoms of systemic infection after inoculation with BCG. Given the extended period during which BCG can be excreted, patients who undergo this treatment should also be advised to disinfect their urine to avoid infecting others.

- 1 Zumla A, Grange J. Clinical review—tuberculosis. *BMJ* 1998;316:1962-4.
- 2 Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. *N Engl J Med* 1991;325:1205-9.
- 3 Lotte A, Wasz-Hockert O, Poisson V, Dumitrescu N, Verron M, Couvet E. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. *Adv Tuberc Res* 1984;21:107-93.
- 4 Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596-600.