

Correspondence

Multidrug-Resistant *Streptococcus pneumoniae*

To the Editor: In their study of the prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States, Whitney et al. (Dec. 28 issue)¹ report differences in the prevalence of resistance according to region, age, and race. We investigated whether these findings reflect patterns found in hospitalized patients and evaluated recent changes in the prevalence of drug-resistant streptococcus species among inpatients.

We used the Solucient projected inpatient data base for 1997 through 2000. This is an all-payer data base that contains information on more than 17 million inpatient discharges in the United States each year and has been used for comparisons of hospital-admissions data and the results of surveillance by the Centers for Disease Control and Prevention.² Our cohort included 812,088 patients with one or more diagnosis codes from the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) indicating infection with streptococcus species, of whom 12,771 (1.57 percent) also had codes indicating antibiotic resistance.

We evaluated the increase in the prevalence of drug-resistant streptococcus in the inpatient setting from the first quarter of 1997 through the first quarter of 2000. We found a significant increase in the rate of resistant streptococcal infections (Fig. 1). Patients who were infected with resistant organisms were 58 percent more likely to die than those with nonresistant streptococcal infections ($P < 0.001$), male patients were 40 percent more likely to have a resistant organism than female patients ($P < 0.001$), and whites were 18 percent more likely to have a resistant organism than blacks ($P < 0.001$). Infection with a resistant strain was associated with a five-day increase in the length of stay. The prevalence

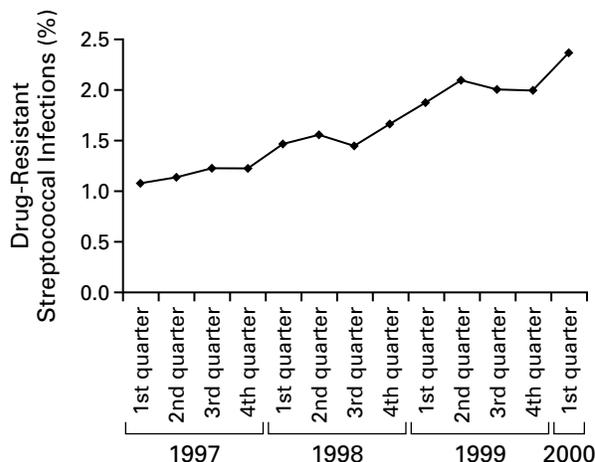


Figure 1. Prevalence of Drug-Resistant Streptococcal Infections among Inpatients in U.S. Hospitals from the First Quarter of 1997 through the First Quarter of 2000.

rates ranged from a low of 1.49 percent in the Northeast to a high of 1.65 percent in the West ($P < 0.001$).

DAVID A. FOSTER, PH.D., M.P.H.
SIVANA T. HELLER, M.D., M.P.H.
JANET K. YOUNG, M.D., M.H.S.A.

Solucient
Ann Arbor, MI 48108

1. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000;343:1917-24.

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To the Editor: The cornerstone of the recommendations of Whitney et al. with regard to preventing pneumococcal

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disease is vaccination. There have been three double-blind, randomized, placebo-controlled trials that cast doubt on the ability of vaccination to prevent pneumococcal disease.¹⁻³ It seems that the true value of pneumococcal vaccine is unclear. In the light of these studies, what recommendations should be made regarding the use of these vaccines?

DONALD TAYLOE, M.D.

Fresno Veterans Affairs Medical Center
Fresno, CA 93703

1. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;315:1318-27.
2. Ortvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998;351:399-403.
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To the Editor: The editorial on antibiotic resistance by Wenzel and Edmond¹ covers a vitally important subject of global concern.² However, their statement that the degree of antibiotic use in the United States "is equivalent to nearly 30 prescriptions per 100 persons per year and to 4.1 kg (9 lb) of antibiotics per 100 persons per year" is misleading. The implication is that each of these 30 prescriptions involves an average total dose of more than 136 g. Inappropriate prescribing is a serious problem, but it has yet to reach such colossal proportions. On the basis of the authors' figures, total U.S. consumption (both animal and human) would average 8.2 kg apiece. However, human usage should be quantified from actual data, not by dividing the total consumption of 22.7 million kg by 50 percent.

Wenzel and Edmond state that 160 million prescriptions for antibiotics are written annually in a country with a population of 275 million people, which they then calculate as being equivalent in terms of use to 30 prescriptions per 100 persons per year. The number would actually be slightly less than 60. This would cut the calculated average prescription size to less than 70 g, a high, but more reasonable figure.

Could the authors restate these data, which are so important to our future control of microbial infections, in both humans and animals?

RICHARD S. WILBUR, M.D., J.D.
Royal Society of Medicine Foundation
Lake Forest, IL 60045

1. Wenzel RP, Edmond MB. Managing antibiotic resistance. *N Engl J Med* 2000;343:1961-3.
2. Soulsby L, Wilbur RS, eds. Antimicrobial resistance. London: Royal Society of Medicine Press, 2001.

Dr. Whitney replies:

To the Editor: The data of Foster and colleagues are intriguing. The authors report significant associations between a diagnosis code indicating antibiotic resistance and male sex, the risk of death, and the length of the hospital stay. Unfortunately, insufficient details are provided regarding the search strategy they used, since the ICD-9-CM code for streptococcal sepsis (038.0) may reflect illnesses caused by

a variety of pathogens (e.g., group A or group B streptococci) and it is not clear whether codes for *S. pneumoniae* (e.g., 038.2 and 481) were included. Furthermore, the sensitivity of the use of ICD-9-CM codes as a means of identifying antibiotic resistance is uncertain. A temporal increase in the frequency of codes indicating resistance might reflect increased testing, changes in coding practices, or increased resistance of particular pathogens.

The low prevalence of resistance identified makes us doubt that the strategy based on ICD-9-CM codes was a sensitive means of identifying pneumococcal infections and testing for resistance. In addition, patients with complicated hospital courses, and perhaps other infections with resistant organisms, may have been more likely to receive codes indicating antibiotic resistance than patients who had an uncomplicated infection with a resistant streptococcal species. Without information on the type of streptococci and the sensitivity and specificity of their search strategy, it is difficult to reach any conclusions about the findings of Foster and colleagues.

Pneumococcal polysaccharide vaccines are effective against invasive disease, such as bacteremia and bacteremic pneumonia, in many populations of patients.^{1,2} In immunocompromised persons, such as those with human immunodeficiency virus (HIV) infection or AIDS, such vaccines may be effective against invasive disease only in certain subgroups.^{3,4} Therefore, pneumococcal polysaccharide vaccine should be given as early as possible after the diagnosis of HIV infection; if the diagnosis is made later in the course, the vaccine should be given after the initiation of antiretroviral therapy. The efficacy of the vaccine against nonbacteremic pneumonia has not been clearly demonstrated; whether this is due to a true lack of efficacy or to problems in determining the cause of pneumonia is unclear. Although the study from Sweden⁵ that is cited by Dr. Tayloe did not find the vaccine to have a protective effect against pneumococcal pneumonia, the test used for the diagnosis was subsequently found to be nonspecific.⁶ Since invasive pneumococcal disease carries a high risk of death, especially in the elderly and persons with chronic illnesses, the recommendations for the use of pneumococcal polysaccharide vaccine for these patients are appropriate. Given the increasing difficulties in treating pneumococcal infections owing to the rise of multidrug-resistant organisms, the use of pneumococcal vaccines should be actively promoted.

CYNTHIA G. WHITNEY, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA 30333

1. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453-60.
2. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. *JAMA* 1993;270:1826-31.
3. Dworkin MS, Ward JW, Carpenter LM, et al. Pneumococcal disease among HIV-infected persons: incidence, risk factors, and impact of vaccination. *Clin Infect Dis* (in press).
4. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med* 2000;160:2633-8.
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6. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2001;32:534-8.

The editorialists reply:

To the Editor: In our editorial, we quoted Levy, who estimated that in 1996 160 million prescriptions were written for antibiotics in the United States and more than 50 million lb (22.7 million kg) of antibiotics was produced for use in people, animals, and agriculture.¹ Approximately half those antibiotics (25 million lb [11.4 million kg]) were used by people. Because there are no specific data on prescribing profiles for the U.S. population, we calculated an average from the data: 25 million lb for 275 million people, or 9 lb (4.1 kg) per 100 persons per year. If 80 million prescriptions (half the total) were for use in people, the use of similar calculations would yield a value of 29.1 prescriptions per 100 persons per year.

The congressional Office of Technology Assessment estimated that in 1985, 17.6 million lb (8.0 million kg) of antibiotics was prescribed for use in animals alone — for treatment, disease prevention, and growth promotion.² Assuming that equal quantities (17.6 million lb) were used for people in 1985 and that such use has increased over the past 15 years, we find that there is consistency in the pattern of the various gross estimates.

Nevertheless, Dr. Wilbur's point about our ability to estimate the average use per person or use per prescription without available data is well taken. Referring to data from the Office of Technology Assessment, the Institute of Medicine in 1998 reported annual antibiotic use in humans in different terms: approximately 190 million defined daily doses were used in hospitals, and approximately 145 million courses were used in the community.³ If one third to one half of the 35 million patients who are hospitalized in the United States each year receive antibiotics, the number of defined daily doses would be 16.3 to 10.9 per person. However, some patients in critical care units and others who have immunosuppression with fever and neutropenia receive multiple antibiotics at high doses for weeks at a time, far exceeding the average use. In a study of eight intensive care units, Gaynes and Monnet reported that the use of vancomycin ranged from 10 to 70 defined daily doses per 1000 patient-days and the use of third-generation cephalosporins ranged from 17 to 154 defined daily doses per 1000 patient-days.⁴ Wide variation in use among outpatients must also occur.

We conclude that a large tonnage of antibiotics is prescribed for people in the United States. Measures of use vary considerably from study to study. Most important, precise profiles of the distribution of antibiotics and the number of prescriptions written for people in the community, hospital, or extended care facilities are unknown and await accurate national surveillance.

RICHARD P. WENZEL, M.D.
MICHAEL B. EDMOND, M.D., M.P.H.
Virginia Commonwealth University
Richmond, VA 23298-0663

1. Levy SB. Antibiotic resistance: an ecological imbalance. In: Ciba Foundation. Antibiotic resistance: origins, evolution, selection and spread. Chichester, England: John Wiley, 1997:1-14.

2. Antibiotics in animal husbandry. In: Office of Technology Assessment, Congress of the United States. Impacts of antibiotic-resistant bacteria. Washington, D.C.: Government Printing Office, 1995:155-66.

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Cellular Telephones and Brain Tumors

To the Editor: The article by Inskip et al. (Jan. 11 issue)¹ provides reassuring findings that cellular-telephone use is not associated with an increased risk of brain tumors, but the study has some limitations that are due to its retrospective design. Exposure was assessed by interviews, and recall bias, one of the main pitfalls in case-control studies, may be a problem because patients with brain tumors can have impaired memory.

Since telephone companies keep very accurate records of the calls of their customers, it would have been possible to document cellular-telephone use objectively if these data were accessible. Although legal problems might arise, most subjects would probably consent to the retrieval by investigators of data on the total duration of their calls, with no further details. The telephone companies should certainly be blinded to the health status of the customers whose data they provide. Because of the objectivity of billing records, such a design could provide more reliable data on the association between cellular-telephone use and brain tumors.

MUSTAFA ERMAN, M.D.
ISMAIL CELIK, M.D.
AYSE KARS, M.D.
Hacettepe University
06100 Ankara, Turkey

1. Inskip PD, Tarone RE, Hatch EE, et al. Cellular-telephone use and brain tumors. *N Engl J Med* 2001;344:79-86.

To the Editor: The study by Inskip et al. has a number of serious deficiencies. The hypothesis that was tested was that there is no association between the frequency of brain tumors (as determined by hospital admissions) and ever having used cellular telephones regularly. Consider the possibility that before the diagnosis of a brain tumor, a physician had advised each of these patients to purchase a mobile telephone for use in emergencies. If that had been the case, the study would have found an increased relative risk in users of cellular telephones, but the causality would have been reversed. I wonder whether the authors have considered the possibility that there might be confounding due to the use of a cellular telephone on the advice of a physician. (Among the controls, a considerable proportion of the patients had cardiovascular diseases — a circumstance in which the purchase of a cellular telephone is often recommended.)

It is indispensable in case-control studies to ensure that the condition under investigation precedes the disease outcome. The most important factor in analyzing the possible contribution of cellular-telephone use to brain tumors is latency. For some brain tumors, the interval between malignant transformation and clinical symptoms or diagnosis can exceed 10 or even 20 years.¹⁻⁴ The study did not have

sufficient power to detect a substantially increased risk if exposure to a cellular telephone is considered as contributing to malignant transformation. Such a contribution of exposure to tumor development was not even addressed, let alone tested, by the authors.

MICHAEL KUNDI, DR.PHIL., DR.MED.HABIL.

University of Vienna
A-1095 Vienna, Austria

1. Simmons NE, Laws ER. Glioma occurrence after sellar irradiation: case report and review. *Neurosurgery* 1998;42:172-8.
2. Daentzer D, Boker DK. Strahleninduziertes Meningeom 20 Jahre nach Operation und hochdosierter Radiatio eines Ependymoms. *Zentralbl Neurochir* 1999;60:27-32.
3. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 2000;95:2770-5.
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To the Editor: The results of the study by Inskip et al. include a possible 60 percent increase in the incidence of glioma resulting from reported short-term use of cellular telephones. This increase may not rise to the level of statistical significance, but given the low power of the study, which is due, in part, to the truncated nature of the study period, the authors' reassurances are hard to accept. The broad confidence intervals underscore the deficiencies and uncertainties that undermine the authors' conclusions.

ROBERT C. KANE, M.S.
P.O. Box 133
Blanchardville, WI 53516

The authors reply:

To the Editor: Our study was conducted in response to the concern that brain cancers diagnosed in the early 1990s might have been caused by cellular telephones. The upper confidence limits in our study indicate that if there was such an effect, it was small. We found a relative risk of glioma of 0.9, with an upper 95 percent confidence limit of 1.6, associated with more than 100 hours of cellular-telephone use, and a relative risk of 0.5, with an upper limit of 1.3, associated with more than 500 hours of use. The absence of a dose-response relation for any measure of the level of use argues against an association.

We acknowledged the possibility that our study was conducted too early to detect an effect. Insofar as it is not known at what stage in carcinogenesis, if any, radio-frequency radiation might act, it is not clear what we should expect in terms of an induction period, nor that ionizing radiation should serve as the model, as implied by Kundi.

Kundi's suggestion that there might have been a high rate of cellular-telephone use among the controls with cardiovascular disease is not supported by our data. The relative-risk estimates were insensitive to the inclusion or exclusion of any subgroup of controls. The duration of symptoms before admission to the hospital was less than one year for more than 90 percent of the controls, and the exclusion of cellular-telephone use within the year preceding admission did not materially change our findings.

Erman et al. suggest that cellular-telephone use might have been underreported among patients with tumors because of mental impairment, and they advocate the use of billing records to assess cellular-telephone use. Mental impairment, rare in acoustic neuroma and less common in younger than in elderly patients with glioma or meningioma,¹ is unlikely to have affected substantially the responses of the heaviest cellular-telephone users — namely, young and middle-aged patients. Billing records have been judged inadequate for the assessment of exposure in case-control studies.^{2,3} Cellular-telephone service providers typically maintain detailed billing records for a maximum of one year; those records often include only outgoing calls and do not identify the user of the telephone.^{2,3} Regardless of the limitations of billing records as compared with data from interviews, it is reassuring that a recent cohort study that used service-provider records⁴ had similar findings.

We see the timing of our study relative to the explosive growth in the use of cellular telephones as its most important limitation. A recently launched, multicenter study³ will have greater statistical power to assess risks associated with long induction periods and the use of digital telephones. However, given the extent of exposure to cellular telephones in the population, one would want to identify any excess risk at the earliest possible time.

PETER D. INSKIP, SC.D.
ROBERT E. TARONE, PH.D.
MARTHA S. LINET, M.D.

National Cancer Institute
Bethesda, MD 20892

1. Kleihues P, Cavenee WK. Pathology and genetics of tumours of the nervous system. Lyon, France: International Agency for Research on Cancer, 1997.
2. Dreyer NA, Loughlin JE, Rothman KJ. Epidemiological safety surveillance of cellular telephones in the US. *Radiat Prot Dosim* 1999;83:159-63.
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Allergy and IgE Antibodies

To the Editor: Allergic symptoms are the result of an inflammatory process triggered by an allergen or allergens to which a patient has generated antibodies after a previous exposure. Dr. Kay's review article on allergic diseases (Jan. 4 issue)¹ recognizes only the action of IgE in the inflammatory process and erroneously identifies a response mediated by type 2 helper T cells (Th2) as an exclusively IgE response, ignoring the other epitopes. This may be the result of using immediate hypersensitivity skin-prick tests as the sole means to detect the patient's allergic reactivities. Such tests detect only IgE antibodies. I believe the article is seriously flawed because it ignores the most efficient inflammatory antibodies generated on exposure to antigen — namely, IgG and IgM.

VINCENT A. MARINKOVICH, M.D.
801 Brewster Ave.
Redwood City, CA 94063

1. Kay AB. Allergy and allergic diseases. *N Engl J Med* 2001;344:30-7.

Dr. Kay replies:

To the Editor: Although Dr. Marinkovich is correct to point out that Th2 cells direct the synthesis of IgG, not just of IgE, there is little evidence that antibodies other than IgE cause appreciable damage to tissue in atopic allergic disease. In fact, several studies suggest that IgG, produced either by natural exposure¹ or during immunotherapy² (and often referred to as “blocking antibodies”), may be protective. Furthermore, both persons with atopy and those without atopy produce house-dust-mite-specific and grass-pollen-specific IgG1 and IgG4.³ On the other hand, there are several nonatopic hypersensitivity disorders (which are usually outside the province of the allergist) in which IgG antibodies are clearly pathogenic.

In Gell and Coombs type II (cytolytic or cytotoxic) hypersensitivity reactions, IgG antibodies facilitate the destruction of cells by interacting with antigen on cell surfaces; such damage is the cause of autoimmune hemolytic anemia and certain types of transfusion reactions. IgG can also stimulate cells and so alter their function (or signaling) either as an agonist (e.g., in the case of thyrotropin in Graves' disease) or antagonist (e.g., in the case of anti-acetylcholine-receptor antibody in myasthenia gravis). In type III hypersensitivity reactions (or Arthus-type reactions), antigen-antibody complexes in and around the microvasculature activate complement, leading to a neutrophil-rich inflammatory response and subsequent tissue injury. Examples include immune-complex glomerulonephritis, classic serum sickness, and the farmer's lung group of diseases (hypersensitivity pneumonitis). The role of IgE, IgG, type I helper T cells, and Th2 cells in the pathogenesis of the hypersensitivity disorders is discussed in more detail elsewhere.⁴

A.B. KAY, M.D., PH.D.

National Heart and Lung Institute
London SW3 6LY, United Kingdom

1. Golden DB, Meyers DA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical relevance of the venom-specific immunoglobulin G antibody level during immunotherapy. *J Allergy Clin Immunol* 1982;69:489-93.

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Review of *The Two-Headed Boy*

To the Editor: The hostile review by Berkwits (Jan. 4 issue)¹ of my book *The Two-Headed Boy, and Other Medical Marvels* contains several errors and gives potential readers a deeply misleading image of the book. For instance, Berkwits wrongly states that the patient in one of the historical cases of severe growth retardation, Nicolas Ferry, had progeria; the correct diagnosis, as is clearly stated in the book, is osteodysplastic primordial dwarfism.

The book is based on many years of original research, and versions of some of the chapters have been published in refereed journals of the history of medicine; it is thus

wrong to represent it as being devoid of interest to this community. Berkwits ignores the clear statement in the preface that the book is a descriptive, multidisciplinary group of essays on the history of teratology, rather than a politically correct sociological treatise on the public's fascination with “freaks.” It is also misleading to say that the book “accepts contemporary provincial voices at face value,” as Berkwits laboriously expresses it. I challenge him to find a single chapter in which the medical discussion has not been brought fully up to date; this is something not easily found in the sociological tomes that he seems to like to read.

J. BONDESON, M.D., PH.D.

Imperial College School of Medicine
London W6 8LH, United Kingdom

1. Berkwits M. Review of: *The two-headed boy, and other medical marvels*. *N Engl J Med* 2001;344:71-2.

Dr. Berkwits replies:

To the Editor: Dr. Bondeson writes in his book that “what particularly distinguishes [Nicolas Ferry] from the vast majority of individuals with primordial microcephalic dwarfism is his premature aging” and that given the similarities of his external features to those of persons with progeria, “it seems reasonable to suggest that there is a progeroid variant of osteodysplastic primordial dwarfism” with which he was afflicted. Both diagnoses are speculative, and in my review “progeria” seemed an accurate and richer, if less precise, description of the case, for purposes of conveying it to readers.

I decline to comment on Dr. Bondeson's other points, except to add that his undeniably original research falls short of the standards of cogency and scholarship the *Journal* asks of its authors and presumably would want for its readers. Those who are interested can read the book and judge for themselves.

MICHAEL BERKWITS, M.D.

University of Pennsylvania
Philadelphia, PA 19104

Coexistence of Hypertrophic Cardiomyopathy and Fibromuscular Dysplasia of the Superior Mesenteric Artery

To the Editor: Hypertrophic cardiomyopathy and fibromuscular dysplasia of the superior mesenteric artery that causes ischemic colitis are rare clinical entities. Their coexistence would probably be considered incidental, but they have some similarities. We describe a 33-year-old man with hypertrophic cardiomyopathy who was admitted to our hospital because of diffuse abdominal pain. The cardiomyopathy had been diagnosed by echocardiography three years before, after his father, who died suddenly, was found at autopsy to have had hypertrophic cardiomyopathy. The patient had no cardiac symptoms, but he did have left ventricular hypertrophy on electrocardiography.

During the next 24 hours, signs of peritoneal irritation

developed. Exploratory laparotomy revealed gangrene of a 25-cm segment of the small bowel, about 50 cm proximal to the ileocecal valve. The gangrenous segment was resected, and continuity was restored by end-to-end anastomosis. His postoperative course was uneventful.

Pathological examination of the resected bowel showed transmural infarction and an abnormally large, muscular artery in the mesentery. Histologic examination of sections of this artery showed marked thickening of the media due to hyperplasia, along with irregular arrangement of the smooth-muscle fibers. The artery was very stenotic, with a lumen the diameter of a pinpoint. In the absence of any inflammatory infiltrate or atheromatous, myxoid, or fibrinoid changes, the findings were diagnostic of fibromuscular dysplasia.

The patient then underwent digital subtraction angiography of the celiac and mesenteric arteries, which revealed a "chain of beads" appearance (characteristic of fibromuscular dysplasia) in a branch of the superior mesenteric artery (Fig. 1) and obstruction of the ascending branch of the left colic artery. The renal arteries, the celiac axis, and the iliac arteries were normal. Eighteen months after the operation, the patient was asymptomatic.

The cause of fibromuscular dysplasia is not known. Some have suggested that it is an autosomal dominant disorder with variable penetrance.^{1,2} Hypertrophic cardiomyopathy is also an autosomal dominant disorder with a high degree of penetrance. However, none of the patients with hypertrophic cardiomyopathy in whom specific mutations were identified also had fibromuscular dysplasia. There are also structural similarities between the two disorders, such as a severe disorganization of the muscle fibers.

Considering these similarities, as well as the coexistence of these clinical entities in at least two cases,³ we wonder whether the disorders are part of the same syndrome.

MICHAEL SAFIOLEAS, M.D.

JOHN KAKISIS, M.D.

CHRISTINE MANTI, M.D.

Athens University Medical School
10674 Athens, Greece

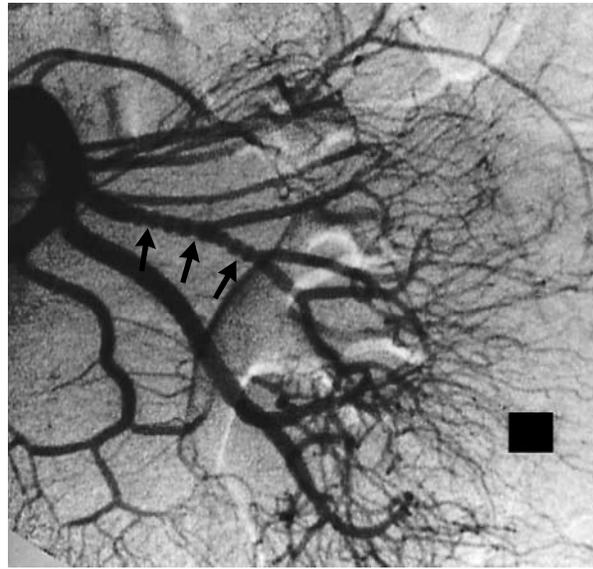


Figure 1. Digital Subtractive Angiography of the Superior Mesenteric Artery, Showing a "Chain of Beads" Appearance (Arrows) in a Branch of the Artery.

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3. Case Records of the Massachusetts General Hospital (Case 9-1995). *N Engl J Med* 1995;332:804-10.

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