Cardiomyopathy with mitochondrial damage associated with nucleoside reverse-transcriptase inhibitors: letter

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Obesity and the Risk of Heart Failure

To the Editor: The report by Kenchaiah et al. (Aug. 1 issue) and the accompanying editorial by Massie2 show the important association between any increased body-mass index and the risk of heart failure. However, several reports have now indicated that abdominal fat may be at least as important as body-mass index in determining cardiac risk. Lakka et al.3 found that the waist-to-hip ratio provided additional information beyond body-mass index that helped in predicting coronary heart disease, whereas the reverse did not apply. That study, involving 1346 Finnish men 42 to 60 years of age, showed an increase by nearly a factor of three in the risk of coronary events in men with a waist-to-hip ratio of 0.91 or greater.

During eight years of follow-up in the Nurses’ Health Study, Rexrode et al.4 found that the waist-to-hip ratio and waist circumference were strongly and independently associated with an increased risk of coronary heart disease among women with a body-mass index of 25 or less. They noted that after adjustment for body-mass index and other cardiac risk factors, women with a waist-to-hip ratio of 0.88 or higher had a relative risk of coronary heart disease of 3.25, as compared with those with a ratio below 0.72. The more recent focus on visceral fat as an even more sensitive risk factor for vascular disease and diabetes5 may be a further refinement.

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To the Editor: The report on obesity as a risk factor for heart failure and the accompanying editorial bring to mind the fact that the heart normally oxidizes fat for contraction.1 Why, then, does the heart fail in the midst of plenty? Experiments in obese rats suggest that impaired oxidation of fatty acids by the heart results in the accumulation of triglycerides in cardiomyocytes.2 It seems that Rudolph Virchow already had it right in 1858 when he wrote that “the hearts described by the old anatomists as fatty were in a great measure only
To the Editor: The identification of obesity as a prevalent and modifiable risk factor for congestive heart failure suggests the pressing need for a public health response. A serious public-information campaign coupled with clearly marked calorie counts on food items — especially fast food — might motivate consumers, even subliminally, to develop more healthful habits. The complicity of the food industry in fostering norms of unhealthful eating and in seducing generations of young people ought to be viewed in much the same way as that of the tobacco industry with respect to its promotion of tobacco. The cure for our society’s dietary excess and consequent cardiac disease should not be a pharmacopoeia of magic bullets, but rather some sobering doses of education and moderation.

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The authors reply:

To the Editor: We agree with Dr. O’Brien’s observation that assessment of regional indexes of adiposity, such as the waist circumference or waist-to-hip ratio, may provide incremental information regarding the risk of heart failure. We did not evaluate these indexes in our investigation.

With reference to Dr. Maurer’s comments, we would like to emphasize the consistency in the relation between body-mass index and the risk of heart failure in women and men in multiple analyses detailed in our report. We presented data on preserved as compared with impaired left ventricular ejection fraction in patients with heart failure in a small subgroup of participants for whom such information was available, and we noted the occurrence of both systolic and diastolic heart failure in obese persons. However, additional studies are required to examine the potential contribution of increased body-mass index to diastolic heart failure.

Dr. Dart notes the possible role of obstructive sleep apnea as a mechanism for heart failure in obese persons. We did not evaluate sleep-disordered breathing in our report. We appreciate the historical perspective provided by Dr. Taegtmeyer and Mr. Wilson, and we agree with Dr. Jenny-Avital’s call for urgent and resolute measures to tackle obesity at an individual level and on a societal scale in order to curb the current epidemic and to prevent the numerous health hazards associated with excess weight.

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The editorialist replies:

To the Editor: I agree with Dr. O’Brien that the pattern of fat distribution is probably an important factor in the association between overweight—obesity and heart failure. The paper by Kenchaiah et al. did not report the waist-to-hip ratio, but I speculated that the increased risk of heart failure was in substantial part explained by the metabolic syndrome, an accompaniment of the excessive accumulation of visceral fat.


The New England Journal of Medicine

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To the Editor: In the recent study by Kenchaiah et al. and the accompanying editorial by Massic, the relation between obesity and heart failure is discussed in great detail. However, only passing reference is made to obstructive sleep apnea in these patients as a possible contributing factor. As Massic notes, “obesity-related hyperventilation and sleep apnea may also contribute.” In the literature, obstructive sleep apnea is a well-documented coexisting condition in obese persons and has been considered an important contributory factor to cardiovascular complications, including hypertension, congestive heart failure, arrhythmias, stroke, and even sudden death syndrome. Furthermore, increasing obesity and more severe obstructive sleep apnea are often noted to occur in parallel. Is it possible that obstructive sleep apnea may have had a bigger role in the risk of heart failure that occurred with worsening obesity in this population?

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Drug Resistance among Patients Recently Infected with HIV

To the Editor: The retrospective analysis by Little et al. (Aug. 8 issue) provides further evidence of the transmission of drug-resistant human immunodeficiency virus type 1 (HIV-1) and attempts to relate detection of resistant virus before antiretroviral therapy to suboptimal virologic response. However, the authors’ recommendations for universal baseline resistance testing and abandonment of empirical treatment are premature.

Ascertainment of baseline viral resistance is not recommended by the current guidelines except in cases of virologic failure or incomplete viral suppression after initial therapy. Little et al. did show that the time to viral suppression was shorter and the time to treatment failure was longer in patients infected with drug-susceptible virus; nevertheless, complete viral suppression was achieved in all but one patient by 24 weeks, regardless of the susceptibility patterns. In fact, the investigators attempted to determine whether inferior response rates were the result of the acquisition of resistant virus or the use of less active regimens. The number of active drugs did not significantly correlate with the time to viral suppression. Moreover, evidence from prospective studies (the VIRADAPT Study and the Genotypic Anti-retroviral Resistance Testing Study) supporting the usefulness of resistance testing involved patients with virologic failure, not patients initiating therapy.

Base-line determination of resistance should not direct a clinician’s choice of antiretroviral agents at this time, since it is unlikely to affect initial viral suppression substantially. On the contrary, it may result in the avoidance of potentially effective regimens and premature abandonment of active agents in an arena in which our arsenal is already limited.

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achieved and those who had a rebound of viremia during treatment, until the first measure of virologic failure, which was typically associated with an abrupt virologic rebound that was not related to an initial suboptimal response to treatment.

We do not believe that the observed high rate of viral suppression in our study should be considered equivalent to successful treatment. Rather, sustained viral suppression should be the hallmark of successful treatment. The longer time needed to achieve complete viral suppression in patients with drug-resistant virus may permit sufficient additional rounds of viral replication to select for additional drug-resistant variants during this initial treatment period, particularly in patients who present with primary HIV infection and higher viral loads than are typically observed at later stages of HIV infection. Responses to antiretroviral treatment in subjects who have not previously received treatment are generally superior to those in subjects who have previously received treatment. Furthermore, there is an association between the number of drug-resistance mutations at baseline and subsequent treatment failure among patients who have previously received treatment and are receiving salvage therapy. We believe these data, in addition to our observations regarding the response to treatment, support the usefulness of routine screening for drug resistance in recently infected patients.

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Editor’s note: Dr. Richman has reported serving as a consultant for Virologic.


Risperidone in Children with Autism and Serious Behavioral Problems

To the Editor: The article reporting on risperidone use in children with autism (Aug. 1 issue) left many questions unanswered. Over an eight-week period, the treatment group had documented weight gains of about 6 lb (2.7 kg). The article indicates that increased “fatigue, drowsiness, dizziness, and drooling” occurred at significant rates. One has to wonder whether the increased drowsiness and dizziness in the children was just one of many unaccounted for variables that lessened their “irritability.”

After working with persons with autism for nearly 20 years, I can tell you that we absolutely know how to intervene with, teach, and support even very disruptive children with autism. Although certain medications can sometimes be helpful adjuncts, the key is to administer a comprehensive behavioral assessment in order to identify why such irritability exists. In my experience, reasons may include misinterpreted information, the lack of skills needed for communication and social interaction, and sensory intolerance.

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Hyperprolactinemia-induced hypogonadism is particularly deleterious in pubertal adolescents, whose skeletons should be accumulating calcium toward the achievement of peak bone mass. Failure to accumulate calcium will lead to premature osteoporosis.

As an endocrinologist with a large component of my practice devoted to persons with developmental disabilities, I see many 20-year-old and 30-year-old adults with T scores for bone mineral density of −3 and −4. Too frequently, these patients have received polypharmaceutical therapy with anticonvulsants, antipsychotics (typical and atypical), and selective serotonin-reuptake–inhibitor antidepressants. Psychiatrists treating adolescents with behavioral problems should consider using atypical antipsychotics that do not induce hyperprolactinemia or should monitor their patients’ prolactin levels. Fortunately, the prolactin levels can be brought back to normal with the use of dopamine agents, such as bromocriptine or cabergoline, without interference with the psychiatric benefits of the antipsychotics.

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To the Editor: The article on risperidone describes the drug as well tolerated and effective for the treatment of tantrums, aggression, or self-injurious behavior in children with autism. Conspicuously absent from the side-effect profile was risperidone-associated priapism.1 We recently treated a young male patient with risperidone-associated priapism for whom risperidone was prescribed for bipolar disease and schizoaffective disorder. While receiving risperidone (over the course of one year), he had new-onset, recurrent, prolonged erections lasting two to four hours, but since he had never been informed of the possibility of, or the meaning of, risperidone-associated priapism, he did not inform his physician of the unusual erectile activity. Ultimately, he had a painful, 36-hour erection that required surgical shunting and subsequently has rendered him permanently impotent; someday, he will require insertion of a penile prosthesis. Thisiatrogenic tragedy would probably have been prevented with improved communication between the physician and the patient.

We have identified several case reports of risperidone-associated priapism.2-4 In addition, the package insert for risperidone lists priapism as a side effect. Priapism is a pathologic condition in which a penile erection persists beyond or is unrelated to sexual stimulation. Ischemic priapism, characterized by a painful erection without cavernous arterial inflow, is a compartment syndrome requiring urgent intervention to avoid such potential consequences as corporal fibrosis and permanent impotence.5 Despite published studies relating risperidone or other psychotropic agents with priapism, it is our experience that few patients, responsible health care providers, or family members are appropriately informed about this serious side effect.

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The authors reply:

To the Editor: We agree with Dr. Sandler that behavioral interventions are essential in the treatment of children with autism. However, high-quality behavioral interventions are not available in all communities, and access to specialized programs may be limited. Most studies of behavioral therapy in children with autism have involved small samples and highly individualized treatments, which has hindered dis-
a patient with only sinus-node dysfunction, it would have been both physiologic and less expensive. The only justification for dual-chamber pacing in these patients would be the presumption of associated atrioventricular-node dysfunction, but the associated presence of atrioventricular-node disease in these patients was not mentioned. Single-chamber atrial pacing would have eliminated the problem of the pacemaker syndrome and undoubtedly the increased frequency of atrial fibrillation that was noted with ventricular-demand pacing.

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The authors reply:

To the Editor: Dr. Blackman raises the interesting point that for patients with sinus-node dysfunction and normal atrioventricular conduction, atrial pacing alone should suffice to provide atrioventricular synchrony. Single-chamber atrial pacing is probably safe in carefully screened patients with sinus-node dysfunction. In a clinical series of 399 Danish patients with normal atrioventricular and intraventricular conduction in whom atrial pacemakers were implanted, the rate of development of atrioventricular block was 1.7 percent per year.1 In our study, however, we did not study single-chamber atrial pacing for two reasons. First, atrial pacing is rarely used in the United States. We designed the trial to compare directly the two most commonly used pacing modes in the United States—single-chamber ventricular and dual-chamber. Second, atrioventricular block was present in 21 percent of our study population, and an intraventricular block (QRS interval >120 msec) was present in 22 percent.2 Thus, in order to achieve the most broadly relevant results, we chose to compare dual-chamber with single-chamber ventricular pacing.

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Variant Cystic Fibrosis Phenotypes in the Absence of CFTR Mutations

To the Editor: The best interpretation of the data presented by Groman et al. (Aug. 8 issue)1 is that their patients had variant cystic fibrosis phenotypes in the absence of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene but that these patients had similar but different diagnoses. In their accompanying editorial, Knowles and Durie2 allude to this when they comment on the lack of phenotypic information and make a number of suggestions that could unify a cystic fibrosis–like phenotype and laboratory abnormalities with other disorders, including malnutrition, adrenal disorders, and hypergammaglobulinemia with skin changes. Pseudohypoaldosteronism type I is an autosomal recessive disorder caused by mutations in the genes for the alpha, beta, and gamma subunits of the epithelial sodium channel (Online Mendelian Inheritance in Man [OMIM] number 264350). This condition results in disordered sweat and salivary electrolytes as well as renal tubular salt wastage and should also, at least theoretically, result in potential changes similar to those in cystic fibrosis. Patients have excess liquid in the airways and cystic fibrosis–like symptoms, including chest congestion, coughing, and wheezing.3 Recurrent lower respiratory tract infections4 may result, and Pseudomonas aeruginosa bronchopneumonia has occasionally been reported.5 It is possible that this condition or a variant form of it acts as a doppelgänger for cystic fibrosis. More clinical information is required, including data on urinary electrolytes and circulating aldosterone levels, before it can be concluded that the patients described by Groman et al. had a variant form of cystic fibrosis.

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The authors reply:

To the Editor: Both Dr. Couper and Drs. Knowles and Durie in their editorial suggest that patients who
had nonclassic cystic fibrosis without CFTR mutations may have had variant forms of known disorders with organ-system involvement similar to that in cystic fibrosis. However, we would like to emphasize that patients who had nonclassic cystic fibrosis without mutations could not be distinguished from those who had nonclassic cystic fibrosis with mutations by clinicians who routinely differentiate cystic fibrosis from other disorders. Our results highlight the usefulness of genetic analysis for segregating patients into groups with disorders that have known causes (e.g., CFTR dysfunction) versus groups with disorders that have uncertain causes and that warrant further clinical evaluation.

Dr. Couper specifically sites pseudohypoaldosteronism type I as a possible cause of the nonclassic cystic fibrosis phenotype, yet none of our patients were reported to have had the profound hyponatremic or hyperkalemic dehydration in the neonatal period that uniformly results from loss-of-function mutations in the epithelial sodium channel (EnaC) genes resulting in pseudohypoaldosteronism. It is possible that "mild" EnaC mutations result in an attenuated pseudohypoaldosteronism phenotype that has yet to be recognized, and it is also possible that the variant pseudohypoaldosteronism phenotype overlaps with nonclassic cystic fibrosis. Dr. Couper's suggestion is worthy of investigation now that the constellation of clinical features currently recognized as nonclassic cystic fibrosis has been shown to have causes other than CFTR dysfunction. Thus, we agree that extensive clinical investigation may reveal variant forms of diseases with known causes (e.g., the Shwachman–Diamond syndrome, primary ciliary dyskinesia, or pseudohypoaldosteronism), but we also suggest that these investigations will lead to the recognition of nonclassic cystic fibrosis with novel causes.

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Availability of Neonatal Intensive Care and Neonatal Mortality

To the Editor: The article by Goodman et al. (May 16 issue) and the accompanying editorial by Grumbach criticize what these authors interpret as excessive concentrations of neonatologists in response to profit-maximizing behavior by hospitals — proof that there are too many specialists. However, a casual inspection of the maps in Figure 1 of the article reveals that most areas with high ratios of neonatologists to neonates are not hotbeds of health care competition but, rather, sparsely populated regions of the country, such as Alaska, Appalachia, northern Maine, western Texas, and the Dakotas. These higher ratios do not represent an "irrational and inequitable deployment" of specialists, as Grumbach states. Instead, this is what happens when 2275 neonatologists distribute themselves among 285 million people who are spread throughout 3000 counties — more counties than neonatologists — and they do so in units of 1. But what if, by Goodman's estimates, a community needs 0.4 or 2.2 neonatologists? It cannot be done. Even worse, some areas get none. And therein lies the difficulty of conducting geographic analyses like this one for specialties that are so small. The truth is that we are on the cusp of progressively worsening shortages of specialists. Responding to these shortages will be difficult and costly. What is needed now is rigorous and objective workforce planning.

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To the Editor: I take exception to the contention that a ratio of 4.3 neonatologists per 10,000 births is adequate to prevent increased mortality. Within the past several years, the American Academy of Pediatrics has reduced the service requirement for pediatric residents in the neonatal unit. Many who complete residency training are unable to take care of critically ill neonates. The authors neglect to consider the real-world implications of fewer neonatologists. Our unit has a catchment area with 5000 births per year. We have a census of 40 babies per day. With a 100-hour workweek, four of us must make rounds daily to finish in a timely manner. With 10,000 births, the census would double. How is it proposed that we double our workload?

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Editor's note: Dr. Goldstein is an employee of Pediatrix Medical Group.

To the Editor: To evaluate the adequacy or abundance of neonatology services, we believe additional issues should be considered. Although Goodman et al. excluded 429 neonatologists who spent the majority of their time outside of direct clinical care, they did not take into account the distribution of work time by clinically active neonatologists. Stoddard et al. reported that 56 percent of the time spent by neonatologists was in areas other than direct care, such as administration, teaching, and research. Pollack et al. reported that 60 percent of neonatology practices were pro-
viding newborn care, much of which is primary care for babies discharged from the neonatal intensive care unit. The role of the neonatologist is a complex one in today’s health care environment. The fact that the mortality rate in the first 27 days of life is low regardless of neonatal-care staffing is more a testament to the hard work and technological advances that we have seen in neonatology in the past few years than proof that we are overgrown as a specialty.

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IVAN HAND, M.D.


The authors reply:

To the Editor: The findings reported by Goodman et al. may have an explanation not discussed in their article or in the editorial. Many neonatologists now care for infants who do not have low birth weight and are not extremely ill. In doing so, neonatologists have expanded their clinical activities to provide care for infants traditionally cared for by pediatricians. There are two explanations for this change in practice. First, many office-based pediatricians practice in managed-care settings that discourage them from leaving patients with scheduled office visits to care for unscheduled births, even though the infants may not prove to be particularly ill. Second, over the past decade, the Residency Review Committee for Pediatrics has substantially decreased the portion of pediatric training devoted to neonatal intensive care. As a result, recently graduated pediatricians are less experienced — hence, less comfortable — in the resuscitation and subsequent care of moderately or transiently sick neonates. These factors have expanded the role of neonatologists to include the care of relatively low-risk neonates, an area of practice unlikely to affect neonatal mortality, which was the primary outcome measure in the study by Goodman et al.

The New England Journal of Medicine

IVAN HAND, M.D.

To the Editor: Dr. Cooper’s suggestion that a large supply of neonatologists is a rural phenomenon is incorrect. Although the large rural areas on the map catch the eye, there is no relation between the rural or urban nature of Neonatal Intensive Care Regions and the number of neonatologists per newborn. The full range of the supply, from very low to very high, is present in both urban and rural areas.1

Drs. Hand and Noble note that we ignored the nonclinical responsibilities of neonatologists, but there is no evidence that this additional work varies significantly in relation to the fourfold regional variation in the supply of neonatologists. We tested several definitions of the clinical work of neonatologists; our findings were robust in these sensitivity analyses. We agree with Dr. Goldstein and Dr. Milley that the training time in neonatal intensive care units has decreased since we were pediatric house officers, and general pediatricians with less training may add to the responsibilities of neonatologists. Yet many neonatologists have sufficient time to replace general pediatricians in providing care for low-risk newborns — at a time when the number of patients per physician is declining in both specialties.2,3 Although neonatologists are busy, 68 percent report that they face competition for their services, and 65 percent predict that their communities will not need additional neonatologists in the next three to five years.4

We did not suggest that there are too many specialists in the United States. Dr. Cooper’s assertion that there is an impending shortage is based on the assumptions that additional physicians will settle where patients’ needs are greater and that adding more specialists will result in improved outcomes. Our study suggests that, for neonatology at least, these assumptions are flawed. The fourfold regional variation in the supply of neonatologists is not explained by differences in newborn risk factors, and a larger supply was not related to lower neonatal mortality, beyond the second (low) quintile of supply.1 Until it is known whether greater numbers of physicians in other specialties would further benefit their patients and populations, we need to temper our enthusiasm for a larger supply of physicians. We expect evidence of safety and effectiveness before adopting new medical interventions. Why not hold further expansion of the supply of physicians to the same standard?

Our analyses do not slight the remarkable accomplishment of neonatology in improving birth-weight–specific outcomes. The next great achievement would be attaining levels of overall perinatal health outcomes that are similar to those for women and newborns in other developed countries.5

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The editorialist replies:

To the Editor: The study by Goodman et al. and the letters in response to their report illustrate the challenges in reconciling the day-to-day experiences of clinicians with evidence about the performance of the health care system viewed at a more “macro” level. The study by Goodman et al. does not discount the notion that neonatologists and newborn intensive care units, when properly deployed, can improve health outcomes for high-risk babies. However, the study does show that many regions of the United States have a relatively large supply of neonatologists, yet have mortality rates among newborns that are no lower than those in regions with fewer neonatologists and intensive care units. National trends in managed care, residents’ work hours, and related factors do not account for the failure of this regional variation in supply to produce differences in outcomes. The findings of Goodman et al. illustrate the unsettling paradox of health care in the United States: specialist physicians appear to be working hard and experiencing pressure to do more, whether they work in areas with many or few physicians, yet there is a lack of clear evidence that a greater supply of specialty resources is producing better outcomes for patients. Research is needed to identify meaningful measures of outcomes other than mortality (the measure used in this study) that may be sensitive to differences in the regional supply of specialists, as well as to identify possible reasons why increases in supply may not be producing improvements in health.

This paradox also points out why the declaration of a shortage of physicians, such as that of Dr. Cooper, should be received with skepticism and a request for a clearer definition of “shortage.” If it simply means that the health care system could keep more physicians busy and gainfully employed, then this definition of shortage may apply to the United States (and is likely to apply no matter how many more physicians the United States produces). If “shortage” means that more physicians would produce better health, then the study by Goodman et al. suggests that there is not yet evidence to justify the conclusion that a meaningful shortage of specialists exists.

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Cardiomyopathy with Mitochondrial Damage Associated with Nucleoside Reverse-Transcriptase Inhibitors

To the Editor: In July 2000, a 58-year-old man infected with the human immunodeficiency virus (HIV) began treatment with highly active antiretroviral therapy, which initially consisted of zidovudine, lamivudine, and ritonavir-boosted indinavir. After three months, a buffalo hump, anemia, and...
proximal muscle weakness developed, and the regimen was therefore switched to stavudine, lamivudine, and nevirapine. Because of pain in his legs, stavudine was replaced with abacavir three months later.

In February 2001, the patient was admitted to our hospital because of progressive exertional dyspnea and peripheral edema. At that time, his CD4 count had risen to 160 per cubic millimeter and plasma HIV RNA was undetectable (<50 copies per milliliter). At presentation, enlargement of the heart and a pleural effusion were seen on a chest radiograph. Echocardiography showed severe dilated cardiomyopathy. Left-sided catheterization showed normal coronary arteries, and a myocardial-biopsy specimen was obtained through right-sided catheterization, which was complicated by a tamponade due to an unusually thin cardiac wall. Histologic examination showed hypertrophic myocardial tissue without any signs of inflammation or infection. Electron microscopy showed striking accumulations of myelin figures in a considerable proportion of the mitochondria. In some fields, cytoplasmic areas were filled with mitochondria that were stuffed with large myelin figures (Fig. 1A and 1B). Such changes are highly suggestive of selective mitochondrial damage. Since the nucleoside reverse-transcriptase inhibitors with the greatest mitochondrial toxicity (stavudine and zidovudine) had already been withdrawn shortly before admission, treatment with an angiotensin-converting–enzyme inhibitor, furosemide, and digoxin was started. The patient’s condition improved slowly. The most recent echocardiographic study showed improvement in the cardiac dimensions.

Dilated cardiomyopathy is believed to be caused by a direct action of HIV on the myocardial tissue or an autoimmune process induced by HIV or possibly other cardiotropic viruses. In animal models, there is clear evidence of cardiomyopathy due to the use of zidovudine, but in humans, such an association has been described only in children. In general, nucleoside reverse-transcriptase inhibitors are not believed to cause cardiomyopathy. However, nucleoside reverse-transcriptase inhibitors — in particular, zalcitabine, didanosine, stavudine, and zidovudine — can have mitochondrial toxic effects in several other tissues.

This case demonstrates cardiomyopathy associated with severe mitochondrial damage in an HIV-infected patient after treatment with nucleoside reverse-transcriptase inhibitors that have mitochondrial toxicity, which improved after these drugs were stopped.

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