

tein without altering its synthesis.¹³ A related study by Brown and colleagues suggests that the predominant increase in the size of large HDL particles with lipid-altering treatment in these patients may be consistent with a slower catabolic rate.¹² Therefore, niacin may be altering the expression of proteins responsible for the formation of HDL, and one of the antioxidants could be interfering with this process.¹² The increase in apo A-I, however, was not blunted by antioxidant therapy, and low serum apo A-I levels are also predictive of coronary artery disease, independently of the HDL level.¹⁴

Although antioxidant therapy does not appear to be useful in patients with low HDL cholesterol levels, the possibility that it may have a benefit in other patients with cardiovascular disease has not been excluded. Would antioxidant therapy have greater value in patients who are subjected to oxidative stress, such as those with unstable coronary syndromes, smokers, or those with certain nutritional deficiencies? Relevant to this question is another study reported in this issue of the *Journal* by Schnyder et al.,¹⁵ who investigated the effect of actively lowering plasma homocysteine levels on the rate of restenosis after coronary angioplasty. A high frequency of premature atherosclerosis has been found among patients with homocystinuria, suggesting that hyperhomocysteinemia contributes to cardiovascular disease.¹⁶ In this study, patients receiving a combination of folic acid, vitamin B₁₂, and pyridoxine had a larger minimal luminal diameter and a lower rate of restenosis in the target lesion. These changes are especially notable because of the brevity of the treatment period, which was only six months. The mechanism responsible for these changes is not completely understood, but it has been proposed that lowering homocysteine levels may influence vascular disease through oxidant effects.¹⁵ Such an interpretation suggests that antioxidant treatment could be useful in patients with acute injury, but it does not exclude the possibility that another homocysteine-dependent effect is responsible for the benefit that was found.

In summary, in patients with low HDL cholesterol levels, treatment with a statin and niacin is associated with the regression of plaque and a decrease in the incidence of cardiac events. Antioxidant supplementation in this population may interfere with the potential benefits of lipid-altering therapy. Although intriguing, these results cannot be extrapolated to other populations, primary-prevention settings, or other lipid-altering combinations, especially in the light of the recent concern about the side effects of statins. However, these data demonstrate the importance of targeting HDL cholesterol levels and support the conclusion that a larger study is warranted. Although this study cannot completely refute claims that other combinations of antioxidant treatments are useful in distinct populations, the findings add to the growing body of

evidence that certain supplemental antioxidant regimens have limited benefit in patients with cardiovascular disease.

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TULAREMIA REVISITED

TULAREMIA, which is caused by the gram-negative bacillus *Francisella tularensis*, is now a rare infection in the United States. The peak incidence was

in 1939, when about 2300 cases were reported. The decline may be related to the fact that wild rabbits are no longer sold in markets and perhaps to an increased awareness among hunters of the risks posed by sick rabbits. In 2000, 142 infections were reported in the United States, including the 11 from the epidemic described by Feldman et al. in this issue of the *Journal*.¹ Most of the cases now occur in Missouri, Arkansas, Oklahoma, and Kansas. Cottontail rabbits are a prime reservoir in many states, as are jack rabbits in states west of the Mississippi River. These rabbits are found primarily in the United States and to a lesser extent in Mexico and Central America. Tick bites appear to be the main mode of transmission to humans in the summer months, and exposure to rabbits is the chief mode of transmission in the fall and winter, the small-game-hunting season.

Massachusetts usually has a few cases of tularemia per year. From 1953 through 1977 there were 20 cases, 4 of which were on Martha's Vineyard. An epidemic occurred on the island in 1978² and was similar in size to the one described by Feldman et al. In 1978, 141 cases were reported in the United States, 15 of which occurred on Martha's Vineyard. Thirteen of the 15 patients on Martha's Vineyard had pneumonic disease, and 2 had ulceroglandular tularemia. Seven of the patients were staying at one cottage and were apparently exposed to the bacteria during the first week of August, since no one who visited the cottage in the preceding or following weeks became ill. The epidemiologic study indicated that two dogs living at the cottage caught rabbits on numerous occasions. It was a rainy week, and the dogs shook the moisture from their fur on entering the cottage and perhaps aerosolized *F. tularensis*. Both dogs had serologic evidence of exposure to the bacteria. Two of the patients with sporadic cases were gardeners, and one was a sheep-shearer.

The patients in the current epidemic on Martha's Vineyard had mowed lawns and cut brush before becoming ill. Gardening and lawn care have become high-risk occupations on the island, presumably because of the aerosols generated by the mowing activities. One unique feature of aerosolized *F. tularensis* is that the infectivity of the organism declines by 10 percent over a period of three hours despite the ability to isolate the organism on culture medium.³ This finding has been demonstrated in experimental studies in humans and monkeys. Feldman et al. were unable to demonstrate the presence of infective aerosols but noted that several environmental factors may have influenced their negative results. In both the current and the earlier epidemic, pneumonitis rather than ulceroglandular disease was the most common form of the disease, suggesting that aerosols were the method of infection.

As noted by Feldman et al., there are two types of *F. tularensis*. Type A, the cause of both epidemics on

Martha's Vineyard, was until recently thought to exist only in the United States and Canada. In 1998 type A organisms were isolated in Slovakia⁴ that had the biochemical and in vivo characteristics of type A isolates found in North America. Type B is found in Europe and Asia but also in the United States. Its primary reservoirs are rodents, voles, muskrats, and beavers, as well as water and mud contaminated by these animals. Type A is lethal to guinea pigs and rabbits, whereas type B is not. The subcutaneous injection of 10 to 1 million type A organisms is usually fatal to domestic rabbits, whereas inoculation with 1 million type B organisms does not cause death in these animals. Infection with as few as 50 type A organisms by either the subcutaneous or aerosol route will induce moderately severe disease in humans, whereas inoculation with 12,000 type B organisms produces mild, self-limiting infection.

The domestic rabbit is the prime source of serious infections in humans. Transmission may occur through direct contact, contact with aerosolized bacteria, or the ingestion of infected tissue or, indirectly, through the bite of a colonized tick, deerfly, or flea that has fed on a sick rabbit. Type A organisms can also be transmitted indirectly through a bite from pets and wild animals, such as raccoons, snakes, and coyotes, which have bitten a sick or dead rabbit and thus have the bacteria in their mouths. These types of exposure can lead to primary pneumonic tularemia or ulceroglandular, typhoidal, or oculoglandular disease. In 1968, an epidemic of ulceroglandular tularemia occurred in Vermont⁵ in which the type B strain was transmitted to humans during an epizootic in muskrats. The 75 patients identified had mild-to-moderate ulceroglandular disease, which was acquired by handling trapped or killed muskrats. A few of the patients had asymptomatic illness.

Rare diseases such as tularemia are obviously not part of the differential diagnosis in a patient with community-acquired pneumonia. Making the diagnosis when *F. tularensis* is the etiologic agent requires physicians to include, as part of the history taking, questions about contact with rabbits, insect bites, and travel to or residence in areas of endemic disease. Infected patients may have a rapid onset of fever, with cough and substernal burning. A finding of ill-defined infiltrates on a chest x-ray film is helpful. Serologic data are definitive, but antibody titers take about a week to become positive. The finding of a single titer of more than 1:160 in a patient who has been ill for more than a week provides strong evidence of the diagnosis. Antibodies against both type A and type B strains react to the antigen used in the agglutination test.

Organisms can be cultured from sputum, from gastric-lavage fluid, and less often, from blood. The laboratory must be informed that *F. tularensis* may be present in the specimens, not only because special medium must be used, but also because of the danger of

laboratory-acquired infections in the absence of the use of negative-pressure, protective hoods to culture specimens and identify organisms. Several of the early investigators, including Edward Francis, for whom the organism was named,⁶ attempted to isolate and culture this organism, became ill, and took several months to recuperate.

An epidemic of type A tularemia occurred in Oklahoma in the summer of 2000⁷ that involved 11 cases, 1 of which was fatal. One of the cases was in a microbiologist who worked with the blood cultures from the patient who died. Because she was initially thought to have food poisoning, a 10-day course of levofloxacin was prescribed. The fluoroquinolones have excellent in vitro activity against *F. tularensis* and probably helped eradicate her infection, although only a few cases have been reported to be cured by these drugs. An organism isolated initially from blood was identified as an actinobacillus. The diagnosis of tularemia was later confirmed on the basis of serologic titers after the blood cultures were found by the state laboratory to contain *F. tularensis*. Unfortunately, the patient who died had been severely ill with a fever of unknown origin, and appropriate antibiotics for tularemia were not prescribed until too late in the course of his disease.

There will continue to be epidemics of tularemia. Given the widespread possibilities of acquiring the disease from animals, it is surprising that more cases do not occur. Perhaps some of the patients in whom

community-acquired pneumonia is diagnosed but the etiologic agent is not identified actually have tularemia and are coincidentally cured by the serendipitous choice of fluoroquinolones or aminoglycoside antibiotics as a treatment. A serologic survey of year-round residents of Martha's Vineyard and of the people who have spent summers there for many years would provide background information that could help us better understand the next epidemic of tularemia.

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