bulk-isolated cell preparations (12). Our results now clearly demonstrate that in genetic galactosylceramidase deficiency, rapidly progressive accumulation of psychosine in white matter occurs from very early stages of the disease. This finding establishes step ii of the psychosine hypothesis.

Although the fundamental genetic defects of most of the lysosomal storage disorders have been clarified, the molecular mechanisms that lead to the clinical and pathological manifestations remain largely obscure. While the psychosine hypothesis has by no means been proven, evidence accumulated in the past dozen years since its proposal has made it a probable explanation for the biochemical pathogenesis of globoid cell leukodystrophy. Similar mechanisms may play important roles in the pathogenesis of other lysosomal storage diseases. In an analogous disease, Gaucher disease, which is caused by a genetic defect of glucosylceramide, presence of glucosylsphingosine in the spleen has been shown (13), and more recent data suggested a correlation between the amount of glucosylsphingosine in the brain of patients and the degree of neurological involvement (14). In other diseases also, abnormal accumulation of "normal" constituents may not be sufficient to account for clinical and pathological manifestations. Attention to possible involvement of "abnormal" constituents may prove rewarding.

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References and Notes
15. The data in this report were presented in part at the 15th annual meeting of the American Society for Neurochemistry, Portland, Ore., March 1984, and were published in an abstract form (H. Iiguso and K. Suzuki, Trans. Am. Soc. Neurochem. 15, 104 (1984)). This investigation was supported by PHS research grants, NS-10885, NS-1921, NS-03356, and HD-01799. M.-T. Vanier, Lyon, France, kindly provided us with the lipid extract of the white matter of patient F.L.

11 January 1984; accepted 19 March 1984

Is α₁-Protease Inhibitor Inactivated by Smoking?

Stone et al. (1) report that functional α₁-protease inhibitor (α₁-PI) in the lower respiratory tract is not decreased by cigarette smoking, whereas Gadek et al. (2) and Carp et al. (3) found decreased functional α₁-PI in the lower respiratory tract of smokers. Carp also found 4 mole of methionine sulfoxide per mole of inactive α₁-PI in lung lavage fluids of smokers but oxidized methionine was not found in α₁-PI of nonsmokers (3). Oxidation of two to four methionine residues in α₁-PI has been associated with loss of its inhibitory activity toward human neutrophil elastase (4, 5). The apparent contradictions between Stone’s observations and the above findings are perplexing and suggest that further studies are needed. In future experiments, it may be helpful if the following points are borne in mind.

Ideally, focal areas of centrilobular emphysema would be sampled, rather than whole lung. This being impractical, some effort should at least be made to lavage superior segments of the lung, since lesions of centrilobular emphysema in smokers are more common and more severe in the upper than in the lower zones of the lung (6). Also, subject selection may be critical; heavier smokers of unfiltered high-tar cigarettes should be preferred, especially those with signs of airflow limitation.

Furthermore, as mentioned by Stone et al. in their report, the time interval between smoking and lavage may be an important variable. One of us (S.K.C.) recently explored the time course of lung α₁-PI inactivation in mice after short-term and long-term exposure to smoke. Inactivation of α₁-PI occurred much sooner after a standard smoke exposure if the animals had been repeatedly exposed to smoke beforehand. Recovery of normal values of lung α₁-PI activity after the standard smoke exposure also occurred earlier in mice that inhaled smoke frequently than in mice never previously challenged with smoke. Despite this, the extent of α₁-PI inactivation was the same or greater in the group repeatedly exposed to smoke. Although these results were obtained in an animal model and their direct extrapolation to humans may be unwarranted, humans who are heavy smokers could also have significant decreases in lung α₁-PI activity immediately after smoking, but these decreases may be transient.

We agree with Stone et al. that "additional studies of the effects of cigarette smoke on α₁-PI in the lower respiratory tract are needed" and look forward to an eventual resolution of this controversy.

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References and Notes

11 October 1983; accepted 16 February 1984

Stone et al. (1) recently reported that functional α₁-protease inhibitor (α₁-PI) in the bronchoalveolar lavage fluid of smokers is not decreased. They cited our study (2) in which we assayed α₁-PI in lung fluid from young smokers who were subjected to bronchoalveolar lavage before smoking, and again 10 to 60 minutes after smoking. We later studied another 18 smokers and found no significant decrease in α₁-PI activity in lung fluids of smokers after smoking, except in smokers who were subjected to lavage 1 hour after smoking two cigarettes; these smokers showed a statistically significant mean decrease of 10 percent in α₁-PI activity compared with the values before smoking.

Stone et al. reported that α₁-PI in the lung fluids of nonsmokers was only 47 percent active, whereas the data of Carp et al. (3) indicated a mean activity of 118 percent; we found it about 90 percent active. We had initially reported (2) that
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Science 224 (4650), 755-756.
DOI: 10.1126/science.6609431