

otic trials that additional information concerning the role of *C. pneumoniae* in atherosclerosis and the treatment of chronic atherosclerotic lesions would be desirable. We believed that the possibility of an additional effective treatment for coronary heart disease was of such importance to the public health that we undertook the trials with the information then available.

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Histone Deacetylase Activity and COPD

TO THE EDITOR: In their study, Ito and colleagues (May 12 issue)¹ observed reductions in both the activity and expression of histone deacetylases (HDACs), especially HDAC2, in patients with chronic obstructive pulmonary disease (COPD). In addition, the activity inversely correlated with the severity of COPD.

Histone-modifying enzymes play essential roles in gene regulation.² The balance between histone acetylation and deacetylation appears to be crucial to normal cell growth. Disruption of either of these molecular mechanisms has been associated with the development of cancer. Several molecules and genes have been identified or developed or both to inhibit HDACs.³ Valproic acid, an antiepileptic drug that has been commercially available for decades, has been found to inhibit HDACs, including HDAC2.⁴ However, there is no evidence that valproic acid worsens pulmonary function in patients taking the medicine.⁵ The “chicken-and-egg” conundrum remains unresolved: Does the reduction of HDAC activity cause severe COPD, or is it a secondary event?

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1. Ito K, Ito M, Elliott WM, et al. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* 2005; 352:1967-76.
2. Kornberg RD, Lorch Y. Twenty-five years of the nucleosome, fundamental particle of the eukaryote chromosome. *Cell* 1999;98: 285-94.
3. Marks PA, Richon VM, Miller T, Kelly WK. Histone deacetylase inhibitors. *Adv Cancer Res* 2004;91:137-68.
4. Kramer OH, Zhu P, Ostendorff HP, et al. The histone deacetylase inhibitor valproic acid selectively induces proteasomal degradation of HDAC2. *EMBO J* 2003;22:3411-20.
5. Physicians' desk reference. 58th ed. Montvale, NJ.: Thomson PDR, 2004.

TO THE EDITOR: The following statement in the Discussion section of the article by Ito et al. is rather confusing: “In the present study, there was a positive correlation between HDAC activity and disease severity, as measured by the percent of predicted FEV₁ [forced expiratory volume in one second]. . . .” The Results section, Figure 1D, and the abstract clearly indicate that there was apparently a negative correlation between HDAC activity and disease severity. I assume that the authors meant to say that there was a positive correlation between HDAC activity and FEV₁.

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THE AUTHORS REPLY: Histone modification regulates many genes, including those involved in normal cell growth. Eleven classic HDACs have been identified.¹ In patients with COPD, we found a marked reduction in HDAC2, with lesser reductions in HDAC5 and HDAC8. Different HDACs appear to be involved in different cellular functions and presumably regulate different sets of genes. Indeed, the targeted reduction of HDAC2 through RNA interference results in reduced responsiveness to corticosteroids in a human epithelial cell line (A549), whereas this reduction is not observed when other classic HDACs are inhibited.² Valproate, a nonselective inhibitor of classic HDACs, is associated with 50 percent inhibition of HDAC activity at approximately 200 µg per milliliter (1.4 mmol per liter) in A549 cells. Steady-state plasma concentrations of valproate in patients with epilepsy are 50 to 100 µg per milliliter (0.3 to 0.7 mmol per liter), so it is possible that clinical doses may have

some HDAC inhibitory effect, enhancing inflammation or reducing responsiveness to corticosteroids in patients with inflammatory diseases. There is one report of increased circulating proinflammatory cytokines in children with epilepsy treated with valproic acid.³ However, we are not aware that a worsening of inflammatory diseases has been investigated or reported with valproate. We agree with Dr. Lin that it is not certain whether the reduction in HDAC activity is a consequence or a cause of severe COPD, but we would like to suggest that it is both and that it provides a molecular basis for the increasing pulmonary inflammation as COPD progresses.

We agree with Dr. Bhowmik that the sentence in the Discussion was incorrectly written. We should

have stated that there was a negative correlation between HDAC activity and disease severity.

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Nephrogenic Syndrome of Inappropriate Antidiuresis

TO THE EDITOR: The elegant work presented by Feldman et al. (May 5 issue)¹ shows that point mutations in codon 137 of the V2 vasopressin receptor (V2R) can result in either a loss-of-function mutation (R137H, which is associated with congenital nephrogenic diabetes insipidus) or a gain-of-function mutation (R137C or R137L, which is associated with the congenital nephrogenic syndrome of inappropriate antidiuresis). In the Discussion section of the article, the authors mention the possibility of an activating mutation in aquaporin-2. Because the clinical data were also consistent with this differential diagnosis, how was this possibility ruled out so as to arrive at the initial hypothesis that these infants had hyperactive V2Rs?

The authors also state that arginine vasopressin (AVP) antagonists "would probably be ineffective, given the ligand-independent nature of the lesion." However, subtle conformational changes can take place when a ligand binds to a receptor. Therefore, is it not plausible that some of these conformations could effectively down-regulate activity?

Finally, the acronym "NSIAD" (nephrogenic syndrome of inappropriate antidiuresis) might easily be mistaken for the much more familiar "NSAID" (nonsteroidal antiinflammatory drug). Perhaps renaming the syndrome "congenital pseudo-SIADH" (where SIADH denotes the syndrome of inappropriate antidiuretic hormone secretion) could be considered.

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1. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med* 2005;352:1884-90.

TO THE EDITOR: Feldman et al. state that since the AVP assay is not optimized to identify low values, sequencing the V2R gene (*AVPR2*) before NSIAD is diagnosed is recommended. They also suggest that there may be additional defects in the V2R signaling cascade in patients who have an NSIAD phenotype but not a V2R mutation. However, the plasma AVP level is low in many acquired diseases in the absence of a V2R gene mutation or defects in the signaling cascade. Thus, such conclusions seem unwarranted.

AVP secretion is almost totally suppressed when the plasma osmolality falls below 275 to 280 mOsm per kilogram, so the plasma osmolality should be measured simultaneously with the plasma AVP level.¹ Moreover, the plasma AVP level is low and the plasma osmolality is normal in patients with the type D secretion pattern of SIADH.² Increased sensitivity to AVP or other antidiuretic substances, such as chlorpropamide or the antidiuretic substance produced in prolactinoma, may be present in such patients.^{3,4} The authors might recommend se-