the levels of protease nexin-1 are diminished in the brain in Alzheimer's disease because much of the nexin-1 is sequestered in nexin-1–thrombin complexes. Such an accumulation of nexin-1–thrombin complexes would be consistent with defective clearance resulting from the blockade of the serpin-clearance receptor. The level of the serpin protease inhibitor–protease complex is more likely to reflect the state of the clearance receptor than is the level of the free serpin, since the clearance receptor binds only to the complex.[2-4] To our knowledge, the levels of other serpin–protease complexes have not been determined in Alzheimer's disease.

The question was raised whether diminished clearance of the serpin–protease complex as a result of β-amyloid–binding activity could have any effect on protease activity, since the protease is presumably irreversibly inhibited in the complex before the complex is cleared. The "irreversibility" of the serpin–protease complex is based on in vitro experiments showing the stability of the complex in sodium dodecyl sulfate and urea-gel systems.[5,6] However, it is not known whether the active protease can be regenerated from the complex in vivo. This could happen, for example, if the complex was cleaved by a free protease, regenerating the activity of the protease in the complex. Alternatively, the binding of β-amyloid to the serpin receptor may not directly affect proteolytic activity, but rather may serve as a nidus for the aggregation of β-amyloid and the disruption of the membrane. It should be emphasized that the central issue of whether β-amyloid interacts with a serpin receptor in the brain remains to be resolved.

Drs. Schmaier and Van Nostrand are correct in pointing out that platelets generally do not synthesize protein. However, exceptions to this rule have been reported.[7-9] There is recent evidence for the synthesis of amyloid precursor protein in isolated preparations of human platelets.[10] Whether the amount synthesized represents a substantial proportion of the amyloid precursor protein in platelets relative to the amount of protein synthesized in megakaryocytes remains to be determined.

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POLYMYOSITIS

To the Editor: In his excellent review (Nov. 21 issue),[1] Dr. Dalakas referred to a case of polymyositis that we described[2] as one that was "mediated by T cells expressing the γ/δ receptor, which have cytotoxic activity restricted to the MHC-I [major-histocompatibility-complex class I] antigen." We wish to emphasize that the mere colocalization of MHC-I antigen and γ/δ T cells does not necessarily imply that the antigen functions as the restrictive element of γ/δ T cells. Although the existence of γ/δ T cells recognizing MHC-I antigen has been formally demonstrated,[3] the majority of such cells apparently recognize antigens either independently of MHC molecules or in association with nonclassic MHC molecules.[4,5] In our investigation we tested for CD1, an MHC-related molecule coded outside the MHC.[5] The results were negative.[2] However, there are more than 10 other loci in the MHC region in humans, some of which express MHC-related proteins that could be involved in the recognition of antigens by γ/δ T cells.[4,5]

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Dr. Dalakas replies:

To the Editor: I appreciate the clarification by Drs. Hohlfeld and Engel. In their case report of polymyositis,[1] however, they have elegantly demonstrated that cytotoxic γ/δ T cells surrounded muscle fibers expressing both the heat-shock protein 65 and the MHC-I antigen, but not CD1, a molecule that bears some homology to MHC molecules. Because γ/δ T cells respond to antigen-presenting cells pulsed with heat-shock protein 65,[2] the coexpression of MHC-I and heat-shock protein 65 by the same muscle fibers suggests that in their case MHC-I might have been the surface-restricting molecule. This conclusion[3] does not exclude the possibility that in polymyositis mediated by γ/δ T cells, other heretofore unidentified MHC-related proteins can participate in the recognition of muscle antigens, as correctly pointed out by Hohlfeld and Engel.

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LEAD LEVELS IN PREINDUSTRIAL HUMANS

To the Editor: We estimate that the natural blood lead concentration of humans is about 0.8 nmol per liter (0.016 μg per deciliter). This estimate is 50- to 200-fold lower than the lowest reported blood lead levels of contemporary humans in remote regions of the southern (39 nmol per liter)[1] and northern (160 nmol per liter)[2] hemispheres. It is more than two orders of magnitude (i.e., 600-fold) lower than the upper blood lead concentration of 480 nmol per liter (10 μg per deciliter) that is currently considered acceptable for children.[3]

This estimate of the natural blood lead concentration of humans was obtained by extrapolation of a simple linear regression ($R = 0.959$, $P<0.01$) of bone lead and blood lead concentrations in humans and laboratory animals to the skeletal lead levels of preindustrial humans (0.06 nmol per gram of ash weight)[4] (Fig. 1). We included paired bone lead and blood lead concentrations of envi-

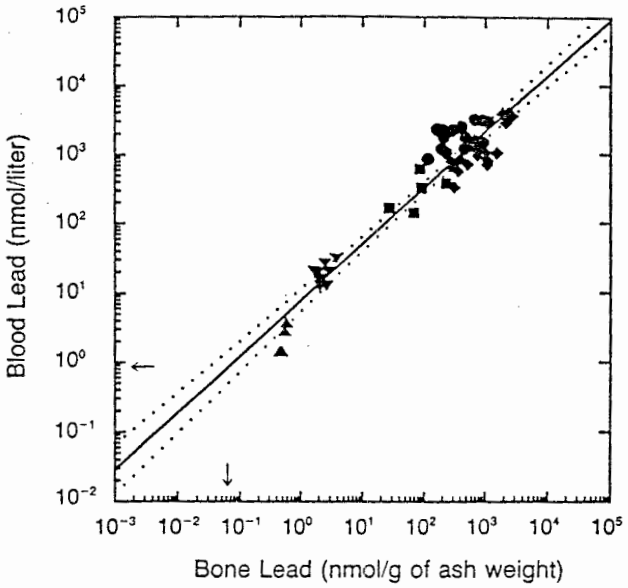

Figure 1. Blood Lead Concentration of Preindustrial Humans.

The lead concentration in the blood of preindustrial humans (arrow on the ordinate) was derived from the reported concentrations of lead in preindustrial human bone (arrow on the abscissa)[4] by graphical extrapolation of the relation between paired bone and blood lead concentrations of environmentally exposed humans (squares), occupationally exposed humans (circles),[5-10] laboratory rats maintained under standard conditions (diamonds),[11-14] and rats maintained under conditions clean of trace metals (triangles[15] and inverted triangles [unpublished data]). The dotted lines indicate the 95 percent confidence limits.

ronmentally and occupationally exposed humans,[5-10] laboratory rats raised under standard conditions,[12-14] and laboratory rats raised under rigorous conditions clean of trace metals.[15]

We believe this estimate of the natural blood lead concentration of humans is conservatively high. Physiologic mechanisms for clearing lead from blood may be more efficient at very low concentrations, as suggested by the relatively lower ratio of blood lead to bone lead concentrations in rats raised under ultraclean conditions (Fig. 1).

The need for adequate guidelines on blood lead concentrations has been underscored by reports of the prevalence of subclinical lead toxicity in children with lead levels that were previously considered innocuous.[3] Although current guidelines in the United States have identified a blood lead concentration of ≥480 nmol per liter (10 μg per deciliter) as the level of concern for early toxic effects in children, it is now recognized that there may be no threshold concentration for lead toxicity.[3] This is a profound qualification, because average skeletal lead concentrations of contemporary humans are 500- to 1000-fold above natural concentrations,[4] which is consistent with our estimate that the current level that is of concern in children is 600-fold higher than natural blood lead concentrations. We therefore propose that future criteria for safe body burdens of lead should take into account what we estimate to be the natural concentration of lead in preindustrial humans.

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MYELODYSPLASIA AND LEUKEMIA AFTER TREATMENT OF APLASTIC ANEMIA WITH G-CSF

To the Editor: Several clinical trials using recombinant human granulocyte colony-stimulating factor (G-CSF) have demonstrated that patients with severe aplastic anemia are responsive to this agent and that neutrophil counts can be increased in the majority of patients without toxicity.[1] However, little is known about the long-term effects and toxicity of G-CSF in severe aplastic anemia. We treated three children with severe aplastic anemia in whom myelodysplasia with monosomy 7 developed (Table 1). In two of them,

Table 1. Characteristics of Three Boys with Severe Aplastic Anemia in Whom Myelodysplasia Developed during or after Treatment with G-CSF.*

Characteristic	Patient 1	Patient 2	Patient 3
Age at diagnosis of anemia (yr)	5	3	5
Previous treatment	ALG, HDMP, AS, CSA	ALG, HDMP, AS	ALG, HDMP, AS, CSA
Cumulative dose of G-CSF (mg)	33	22	158
Duration of G-CSF treatment (mo)	2	15	11
Bone marrow findings			
At diagnosis of anemia			
Cellularity (%)	<5	<5	<5
Karyotype	NA	NA	46,XY
At diagnosis of myelodysplasia			
Cellularity (%)	50	50	90
Blasts (%)	12	7	3
Karyotype	48,XY,−7,+10, +21,+22	45,XY,−7	45,XY,−7
Time from diagnosis of anemia to diagnosis of myelodysplasia (mo)	37	61	17
Time from initiation of G-CSF to diagnosis of myelodysplasia (mo)	6	15	12
FAB classification at diagnosis of myelodysplasia	Refractory anemia with excess blasts	Refractory anemia with excess blasts	Refractory anemia

*ALG denotes antilymphocyte immunoglobulin, HDMP high-dose methylprednisolone, AS anabolic steroids, CSA cyclosporine, NA not available, and FAB French–American–British Cooperative Group.