veals that CMV isolates from epidemiologically linked hosts are dissimilar, it is more difficult to reach conclusions. Differences could represent an artifact due to incomplete digestion of DNA or labeling of cellular DNA with probes. Of even greater importance is the fact that very little is known about natural events that could result in diversity of strains. For example, Spector et al. have recovered (by restriction-enzyme analysis) several CMV isolates from the same patient, presumably the result of reinfection.[9] In the day-care setting, in which children are exposed to multiple strains of CMV, one could not conclude that dissimilarity of strains rules out horizontal transmission between children.

We agree with Adler's contention that there is more to be learned about the transmission of CMV through the study of children and their parents. There are also important epidemiologic questions that can best be addressed through the laboratory study of viral isolates. However, it is unlikely that the laborious and expensive restriction-enzyme analysis of hundreds of CMV isolates will substantially refine our knowledge about maternal risk. Resources could be better spent in developing a safe, effective CMV vaccine.

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LINKAGE OF THE G8 MARKER ON CHROMOSOME 4 TO HUNTINGTON'S DISEASE IN A LARGE AMERICAN BLACK FAMILY

To the Editor: The recent finding of a polymorphic human DNA marker closely linked to the gene for Huntington's disease may allow preclinical diagnosis of this disorder.[1] Before widespread implementation of preclinical testing, the likelihood that Huntington's disease is caused by genetic alterations at different loci needs to be excluded. Toward that end, large families with more than one affected person are being examined with use of the D4S10(G8) probe. Ideally, such families should have widely diverse ancestral origins, with little apparent genetic admixture. So far, there have been reports of linkage of D4S10 to Huntington's disease in families of Venezuelan,[1] English,[1] German,[2] and Welsh[3] descent. In addition, linkage has been determined in one large American black family.[2] Huntington's disease is extremely rare in black persons.[4] Investigations of such families with no known genetic relationship may provide further strong evidence against heterogeneity in Huntington's disease.

The pedigree shown in Figure 1 is of a large American black family with typical Huntington's disease. The index patient (arrow) was a girl in the fifth generation who died at the age of 17 with juvenile Huntington's disease. Mild incoordination was noted when she was 5, and muscle rigidity, ataxia, declining mental status, and seizures developed slowly. Computerized tomography (CT) of the brain when she was 11 showed bilateral caudate atrophy, and the diagnosis of Huntington's disease was confirmed at autopsy. Numerous other family members are known to have been affected, with onset typically in the 20s, 30s, and 40s and death in the 50s and 60s. A 77-year-old woman (II-2) has been affected for more than 20 years and at this writing has dementia, incontinence, rigidity, hyperreflexia, and constant choreoathetosis.

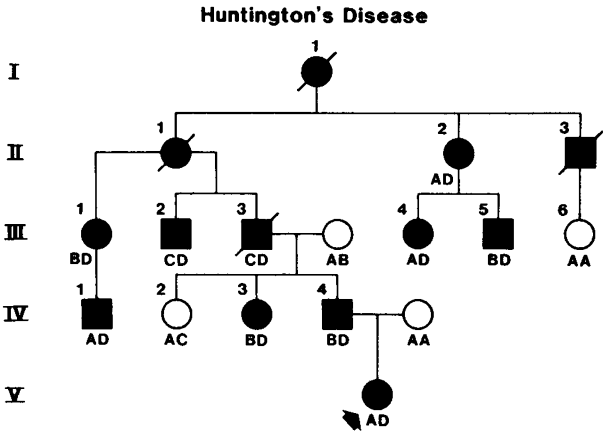

Figure 1. Condensed Pedigree of American Black Family with Huntington's Disease.

Symbols for affected persons are solid, and a diagonal line through the symbol indicates death. G8 haplotypes are shown below each symbol. Subject III-2 refused formal examination, but there was strong circumstantial evidence that he was affected (Babb T, Immken L: personal communication). The G8 haplotype of Subject IV-1 was known to be either BC or AD, and AD was most likely. Although Subject III-3 was deceased, his G8 haplotype could be deduced as CD from those of his spouse and children. Segregation of the D haplotype with Huntington's disease is clearly demonstrated.

Leukocyte DNA from available family members was prepared, and D4S10(G8) haplotypes were determined with use of the restriction enzyme *Hind*III.[1] The DNA haplotypes were determined to be A, B, C, or D according to the nomenclature of Gusella and colleagues.[1] Linkage analysis was performed.[5] Table 1 shows that there were no certain recombinants, suggesting close linkage between G8 and Huntington's disease, with a lod score of 2.76 at 0.0 recombination (odds, 575:1 favoring linkage). Thus, there is still no definite evidence of genetic heterogeneity in Huntington's disease. A few recombinants have been found in previous families, but it is most likely that those families all had a mutation at the same locus on the distal short arm of chromosome 4, approximately five recombination units from D4S10(G8).

Folstein and colleagues[2] have also reported on a black American family with Huntington's disease showing linkage to G8. There is no

Table 1. Lod Scores for Huntington's Disease and D4S10(G8).

Recombination Fraction (θ)	Lod Scores
0.0	2.76
0.01	2.71
0.02	2.66
0.03	2.61
0.04	2.55
0.05	2.50
0.1	2.34
0.2	2.24
0.3	1.09
0.4	0.49

known genetic or geographic overlap between the present family and the family studied by Folstein et al. It is possible that the Huntington's disease gene in both families was introduced many generations ago by a white ancestor, although there is no known admixture.

The finding of a linkage between D4S10(G8) and the gene for Huntington's disease in this large family further strengthens the observation that mutations at multiple loci are unlikely to occur in Huntington's disease. This limitation is therefore not likely to be a major source of error in the application of preclinical testing for persons at risk for Huntington's disease.

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IMPROVEMENT IN HEADACHE ASSOCIATED WITH PROLACTINOMA DURING TREATMENT WITH A SOMATOSTATIN ANALOGUE: AN "N OF 1" STUDY

To the Editor: We have followed with interest the results of long-term treatment of acromegaly with the somatostatin analogue SMS 201-995[1,2] and particularly the dramatic and rapid relief of headache.[3] The mechanism of the analgesic action of SMS 201-995 is unknown but is not apparently related to the fall in growth hormone levels or to tumor shrinkage. This prompted us to assess the effect of SMS on intractable headache that had been present for 12 months in a 37-year-old woman with a macroprolactinoma extending 6 mm above the sella. Her mean daily prolactin levels were 6500 mU per liter (normal range, 125 to 625), with no other abnormality of pituitary function. Bromocriptine (7.5 to 15 mg per day for 15 months) normalized serum prolactin levels and slightly improved the headache (which nevertheless remained especially severe in the evenings), but had no effect on the size of the tumor.

SMS was evaluated in a single-blind, four-day "N of 1" trial[4] in the hospital, five days after bromocriptine withdrawal. Alternate doses of SMS (50 μg) or an equal volume of SMS diluent (placebo) were injected in a standardized fashion by the medical staff at 9 a.m., 3 p.m., and 9 p.m. The patient rated the severity of the headache on a visual-analogue scale from 0 (no headache) to 1 (worst headache ever) just before each injection and one and three hours thereafter (Fig. 1). The headache improved within 30 minutes of all six injections of SMS but worsened markedly after four injections of placebo. Compared with the pre-injection headache score, the one-hour post-injection value improved by 55±14 percent (mean ±SEM) after SMS and worsened by 312±278 percent after placebo ($P<0.01$ for the comparison with SMS; Wilcoxon test); the three-hour score improved by 49±16 percent after SMS and worsened by 615±480 percent after placebo ($P<0.01$). SMS injected at 3 p.m. delayed the evening exacerbation. SMS suppressed growth hormone to levels that were undetectable, but serum prolactin levels were unchanged. The only side effect

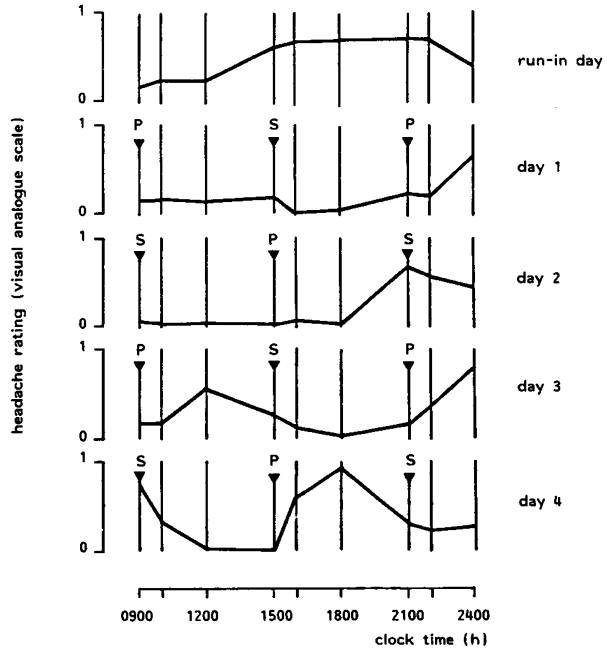

Figure 1. Visual-Analogue Scoring of Headache Severity during a "Run-In" Day (No Injections) followed by a Four-Day Trial of Alternate Injections of SMS 201-995 (S) and Placebo (P), Given at 9 a.m., 3 p.m., and 9 p.m.
Scores ranged from 0 (no headache) to 1 (worst headache ever).

was mild abdominal discomfort one to six hours after injection of SMS.

SMS 201-995 may therefore relieve headache associated with pituitary tumors even when acromegaly is not present. Such headaches are usually attributed to local space-occupying effects but may occur with a radiologically normal fossa[5]; volume effects seem unlikely in view of the very rapid symptomatic response to SMS and the minimal (if any) tumor shrinkage.[1,6] Other mechanisms are suggested by the observation that intrathecal somatostatin is analgesic.[7] Somatostatin and its analogues may influence the affective aspects of pain: some role in mood regulation is suggested by the lowered somatostatin levels in the cerebrospinal fluid of depressed patients.[8] Theoretically, somatostatin could affect the release of unknown algesic peptides (perhaps interfering with the endogenous opioid system) from pituitary tumors.

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