Isua BIF, which spans a factor of 20 in Cr/Th and a factor of 60 in Th/Sc, these ratios overlap average Early and Late Archean basalt, Early and Late Archean andesite, Early Archean graywacke, and Early Archean cratonic shale (*3*) and therefore cannot be used to constrain a unique BIF protolith. In TiO_2 versus P_2O_5 space (Fig. 3C), our samples do not lie in the field of Isua BIFs, as Palin claims. Furthermore, Y/Ho and Zr/Hf ratios for all samples of the quartz-pyroxene rock show no affinity for sediments crystallized in equilibrium with seawater (*4*) but instead have values similar to ultramafic samples from Akilia. Palin rejects structural geologic, mineralogic, and geochemical data indicating that sample AK 38, a thick pyroxenite band not invaded by metasomatic quartz, is integral to the lithology, preferring instead to call it an "exception" relative to other quartz-pyroxene rocks. We categorically reject Palin's claim that the thin banding has an "equivocal" origin, for we clearly demonstrated that it is mineralogically similar to and associated with the boudinage of thicker pyroxenite bands (Fig. 2, B to D).

A BIF origin for the quartz-pyroxene rock was hypothesized on the basis of magnetite layering and "comparison" with other units, such as BIF at Isua (*2*). We reiterate, there is little magnetite in the quartz-pyroxene rock, some enclosing ultramafic rocks contain magnetite, and all pertinent rocks on Akilia possess a penetrative tectonic layering (foliation). Banding in the quartz-pyroxene rocks does not result from quartz-magnetite alternations, as is common at Isua. Consequently, the initial BIF hypothesis has little intrinsic merit and cannot be vindicated by a few, non–source-specific geochemical ratios.

The Fedo and Whitehouse report is also under disussion in this week's Technical Comments (www.sciencemag.org/cgi/full/298/5595/917a).

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The Search for an Amyloid Solution

THE AMYLOID HYPOTHESIS HAS GUIDED research on Alzheimer's disease (AD) for the past decade. The central tenet of the hypothesis has been that aggregation of fibrillar amyloid β (Aβ) into insoluble plaques directly causes neurodegeneration. This viewpoint has been challenged by observations from in vitro models, transgenic mice, and human studies, which suggest that Aβ plaques do not cause neuronal loss, dementia, or tau-positive tangles [for review, see (*1*); c.f. (*2*)].

J. Hardy and D. J. Selkoe had previously championed the neurotoxic role of Aβ from slightly different perspectives (*3*, *4*), but their recent Review ("The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics," *Science*'s Compass, 19 July, p. 353) provides a unified view. This reformulation is a departure from the original hypothesis [c.f. (*5*)] and abandons the postulate that fibrillar Aβ plaques are directly neurotoxic. Instead, they propose that soluble oligomers of Aβ42 are neurotoxic. This new view makes predictions about neurotoxic mechanisms and sites of action of

Aβ that have not been addressed by existing data. It remains to be shown that Aβ42 oligomers do cause "widespread neuronal/neuritic dysfunction and cell death" in vivo and that such neurodegeneration leads to cognitive impairment. The relevance to AD of the "oligomeric amyloid hypothesis" needs to be established by demonstrating that soluble oligomers of Aβ42 are significantly elevated in the interstitial fluid of brains from patients with familial and sporadic AD and with Down syndrome. Until such fundamental issues have been addressed, it would be premature to attempt therapeutic approaches on the basis of the oligomeric amyloid hypothesis. It is ironic that the first test of the new hypothesis in humans will come from therapeutic approaches being developed on the basis of the original amyloid hypothesis. Dissolution of Aβ plaques by immunization therapies or metal chelators will increase the concentration of soluble Aβ oligomers, and if these are toxic, such treatments will hasten the progress of AD.

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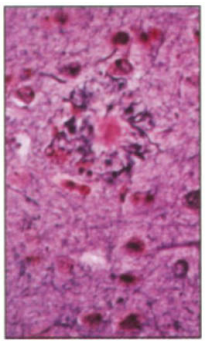
Response

ROBINSON AND BISHOP SEEK TO SIMPLIFY EARLY formulations of the amyloid cascade hypothesis of Alzheimer's disease (AD) in order to claim that the recent inclusion of a potential neurotoxic role for oligomers of the amyloid β protein (Aβ) represents a radical departure—a "new hypothesis." However, a mainstay of the original hypothesis was the evidence that alterations in the amyloid β protein precursor (APP) gene, namely, duplication in trisomy 21 (Down syndrome) and coding mutations in early-onset familial AD, lead invariably to the pathological and clinical features of AD (*1*, *2*). The contemporaneous discovery that Aβ is a normal product of cellular metabolism (*3*–*5*) quickly revealed that inherited APP mutations and trisomy 21 increase the cellular production of soluble Aβ throughout life (*6*–*9*). Early formulations of the amyloid hypothesis were based on this emerging knowledge and began the cascade with genetic alterations that enhance Aβ production (*1*, *2*). Progressive accumulation of the overproduced peptide in the brain was included as an early step in the hypothetical cascade. A gradual modification of the accumulating Aβ to induce progressive fibrillogenesis was explicitly proposed (*1*). This slow formation of large polymers (i.e., amyloid fibrils) implied that intermediate species larger than monomers would occur. Progressive neurotoxic effects on some local neurites were attributed to the accumulating Aβ. To link the defined genetic causes of AD (e.g., trisomy 21, APP mutations, and, later, presenilin mutations) to the observed neuropathology of the disease, the hypothesis postulated that diffuse plaques of Aβ (the earliest microscopically detectable form of aggregated Aβ) and then mature, fibrillar (amyloid) plaques were upstream of other cytopathological and biochemical features of AD, such as neuritic alteration, neurofibrillary tangles, and inflammatory changes (microgliosis and astrocytosis), and that Aβ accumulation, in turn, was upstream of the diffuse plaques (*1*).



Senile (neuritic) plaques showing amyloid core.

CREDIT: MARTIN M. ROTKER/ PHOTO RESEARCHERS, INC.

It is certainly true that those originally favoring the amyloid cascade hypothesis postulated a neurotoxic role for fibrillar Aβ polymers (i.e., amyloid) in the cytopathology of the syndrome, and it remains likely today that amyloid fibrils contribute to local neurotoxicity, perhaps directly but certainly as reservoirs of smaller, more biologically active oligomeric species. That the hypothesis has gradually evolved to include new experimental observations does not obviate the fact that early formal versions of the hypothesis focused on the concept that a rise in brain Aβ levels and subsequent accumulation and gradual fibrillization of the peptide were the initiating factors in AD. Any scientific theory that cannot accommodate new evidence will soon become obsolete, but this is not the case so far for the amyloid hypothesis, now more appropriately thought of as the Aβ hypothesis of AD. Our latest review of the hypothesis does not necessarily "abandon the postulate that fibrillar Aβ plaques are directly neurotoxic," as Robinson and Bishop state, but rather acknowledges that early Aβ aggregates, which were always placed upstream of fibrillar plaques, may have the more important role in early neurotoxicity.

We disagree with two other statements made by Robinson and Bishop. First, it

has already been reported that oligomers of Aβ42 are elevated in AD brain tissue (*10*, *11–14*). This was to be expected from the large elevations of both Aβ monomers and Aβ polymers (amyloid fibrils) observed in AD brains. Second, emerging therapeutic approaches based on the amyloid hypothesis, such as secretase inhibitors and anti-Aβ antibodies, are likely to lower brain levels of all forms of Aβ, including monomers and oligomers, at least based on preclinical data in mouse models (*15–17*). We previously emphasized that any therapy that depolymerized large Aβ assemblies but enhanced dimers and oligomers could prove disadvantageous (*18*); however, most currently contemplated anti-Aβ approaches are unlikely to do this.

Although the amyloid cascade hypothesis of AD has undergone refinement during the last decade to reflect new discoveries, it remains similar to its original form. Only human trials can now show whether chronic Aβ accumulation in the brain accounts for first subtle and later profound impairment of memory and cognition.

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Letters to the Editor

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