Attempts to formulate Alzheimer's disease as a manifestation of general brain aging make assumptions about the nature of the Alzheimer tangle which may not be supported by closer study. Thus it is often thought that because tangle-like structures appear in the brain in the course of a number of neurological disorders (Yagashita et al., 1979; Ishi et al., 1981; Hirano et al., 1983), as a consequence of repeated injury in dementia pugilistica (Corsellis et al., 1973), or as a consequence of intoxication with aluminium salts (Wisniewski et al., 1982), that the classical Alzheimer tangle is a non-specific consequence of disturbance in cortical pyramidal cell function. Indeed the well established relationship between increasing age (over 60 years) and an increasing frequency of plaques and neurofibrillary tangles in the brains of cognitively normal subjects (Tomlinson et al., 1968) has led some to speculate that these lesions may even represent a measure of the "force of senescence" in man (Dayan, 1970).

Of those that have been studied in detail, it is possible to distinguish at least two types of tangle - aluminium induced tangles, and Alzheimer tangles. When the tangles induced by aluminium intoxication are examined ultrastructurally, they are found to consist of dense aggregations of essentially normal neurofilaments. After isolation, these "tangles" can be solubilised readily, and electrophoresis reveals a pattern of bands which is known as the neurofilament triplet (Selkoe et al., 1979). It would appear, therefore, that the tangles induced by aluminium intoxication have analogies with a phenomenon found in cultured cells treated with vinblastin, and described as collapse of the cytoskeleton (Goldman et al., 1979). In circumstances which induce microtubule depolymerisation, the more insoluble components of the cytoskeleton, such as neurofilaments, form an aggregate around the nucleus, which has some superficial morphological resemblance to the Alzheimer tangle.

This situation contrasts with what has been found recently after extraction of the Alzheimer tangle. When isolated tangles are deposited on the electron microscope grid, and residual cytosplasmic contaminants are washed away, the basic structure which is left behind consists predominantly of paired helical filaments in dense arrays (Wischik & Crowther, 1985). In other words, the tangle is made up almost entirely of a distinct class of filaments not seen in the normal brain (Fig. 1). Although PHFs have been known to be present in the tangle for some time (Kidd, 1963), it was conceivable that these filaments represented one point...
Figure 1. Isolated Alzheimer tangle negatively stained at low magnification. Each filament has a diameter of approximately 20 nm. The isolated tangle, which retains the characteristic whorl seen in situ, consists almost exclusively of PHFs arranged in dense bundles.