human specimens were similar to those found in rats. However, the honeycomb-like inclusion bodies often present in old rats' FGP were scarcely seen in old human specimens, although pale lipoidal blebs increased in the inclusion bodies. It is possible that the honeycomb-like structures in rat FGP do not always imply degeneration of the FGP as suggested by Sturrock[8]. According to our unpublished data, these honeycomb structures were rich in lipase and lacking in acid phosphatase, whereas typical dense inclusion bodies in FGP were rich in acid phosphatase, but lacking in lipase.

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Transplantation of human cortex with Alzheimer's disease into rat occipital cortex; a model for the study of Alzheimer disease[1]

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Summary. Senile dementia of the Alzheimer type (SDAT) is a major problem in the human senescent population. As this pathology cannot be reproduced in animals, research into its development is greatly impeded. The technique of implantation of the nervous tissue has been utilized in order to establish an animal model and to test the possible existence of a transmissible agent. When human temporal cortex with Alzheimer's disease is implanted in the occipital cortex of 7-week-old rats, human cerebral tissue containing abundant tangles induces in the receiver cortex a reactive fibrous gliosis. In the processes of the astrocytes, twisted filaments are evident among bundles of normal filaments. These alterations could be induced by the metabolising of abnormal filament subunits or by some infectious agent introduced by the implant.

Senile dementia of the Alzheimer type (SDAT) is a major health problem in the human senescent population. Autopsy screening confirms that of all the pathologies seen in old age, SDAT is certainly the most common and it may account for as much as 80% of all dementias in the elderly[2].

The brains of patients with Alzheimer disease reveal severe abnormalities; neurofibrillary tangles, neuritic or senile plaques, granulo-vacuolar degeneration, Hirano bodies and nerve cell loss. All these alterations are observed during normal brain aging but they are more abundant in SDAT, and may invade all the regions of the brain. However they occur predominantly in the frontal and temporal cortex and in the hippocampus[3].

The most striking morphological impairment in SDAT is the neurofibrillary tangles. These thickened fibers can be visualized by silver impregnation or by polarized light after Congo red staining. At the ultrastructural level they are characterized by paired helical filaments (PHF) crossing one another approximatively every 80 nm. The nature of the material composing the PHF is still uncertain.

The causes of SDAT are still enigmatic; genetic predisposition[4], exogenous toxin[5] and a slow latent virus[6] are suspected. As cholinergic neurons appear to be particularly altered[7], patients have been treated by choline precursors but these trials have been unsuccessful[8].

A major problem in planning research into the process of SDAT is the absence of a fully satisfactory animal model. This pathology cannot be reproduced in animals, and occurs as a natural disease in man only. Several attempts have been performed to simulate Alzheimer disease experimentally in animals. Injections of aluminium salts in rabbits induce neurofibrillary tangles[9], as does administration of alcohol in spinal neurons[10]. The scrapie agent induces in the mouse cortex senile plaques similar to the human ones[11].

However, the results obtained in the experimental models, produced by means of unconventional agents, are much more diverse than expected, and difficult to interpret.

Some previous work performed with the spinal ganglion neurons has shown that the cytoskeleton was dramatically impaired in the senescent rat[12]. In some cases, one of the alterations observed is that the pericaryon can contain local accumulations of filamentous structure similar to the human PHF. The occurrence of these impairments has been also mentioned in one individual of another strain of rats, the normotensive Kyoto[13]. On the basis of these results, our strain of rats has

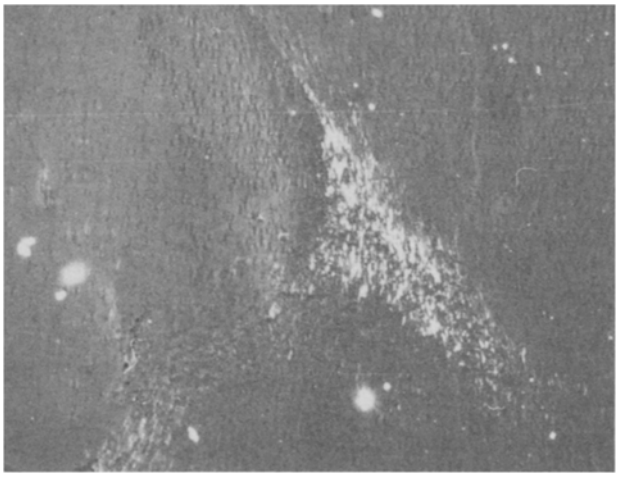

Figure 1. Implant of human cortex with Alzheimer's disease in rat cortex; tangles are visualized by polarized light after Congo red staining.

been used for the tentative establishment of an animal model and to test the existence of some transmissible factors in SDAT by means of transplant techniques.

Fragments of the brain of a patient with severe senile dementia were obtained 8 h post-mortem and conserved in liquid nitrogen. Staining with Congo red confirmed the presence of PHF in the tissue. Small tissue blocks (1 mm^3) taken from the temporal cortex were transplanted into the occipital cortex of 7-week-old rats according to the method of Das[14]. Fragments of normal brain, obtained from an old patient, were used as control. The animals were allowed to survive 8 weeks and then sacrificed by fixative perfusion of a mixture of glutaraldehyde and paraformaldehyde in a 0.1 M phosphate buffer at pH 7.4. The removed brain was prepared for histological study with light and electron microscopy by routine methods.

The human brain graft can be visualized in the rat cortex by polarized light after Congo red staining (fig. 1). The identified PHF are remnants of destroyed neurons presenting neurofibrillary changes. Their structural stability after neuronal death can be attributed to their constitution. It has been suggested that PHF may constitute one type of amyloid, having a beta-pleated sheet configuration and thus being resistant to proteolysis[15,16].

The presence of the graft induces in the rat cortex some modifications characterized by a very poor invasion of macrophages, a vascular proliferation and an intense fibrous astrocyte glial reaction. This fibrous gliosis is a major event in the injured central nervous system and its most prominent feature is glial filament synthesis. The electron microscopic study shows that processes of astrocytes can contain among their filament bundles numerous twisted filaments, similar to PHF (fig. 2). The presence of these abnormal filamentous structures proves that a graft of human cortex with Alzheimer's disease induces modifications in the glial cytoskeleton. It has recently been shown that PHF appear to be strong stimulus for astrocytic reactions when they are not segregated from the environment by the neuronal cell membrane[17]. Moreover, this study demonstrates that they can also induce the appearance of twisted filaments in the glial processes.

There is still controversy about the nature of the glial filaments and the neurofilamentous proteins. According to one hypothesis, glial filaments and the 50 K neurofilament proteins are similar, and the data obtained were interpreted as an indication that the building blocks of neurofilaments and glial filaments are biochemically related[18]. According to another hypothesis, the presence of GFA-like proteins in myelin-free axon preparations is due to glial contamination[19]. However, if the chemical composition of these intermediate neurofilaments is not well known, biochemical and immunological evidence suggests that they represent a fiber system assembled from unique protein subunits[20].

Grafting of tissues with Alzheimer's disease alterations may involve the presence in the receiver cortex not only of PHF but also of some abnormal protein subunit precursors from which these PHF are built. The metabolizing of these subunits in the processes of the reactive astrocytes and their incorporation as precursors into the glial filament network may be the origin of twisted glial filaments. Another possibility is the presence in the transplant of some infectious agent, responsible for the PHF formation, which can contaminate the surrounding cortex. In this case small protein-like infectious particles (prion) could be suspected[5].

From the results of these experiments, it can be concluded that transplantation of human cortex with Alzheimer's disease can induce an Alzheimer-like reaction in the cortex of young rats. If brain transplants prove to be a very practical tool for investigating brain development, they may also prove to be a valuable method for the study of brain aging phenomena.

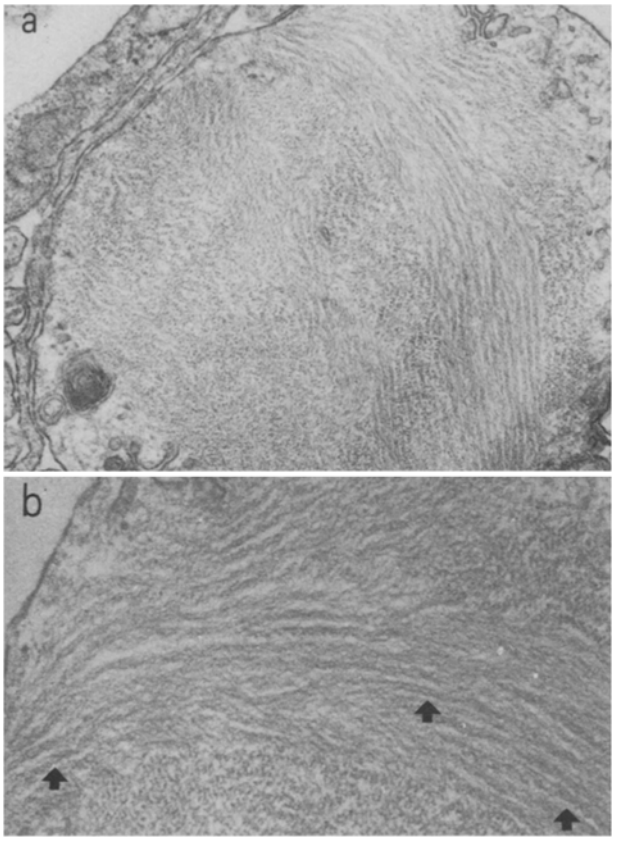

Figure 2. *a* Glial process in the rat cortex surrounding the implant. *b* Among the bundles of filaments, twisted filaments can be observed.

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