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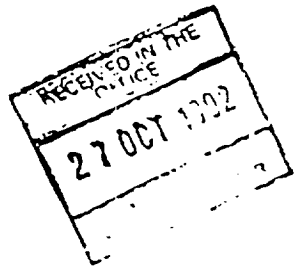

Your reference

Our reference

23 October 1992

IN STRICT CONFIDENCE

Dear Ken,

Transmission of Alzheimer type plaques to primates

I am sending you for information the attached paper prepared by Dr Ridley on the results of a part of a large series of experiments on the transmissibility of various neurodegenerative diseases.

You will see that there will not be any public disclosure of these results until January (at the meeting of the British Neuropathological Society) however I thought you would wish to know about them at this stage. We are preparing a public statement to put the findings into proper context for use either in January or if there are any earlier leaks. We would be happy to discuss drafts with DH if that would be helpful.

If you or your colleagues would like to have further discussion of the findings with the scientists involved and perhaps the Neurosciences Board expert(s) then please let me know and I ensure that arrangements are made.

Yours sincerely,

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92/10.23/1.1

IN CONFIDENCE

TRANSMISSION OF ALZHEIMER-TYPE PLAQUES TO PRIMATES

H F Baker, R M Ridley, L W Duchen, T J Crow, C J Bruton

As part of a larger series of experiments designed to assess the transmissibility of various neurodegenerative diseases including the spongiform encephalopathies (eg Creutzfeldt-Jakob disease and BSE) we injected several marmosets (Callithrix jacchus) intracerebrally with brain homogenate from: 1)a 56 year old patient with severe Alzheimer's disease - ß-amyloid plaques and congophilic angiopathy (CAA) and neurofibrillary tangles; and 2)a 62 year old patient with Gerstmann-Straussler disease, a spongiform encephalopathy with PrP plaques and, in this case, ß-amyloid plaques and CAA. These monkeys were killed more than 6 years after inoculation and their brains were found to contain moderate numbers of ß-amyloid plaques and CAA but no neurofibrillary tangles. The brains of more than 12 monkeys killed at an older age did not contain these changes. ß-amyloid was not found in the brains of monkeys injected with brain material which did not contain ß-amyloid. These results suggest that ß-amyloidosis is a transmissible process resembling the transmissibility of PrP amyloidosis in transmissible dementia and strengthens the parallels between Alzheimer's disease and Creutzfeldt-Jakob disease ~~disease~~.

It should be stressed, however, that we are not claiming to have transmitted Alzheimer's disease because 1)the animals were behaving normally when killed and 2)no neurofibrillary tangles were seen.

We have argued previously that the transmission of spongiform encephalopathy, particularly from the genetic cases (GSS and some CJD), does not imply that the donor cases themselves acquired the disease by infection. We would apply the

same arguments in this case, particularly in view of the genetic basis of some cases of Alzheimer's disease and the extensive epidemiological data which does not link Alzheimer's disease to infection.

DISCLOSURE

This work is currently under preparation for publication but in view of public concern over the transmissible spongiform encephalopathies (eg BSE) and the high incidence of Alzheimer's disease in the general population, it is important that these findings are not discussed openly before full publication.

Furthermore, before disclosure, it is important that interested parties be properly appraised of the data and their implications.

Previous attempts to transmit Alzheimer's disease to rodents and large primates have been unsuccessful. It is our belief that post-mortem tissue from these animals still exists and we are anxious that research workers (in the USA) should not re-examine this material until our data are published.

SAFETY

At this point we would like to stress again the lack of evidence relating Alzheimer's disease to exposure to brain tissue through neurosurgery or occupation. Nevertheless it is appropriate that the proper bodies should consider whether the results of our experiments have any implications for human health.

FURTHER EXPERIMENTS

The interpretation we have made that β-amyloidosis as a self-perpetuating process has important implications for understanding the processes of neurodegeneration, which are best studied at the level of protein chemistry. However, we can see arguments for some transmission experiments including:

1) serial passage of ß-amyloidosis in order to strengthen the evidence of transmissibility;

2) transmission from other cases of Alzheimer's disease in order to establish the generality of this effect;

3) transmissions to primates which are allowed to run their full course, ie to see whether the full syndrome of Alzheimer's disease develops including neurofibrillary tangle formation, astrocytosis, neuronal loss and concomitant cognitive decline. (We are already expert in the neuropsychological assessment of marmosets). It should be remembered that, at the present time, only the amyloidosis has been found to be transmissible such that Alzheimer's disease per se has has not been transmitted;

4) comparison of transmission from cases which contain only CAA and those which contain only ß-amyloid plaques. These two forms of amyloid differ very slightly and it is not known whether this difference is preserved on transmission;

5) establishment of the time course of the development of ß-amyloidosis. The present experiment suggests that the time course is somewhere between 1-5 years;

6) transmission using larger quantities of purified preparations of ß-amyloid. This may reduce the transmission time considerably;

7) transmissions using animals of different initial ages to investigate the relationship between transmission time and chronological age, eg transmission

into mature animals may decrease transmission time through an interaction between the pathological process and senescence;

8) manipulation of transmission time by treatments which may speed up plaque formation, eg by increasing the production of amyloid precursor protein, or which may slow down plaque formation and protect from disease progression.

The proposal is to inoculate about 25 marmosets in the first instance and to replace them in a 'rolling' experiment as they die or are killed according to the experimental design. The marmosets will be kept in the MRC Marmoset Colony in Cambridge. Additional facilities and personnel are not required over and above that awarded to Dr Ridley in an MRC Programme Grant.

A preliminary report of our findings will be presented by Professor L W Duchen at the January 1993 meeting of the British Neuropathological Society.