Matters arising

Lymphocyte capping in Down's syndrome and Alzheimer's disease

Sir: The paper by Duijndam-Van den Berge and Goekoop on a capping defect in Down's syndrome and Alzheimer's disease¹ deserves further comments.

It is quite unusual not to observe an enhancing effect of colchicine upon the capping ability of lymphocytes from normal donors. It is the hallmark of microtubule inhibitors like colchicine or vinblastine to promote a protuberant morphology of the leukocytes and to induce a polar gathering of the con-A receptors.²⁻⁴ Furthermore, in both adult and aged subjects, colchicine has been found to increase the capping rate of con-A⁵ and sheep-erythrocyte receptors⁶ on lymphocytes. Considering this wealth of data, the capping abnormality in the study of Duijndam-Van den Berge and Goekoop seems to affect the control subjects. So far, it is difficult to admit an aetiological role of the microtubular system in Alzheimer's disease other than a speculative one.

Concerning the Down's syndrome, the point is no more clear. Low spontaneous capping rates have been reported^{1,7} but also higher rates.⁸ Such a discrepancy does not support any general theory about cytoskeletal defects in Down's syndrome.

In my opinion, the link between these disorders and microtubules in lymphocyte capping still remains to be demonstrated and general conclusions are misleading.

D BROHÉE

Laboratory Experimental Medicine,
Department of Internal Medicine,
CHU André Vésale,
6110 Montigny-le-Tilleul,
Belgium

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Duijndam-Van den Berge and Goekoop reply:

In his comment on our report Dr Brohée reasons from the supposition that we used untreated lymphocytes. Indeed, if we had done so an enhancement of the capping rate by colchicine would be the normal finding and the absence of a colchicine effect should be interpreted as the abnormality. In fact, however, we did pretreat the cells by cooling them at 0-4°C. Con-A capping is enhanced by either colchicine or low temperatures, resulting in comparable capping rates.¹ Cold treatment causes a partial disassembly of microtubules,² leaving the so called cold-stable microtubules intact. Since cold-stable microtubules are also colchicine resistant³ an enhancement of con-A capping by colchicine in precooled lymphocytes is not to be expected. Our findings in normal subjects and those of Naeim *et al.*,⁴ using a comparable cold treatment, are in agreement with this state of knowledge. Therefore, the colchicine enhancement we found in Down's syndrome and early-onset primary degenerative dementia, using pretreated cells should be interpreted as the abnormality.

Dr Brohée's second point concerning discrepancies between spontaneous capping rates in Down's syndrome deserves further comment. First, all studies published so far⁴⁻⁷ do not concern spontaneous capping rates but rates after cold treatment. This makes the results comparable. None the less we do not believe that the discrepancies of the published results within these experimental conditions are sufficient for a refutation of the cytoskeleton theory in Down's syndrome. For instance in the only study with high capping rates⁶ the mean age of the patients was lower than in the other studies and the effect of ageing on con-A capping in Down's syndrome has not yet been studied.

Secondly, individual colchicine effects after cold treatment were not studied in these young patients. As we have demonstrated in primary degenerative dementia such a colchicine effect is a more discriminating parameter than the simple capping rate. For this reason one should look for the existence of similar abnormalities in young Down's syndrome patients. Instead of early rebuttal we suggest that further research is a better strategy.

In conclusion it seems that Dr Brohée has overlooked an essential detail in our experimental design and that our results can be seen as a support for the hypothesis of a role of the microtubular system in Down's syndrome and early primary degenerative dementia. Whether the recently reported defective assembly of brain microtubules and abnormally phosphorylated microtubule-associated protein tau in Alzheimer's disease⁸ can be associated with the abnormality reported by us remains to be seen.

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