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LETTERS TO THE EDITORS

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Critical Comments on "Propionibacterium acnes in the cortex of patients with Alzheimer's disease" by H. H. Kornhuber (Eur Arch Psychiatry Clin Neurosci, 1996, 246:108–109)

First comment

In his "Letter to the Editor", H. Kornhuber communicates the finding of propionibacterium acnes in the anaerobic cultures of cortical biopsy material from Alzheimer's disease patients in three out of four cases. The lack of propionibacterium growth in the fourth case is explained by the author by the fact that this patient had received an injection of a cephalosporine prior to the biopsy procedure. In contrast to the Alzheimer's disease patients, only one of five control patients (suffering from other neurological disorders) was found positive with respect to propionibacterium acnes growth in anaerobic cultures of cortical biopsy material.

This communication raises several questions. How were the anaerobic cultures exactly made? E.g., had the biopsy material been homogenized prior to transfer to the anaerobic culture medium? What kind of culture system had been applied? Had anaerobic blood cultures been made in parallel and what were the findings with respect to these cultures?

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Beside these technical problems, Kornhubers finding leaves the reader with a number of more fundamental questions: If propionibacterium acnes was a pathogenetic element in Alzheimer's disease, one should expect that the disease is transmissible. However, neither were injections of brain tissue from Alzheimer patients able to induce any pathology in primate brains nor do the spouses of Alzheimer's disease patients display a higher prevalence of the disease. Furthermore, if an infectious agent would be involved in the pathogenesis of Alzheimer disease, its pathologic consequences would not be limited to the cortex. Instead, other areas of the brain should also be involved and a more complex symptomatology would be expected. Finally, if propionibacterium acnes was a pathogenetic element in Alzheimer's disease, treatment with antibiotics in early stages of the disease should prevent progression. However, nothing in this direction has been observed by anybody until now.

Nevertheless, Kornhubers finding deserves attention. However, further studies with larger numbers of both patients and control persons are necessary. Until Kornhubers findings are not confirmed, the presented data should be interpreted with care.

Second comment

Autoimmune processes have been suggested to take place in subgroups of Alzheimer's disease, and it has been shown that patients with rheumatoid arthritis develop Alzheimer's disease less often than controls. It also seems that anti-inflammatory drug treatment prevents from Alzheimer's disease (McGeer and Rogers, 1992; Rogers et al. 1993). It has not been shown, however, that Alzheimer's disease might be attributable to some infection. Thus, the hypothesis that propionibacterium acnes might be implicated in the etiology of Alzheimer's disease is new and, of course, the prospect of treating the resulting infection with cephalosporines is intriguing. However, the material in the study by Kornhuber is too small for any valid conclusions to be drawn. The significant neuropathological

changes in brain tissue from Alzheimer-afflicted patients are usually not of vascular or perivascular type. If microorganisms should gain entrance to brain tissue in Alzheimer's disease because of vessel disorders, the neuropathological changes would most likely occur in the perivascular area.

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Third comment: Acne and Alzheimer's

This is a stimulating idea far off the beaten tracks of amyloid and tau orthodoxy and it may eventually explain the intriguing association between nose-picking and Alzheimer's in Australians (Henderson et al. 1992). Earlier hypotheses zoomed in on the nose as a potential port of entry for a pathogen to be sniffed out (Hardy et al. 1986; Roberts, 1986). Actinomyces (Howard and Pilkington, 1992) and spirochetes (Miklossy, 1993), the most likely suspects, are now rivalled by propionibacterium acnes, another component of the patients' and pathologists' resident skin flora. None of these hypotheses is easily falsified and none deserves to be sneezed at, – but this is the problem. The most obvious explanation for these findings – contamination – needs to be ruled out with some confidence before further studies are undertaken. Science thrives on unorthodox thought, particularly if it holds greater therapeutic promise, and I am not convinced that we do know nearly enough about acne and Alzheimer's.

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H. H. Kornhuber

Reply on critical Comments on "Propionibacterium acnes in the cortex of patients with Alzheimer's disease" by H. H. Kornhuber (Eur Arch Psychiatry Clin Neurosci, 1996, 246:108–109) by J. Bauer; G. G. Gottfries; H. Förstl

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It is important to provide rapid transportation at room temperature from the neurosurgery operating room to the bacteriological laboratory. The stuart medium for the anaerobic culture was used which provides low oxygen and is enriched with CO_2. In the bacteriological laboratory the medium for anaerobic microorganisms was Schaedler blood agar which contains additional Vitamin K and Haemin. Microorganisms were enriched with thioglycolat broth. The bacteria were grown at 35° C under anaerobic conditions for 14 days. The growth of bacteria usually appeared after 4 or 5 days. No homogenisation was necessary for these small amounts of cortical tissue. The biopsy specimen was spread on the agar using an eyelet. The bacteria were differentiated by standard methods and gas chromatography.

The fact that injections of brain tissue from Alzheimer patients were not able to induce pathology in primate brain may be due to Propionibacterium acnes needing an anaerobic milieu for its growth.

There are two reasons why the spouses of patients with Alzheimer's disease do not display a higher prevalence of the disease: 1. The infectious agent, Propionibacterium acnes, is to be found on the skin of most adult humans, 2. the thriving of the anaerobic bacteria in the cortex requires microangiopathy and an anaerobic milieu.

The symptomatology of Alzheimer's disease shows exclusively signs of association cortex damage only in the beginning of the disease; at later stages symptoms of other parts of the brain may occur.

The treatment of Propionibacterium acnes infections is not easy. Large doses of antibiotics over a long period of time may be necessary. In the few patients I was able to treat there had been advanced dementia for years. Nevertheless I have seen a stabilisation in one case and an improvement of memory in another case under treatment with cephalosporines, enalapril and oestrogens.

I agree that the data base so far is too small to draw a definite conclusion. However, in view of the fact that there is no other effective treatment, therapeutic trials may be based on the new data. For further clarification, post mortem studies should be organized.

The state of the small vessels and capillaries in the cerebral cortex of patients with Alzheimer's disease should be reinvestigated. I have, however, little doubt that Scheibel's statements are correct.

Regarding acne and Alzheimer's disease, we are trying to collect some epidemiological data on seroreactivity against Propionibacterium acnes.

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