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EARLY DIAGNOSIS OF ALZHEIMERS'S DISEASE: EXPERIMENTAL STUDIES ON MIDDLE-AGED DYSTHYMIC SUBJECTS AND SUBJECTS WITH AGE-ASSOCIATED MEMORY IMPAIRMENT.

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Research into the earliest stages of Alzheimer's Disease is sparse. One reason is that the origin, course and features of normal and abnormal aging, i.e. dementing syndromes are insufficiently known. The detection of Alzheimer's disease in stages in which no dementia is present appear very difficult if at all possible. Dementia can be assessed only when the disease has progressed into a stage in which moderate intellectual decline is present (stage 4 of the Global Deterioration Scale for Age-Associated Cognitive and Alzheimer's Disease (Reisberg, 1983)). In analogy of the criteria set for dementia by the DSM-III-R (APA, 1986) and NINCDS/ADRA (McKhann et al, 1984), explicit measures are set for Age-Associated Memory Impairment (AAMI, Crook et al, 1986) in an attempt to distinguish persons with benign forms of forgetfulness from abnormal forms. In an earlier experiment in our institute the AAMI criteria were tested for feasibility in the Maastricht Memory Clinic population (MMC). It was found that 25% of the MMC population met the criteria for so-called "normal" Age-Associated Memory Impairment. However, in a study on the cognitive performance between this MMC subpopulation and matched controls, it was shown that there were significant differences on neuropsychological parameters,such as complex speed of information processing, and aspects of memory,like active recall from memory and learning capacity. More or less the same findings were seen in an experiment in which 15 middle-aged dysthymic subjects with cognitive complaints were compared to matched controls. It is hypothesised that elderly people who complain about memory function and whose complaints can be substantiated by neuropsychological screening techniques, do not show cognitive dysfunctions that are "normal" for age or part of dysthymia but that their cognitive dysfunctions might show the very early signs of a dementing process.

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INTRA- AND INTER-DISCIPLINARY CONSENSUS ON THE DIAGNOSIS OF DEMENTIA.

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The purpose of the study was to assess the intra- and interdisciplinary consensus on the diagnosis of dementia before and after a consensus meeting, and to determine whether there was a disciplinary related preference for certain diagnostic categories.

Ninety clinicians from 6 disciplinary categories (i.e. neurologists, psychiatrists, general physicians, psychologists, nursing home physicians and others) filled in an inquiry form which asked them to diagnose 10 case descriptions of patients suspected to suffer from dementia. Five cases were diagnosed before and 5 after a consensus meeting on the diagnosis of dementia. The analyses showed a significant difference between the disciplines in the use of diagnostic categories. Neurologists used the diagnosis 'Dementia of Alzheimer's Type' significantly more often than the other disciplines, while psychiatrists used the diagnosis 'depression' more often than neurologists. Further, more psychiatrists used diagnoses without etiological specification significantly more often than neurologists. General physicians and nursing home physicians used significantly more often diagnoses concerning medication/intoxication than psychologists and psychiatrists. The results also showed that the level of consensus on diagnoses at the syndrome level was higher than on the etiological level. As to the effect of the consensus meeting no significant effects on the level of consensus both within and between the disciplines could not be monitored.

The results implicate that the diagnostic classification of patients suspected to suffer from dementia is biased by the nature of medical specialization. To avoid such a bias and to enhance the quality of differential diagnoses a multidisciplinary approach is thus recommended.

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THE DEMENTIA DIAGNOSIS EXPERT SYSTEM EVINCE IN COMPARISON WITH EXPERT CLINICIANS: AN EVALUATION STUDY

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The purpose of the study was to assess the diagnostic performance of the dementia diagnostic expert system EVINCE-1 in comparison with a large number of clinicians and a multi-disciplinary expert committee in diagnosing 10 patients suspected to suffer from dementia. Eightyfive clinicians from 5 disciplines (i.e. neurologists, psychiatrists, general physicians, psychologists and nursing home physicians) diagnosed 10 case descriptions of patients suspected to suffer from dementia. These 10 case descriptions were also diagnosed by EVINCE-1. Additionally a 'golden standard' obtained through a multi-disciplinary expert committee (i.e. a neurologist, a psychiatrist and a psychologist). This committee diagnosed the same 10 case descriptions. This golden standard was used as reference in the comparison. Each patient was classified according to two types of diagnoses: syndrome and etiological diagnoses. The expert committee reached a consensus (agreement) on the syndrome level diagnoses for all 10 patients and for 9 patients on the etiological level. On the syndrome level the 85 clinicians made 76% of the diagnoses in agreement with the expert committee, while EVINCE-1 diagnosed all 10 case descriptions in agreement with the expert committee. No significant difference was found between the disciplines on the number of correct diagnoses.On the etiological level 53% of the diagnoses made by the 85 clinicians were similar to those of the expert committee, while EVINCE-1 made all 9 etiological diagnoses in agreement with the expert committee. There was a significant difference between the disciplines concerning the number of etiological diagnoses in agreement with the expert committee: Neurologist had significantly more correct diagnoses than the other disciplines, except for the psychologists. The results show that the performance of EVINCE-1 in diagnosing dementia is in perfect agreement with the expert committee on both syndrome and etiological diagnoses and better than the average individual clinician.

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EXPERIMENTAL EVIDENCE FOR A RELATION BETWEEN ACCELERATED COGNITIVE AGING AND FOR BRAIN DYSFUNCTION: AGING AND RISK FACTORS.

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The aim of the study was to investigate the risk factors for brain dysfunction as they affect cognitive functions in so-called "normal" cognitive aging in order to provide information on accelerated aging and dementia. A number of biological or environmental factors are known to hamper an optimal functioning of the brain. These risk factors may be just as relevant to age-associated decline as aging per se. Examples are: closed head injuries, general anaesthesia, or heavy drinking. The hypothesis is that risk factors interact with aging in their effect on cognitive functioning. The authors examined a large group of subjects (N=250) with ages ranging from 20 to 80 in 7 consecutive age cohorts, recruited from the normal population. Detailed neuropsychological anamnesis of all individuals was taken. Subjects were divided into a "risk group" and a "healthy group". To obtain the same number of elderly risk-free individuals (aged about 60, 70 or 80 years), 2 or 3 times as many volunteers had to be recruited. Tests were administered, along with extensive neurological examination. None of the subjects showed major neurological disorders. In all complex or speed-demanding tests, risk subjects performed worse than healthy subjects. The gap between the average performance in both groups became wider in the older age cohorts. In some elderly volunteers in the healthy group, verbal memory performance was as good in young students, whereas some individuals aged 70 or 80 in the risk group showed a globally poor performance in all tests that was in accordance with incipient dementia. At the same time, the differences in performance were already apparent at the age of 40, as was the age-associated decline. These findings have serious implications for cognitive aging research. Many of the effects of aging reported in the literature may result from factors other than aging itself.

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POOL SIZE, SYNTHESIS AND TURNOVER OF CHOLIC ACID AND CHENODEOXYCHOLIC ACID IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS. EFFECT OF URSODEOXYCHOLIC ACID TREATMENT. A.Stiehl, R.Raedsch, G.Rudolph, M.Senn*, R.Endele* and J.Klaus*, Departments of Medicine, University of Heidelberg and of Analytical Biochemistry*, Boehringer Mannheim, FRG.

Patients with primary sclerosing cholangitis have cholestatic liver disease characterized by diseased intra- and extrahepatic bile ducts. The metabolism of bile acids in such patients is unknown. In the present study 13C-cholic acid and 13C-chenodeoxycholic acid were used to determine the kinetics of these bile acids by gas-liquid chromatography-mass spectrometry (F.Stellaard et al., J.Lipid Res 25,1313-1319,1984). In 3 patients with precirrhotic disease the pool size of cholic acid (CA) was on average 358 mg/d and that of chenodeoxycholic acid (CDCA) 495 mg. The fractional turnover rate of CA was 0.48 d^{-1} and that of CDCA 0.43 d^{-1}. The synthesis rate of CA was 138 mg/d and that of CDCA 172 mg/d. Ursodeoxycholic acid (UDCA) treatment (750 mg/d) led to little change in CA pool sizes, to an increase in the synthesis and fractional turnover rates of CA in all patients. UDCA induced changes in CDCA kinetics were less marked. In comparison to healthy controls the pool sizes and synthesis rates of CA and CDCA were reduced whereas the fractional turnover rates on average were relatively high. Bile acid pool sizes were similar to those in alcoholic cirrhosis of the liver (Stiehl et al., Gastroenterology 74,572-77,1978). We conclude that in patients with primary sclerosing cholangitis at an early stage of the disease the metabolism of bile acids is already markedly altered.

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EFFECT OF URSODEOXYCHOLIC ACID (UDCA) ON LIVER FUNCTION (LF) IN PATIENTS WITH CHRONIC ACTIVE HEPATITIS AND CIRRHOSIS

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UDCA improves the cytolytic and/or cholestatic indices of LF in pts with chronic hepatitis and PBC. However,it is not known if UDCA exerts this effect in pts with hepatic cirrhosis of different aetiology. We therefore treated 20 pts with compensated active (transaminase levels 2-10 x the normal value) cirrhosis with UDCA (600 mg/day) for 6 months and looked at LF as assessed by routine LF tests,antipyrine clearance (ApCl)and galactose elimination capacity (GEC).Diagnoses were based on laparoscopy guided liver biopsy and included:alcoholic (AC;n=8),post-necrotic (PNC; n=6) and cryptogenic (CC;n=6) cirrhosis.Exclusion criteria were: HBeAg +, portal hypertension,autoiimune disease. Results:in pts with AC,serum ALT decreased significantly from 149 u/l ± 20 SEM to 81±9 ($p<0.01$) and AST from 222±30 to 140±21 ($p<0.05$).Gamma-GT was reduced,on average, by 49% and LDH by 26%. By contrast,the common markers of cholestasis (serum alkaline phosphatase,bilirubin and bile acids) showed no significant changes.A similar pattern of results was seen in pts with PNC and CC, where serum transaminase decreased by 24-27% and 22-29%, and gamma-GT was reduced by 37% and 50% respectively,although not significantly so. ApCl and GEC were unchanged in all groups. Conclusions: In pts with active cirrhosis of the liver,the functioning hepatic mass and the drug metabolizing capacity,as assessed by the quantitative LF tests,is not affected by UDCA treatment. However,the decrease of biochemical hepatic necrosis (seen especially in alcoholic cirrhosis) may slow down the progression of the disease.