PLATELET MONOAMINE OXIDASE ACTIVITY AND VIT B12 IN DEMENTIA

Thesis

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IN

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INTRODUCTION AND AIM OF THE WORK

Until very recently; the basic science of psychiatry has lagged behind that of most other medical specialties in identifying etiological factors and pathophysiological mechanisms of disease processes, so as to improve diagnosis and treatment. These advances in general medicine, most achieved in the latter half of this century; have followed largely for basic biomedical investigations of the cellular, subcellular and molecular mechanisms underlying the genetic and environmental factors responsible for the cause, manifestation, course and treatment of a large number of medical illnesses.

The basic concept of the medical model in psychiatry is that mental disorders are diseases of the brain and therefore are entirely analogous to diseases of other organ systems **(Hyman and Nestler, 1993).**

Many psychiatric disorders are claimed to be associated with changes of platelet mono-amine oxidase (MAO) activity. Platelet MAO may be an accessible indirect indicator of brain MAO activity. Aging leads to a decline in brain mono amine neutrotransmitter concentration and to increase in brain mono-amine oxidase activity **(Adolfsson et al., 1980).**

Two subtypes of MAO are known, MAO-A and MAO-B. Since platelet MAO is almost entirely of the B-type and since many of alterations in MAO activity in mental disorders are caused by MAO-B

changes, the usefulness of this peripheral model is evident as a marker for possible changes in brain MAO-B activity (Danielczyk **et al., 1988).**

Platelet MAO activity has been found to increase significantly in patients with dementia and was highly correlated with the severity of dementia **(Fischer et al., 1994).**

Recent evidence suggests to that this increase is due to vitamin $\mathbf{B_{12}}$ deficiency **(Parnetti et al., 1992).** But others indicate no association between a low vitamin B_{12} level and high mono-amine oxidase activity **(Fischer et al., 1994).**

In this study we tried to determine the platelet mono amine oxidase activity and serum vitamin B_{12} level and to test the correlation between platelets MAO and serum vitamin B_{12} in dementia with hope that it would help us to find a biological marker for dementia disorder.

CONCEPT OF DEMENTIA

The history of senile dementia begins in the Greco-Roman period with basic concept of senility by pythagoras and hippocrates. During the middle ages, the main contribution was by Roger Bacon in 1290. The first Textbook of Neurology, De Cerebri Morbis, by Jaso de Pratis, included a chapter on dementia (De memoriae deteriments). **In** the 17th century, Thomas Willis recognized intellectual loss with aging. In the 19th century, philippe pinel removed chains from the mentally ill, his student Esquirol wrote the first modern classification of mental disease, including senile dementia. In 1860, morel recognized brain atrophy with aging. The modern history of vascular dementia began in 1896, when emil kraepelin in his textbook of psychiatry included arteriosclerotic dementia among the senile dementia, following the ideas of Otto Binswanger and Alois Alzheimer, who had differentiated clinically and pathologically arteriosclerotic brain lesions from senile dementia and from neurosyphilitic general paresis of the insane **(Roman, 1999).**

When a disease becomes as important as Alzheimer's dementia, there is a natural interest in its medical history and in the origin of the underlying disease concept, most histories of senile dementia commence with Alois Alzheimer's description in 1906 of the first case of Alzheimer's. yet the history of senile dementia before 1906 is quite rich, dating back to the ancient Greek and Roman pilosophers and physicians. Over the 2500 years since ancient times, the concept of senile dementia has evolved from a rather vague nation that mental decline occurred

inevitably in old age, to become defined to day by a distinct set of clinical and pathological features with the potential for treatment and prevention within grasp **(Berchtold and Gotmon, 1998).**

In 1906, Alzheimer presented the first case of the disease which was later named Alzheimer's disease by Kraepelin in 1910. Alzheimer published a very comprehensive paper **in** 1911 in which he discussed the concept of the disease in detail. This publication focuses on the report of a second patient suffering from Alzheimer's disease, the case of Johann F. The detection of neurohistopathological section from this patient found among archives at the institute of neuropathology of the University of Munich. Neuropathologically, the case of Johann F. is plaque only Alzheimer's disease. There is a contraversy in the modern literature as to whether these plaque only cases belong to the modern concept of Alzheimer's disease. A careful analysis of all pros and contras in the literature led to the conclusion that plaque-only cases are also an integrative part of the modern Alzheimer disease concept **(Moller and Graeber, 1998).**

Frontotemporal dementia (FTD) is the second most frequent degenerative cause of dementia. Although described for more than a century, it remains often misdiagnosed, mistaken for Alzheimer's disease or psychiatric disorder **(Pasquier and Petit, 1997).**

Hans-Gerhard Greutzfeldt and Aifons Jakob independently authored clinical and pathological descriptions of a new syndrome in **1920s.** This syndrome, which subsequently came to be named after them

was characterized by dementia, motor and coordination abnormalities, a fatal course and pathologic finding of diffuse spongiform Neuronal degeneration **(Sternbach et al., 1997).**

Circumscribed focal atrophy with frontal lobe dementia and progressive aphasia as described originally by Arnold Pick has been recognized recently as being much more common than previously believed **(Kertesz and Kalvach, 1996).**

MATURATION OF GERIATRIC PSYCHIATRY

Even as our society ages geriatric psychiatry matures as the population ages, the specialty of geriatric psychiatry is also aging. Although geriatric consultants have served the national health service for many years, geriatric psychiatry received official approval by the American board of psychiatry and Neurology only in 1991. Nevertheless almost 1000 persons took the examination to receive certification as a geriatric psychiatrist in 1991. Multiple Journals are now published that directly or indirectly focus on geriatric psychiatry. These include, the American Journal of geriatric psychiatry, the international journal of geriatric psychiatry, aging and mantel health, psychology of aging, the neurobiology of aging and international psychogeriatrics **(Daniel, 1998).**

Geriatric psychiatry has realized many advantages as a mature specialty, Geriatric psychiatrists are accepted as key contributor, not only to the cure and investigation of late life psychiatric disorders, but they are also considered critical to the advancement of the field as a whole, Most academic department of psychiatry have or are in the process of establishing division of geriatric psychiatry and most comprehensive Textbooks of psychiatry include ample chapter that review geriatric psychiatry (Daniel,1998)

Many years ago geriatric psychiatry developed a new paradigm for understanding late psychopathology, primarily by coupling what was known about the normal aging process and what was known about psychiatric disorders in midlife. This coupling led to conceptualization of psychiatric disorders in late life that varied from those in mid life **(Daniel, 1998).**

NORMAL BRAIN AGING

Aging is part of continuos change of function starting at birth and ending by death. When the term aging process is used its does not refere to older adults but to changes tacking place across the entire course of life span development and aging **(Brody, 1992).**

The main part of interest throughout this process was the years of adulthood where those before and after were considered as deviation from the norm rather than manifestation of shifting state of normality, accordingly upon facing a state of altered function it was found to be difficult to separate the effect of aging perse (engeric process) from that caused by disease process (pathogenic process) **(Kenny, 1989).**

The world health organization **(WHO)** developed a classification in which the elderly were those aged 60 to 75 years; the old aged from 76 to 90 years while the very old aged 90 years. This classification however had limited value in describing the physiology of aging which was believed to be a plastic process **(Kenny, 1989).**

Population aging is a world wide experience in north America-Japan- Europ-Australia and New Zealand as well as the farmer USSR, persons 65 years of age and older numbered 146 million in 1990 and represented 12% of the population.

By the years 2025 there regions older population is estimated to reach to 257 million. in Egypt in 1960 there were only 674, 661 individuals which represent 2.6% of the population over the age of 60

years and 333.361 individuals which represent 1.3% of the population above 65 years old.

In 1966 the number increased to 1.403 of subjects or 2.4% of the population above the age of 60 years, while those above 65 years were 824.502 or 1.2% of the population **(CAPMAS , 1990).**

Recently changes in the aging brain had become of great interest because of the marked increase in the number of elderly people surviving throughout the world. In studies concerned with the effects of aging on brain function are key topic was to distinguish healthy from the so called normal aging. (Marchal **et** al., 1992).

Different theories had been introduced to explain process of aging. The one that was readily opposed was termed the (error theory) proposing errors in protein synthesis occurring in structure of DNA molecules or information transferred to messenger RNA. A strong evidence against this theory was that the protein synthesis was similar in aged to that of newborn **(Kenney, 1989).**

Another explanation for the aging process was the genetic theory that was based on the concept that there was some genetic program that set the average upper limit of the life spine for all species i.e. all cells reproduced for a specific number of times and then died and the upper limit differed from one species to another **(Hayslip & Panek, 1989).**

It has been suggested by **Brody (1992)** that all loss occurs in structures that have appeared later in development e.g. in the cerebral cortex, the small sized cells which appeared later in development suffer

the first and largest amount of cell loss with age. This could be seen in the marked loss of associational cells which were considered bear the burden of integrating activity within the brain and were always believed to be the cell type most highly developed within the human brain **(Brody, 1992).**

Other non genetic cellular theories of aging were based on the idea that with passage of time changes took place in the structural elements of cells which would impair their effectiveness to function e.g. the wear and tear theory which assumed that as a result of use (wear and tear) different parts of human body finally become worn out.

However, this theory was not adequate as living organisms unlike machines have developed many mechanisms that permit self repair **(Heyslip and Panek, 1989).**

There are a relation between free radicals and aging; Free radicals were chemical intermediates containing as unpaired electron occurring normally in metabolic reactions where they were highly reactive and had a brief half life. These radicals were not free to differ within the cell which if happened would produce deleterious effects, cells protected themselves against the damage of the free radicals by the enzymes superoxide dismutase and glutathione peroxidase as well as compound containing thiol groups. there was limited evidence that as age progressed the free radicals increased or protective enzymes decreased in activity (**Walters and Calne, 1989).**

Banay-Schwartz et al. (1992) studied the activity of cathepsin. D, the major cerebral protease using hemoglobin as a substrate in separate

regions of the central nervous system of adults and aged subjects they reported that the enzyme activity increased with age in the thalamus hypothalamus, pons, medulla, cerebellum (containing the major portion of cerebral noradrenergic cells). On the other hand the enzyme activity decreased in the dorsal raphe area containing the major portion of cerebral serotonergic cells.

Normal morphologic characteristics in aging brain:

Both post mortem and in vivo imaging studies have demonstrated that advancing age in humans is generally associated with decrease brain tissues size and increased brain cerebrospinal fluid (CSF) volume **(Coffey et al., 1998).**

At the time of birth the weight of the brain was approximately 350 grams. It reached its maximum weight by the early twenties (approximately 1.4 Kg.) after which its started undergoing gradual decline so that by the age of 80 years. The weight loss was accompained grossly by reduction in the cortical areas with flattening of the gyri and widening of sulci, especially in the anterior halves of the hemisphere with slight increase in the size of the ventricles with normal cerebrospinal fluid pressure and increase in the space between the brain and its meninges **(Brody, 1992).**

Measures of cerebral atrophy have been reported to increase with age. white matter abnormalities have been recognized with T2-weighted MR imaging in a substantial number of elderly patients, both demented

and cognitively normal and although the histological alteration underlying these changes vary, both the severity and prevalence of white matter changes have been found to increase with age **(Tell et al., 1998). Hachinski et al. (1987)** proposed the term leuko-araiosis for these white matter abnormalities whose origin and significance are not known.

Coffey et al. (1998) studied the effects of sex on age related changes in the size of regional brain matter and CSF spaces in a large sample of elederly volunteers living independently in the community and their study demonstrated that age specific changes in brain size were significantly greater in men then women for the peripheral (Sulcal) cerebrospinal fluid volume, the lateral (sylvian) fissure cerebrospinal fluid volume and the parieto-occipital region area. Main effects of age were observed for all the remaining brain region examined (cerebral hemisphere volume, frontal region ,temproparietel region, lateral ventricular volume and third ventricle volumes) but these effects were similar in men and women. Also asymmetries in brain structure were not affected by aging in either sex.

Although **Condon et al. (1988)** found that men but not women exhibited a significant correlation between age and the ratio of total brain volume and also **Blatter et al. (1995)** found the same correlation, these correlations were not statistically compared. **Murphy et al. (1996)** reported that men had a significantly greater age related decrease in the ratio of cerebral hemisphere volume to then did women.

The literature is conflicting with regard to the effects of sex on age related changes in temporal lobe size, **Cowell et al. (1994)** and **Murphy et al. (1996)** found that men exhibited greater age related decrease in the ratio of temporal lobe volume to then did women. similarly **Golomb et al. (1993)** found that age related hippocampal atrophy was more common in men than women and **Raz et al. (1997)** observed greater age related inferior temporal volume loss in men than women, in contrast, **Murphy et al., (1996)** actually observed greater temporal lobe atrophy in women than men.

Despite differences in which sex is more affected the published results suggests that sex may impact the age related volume loss of the temporal lobe region. These findings may provide a neuroanatomical substrate for the sex differences noted earlier in age related verbal memory impairment. **Zelinski et al. (1993).**

The literature is also conflicting with regard to the effect of sex on age related changes in frontel lobe size. **Cowell et al. (1994)** and **Murphy et al. (1996)** both observed greater age related frontel lobe volume in man then in women in contrast other have found no sex effects **(Raz et al., 1997).** These discrepant results may reflect differences between studies in samples and brain measures techniques **Coffey et al. (1998).**

Brain morphologic characteristics in humans appears to be sensitive to the effects of both age and sex and converging data suggest that these 2 variables may interact over the life span to influence brain size. these data should provide a useful context within which to interpret

changes in regional brain structures associated with aging (Coffey et al., 1998).

The examination of cortical areas revealed significant cell loss in the frontal lobe (affect, awareness, personality), the superior temporal gyrus (hearing, memory), the occipital lobe (vision)
and the precentralgyrus. The cell loss in nuclei of the brain stem was stated to be unrelated to aging except for the locus ceruleus, a group of melonin containing cells in the pons, where the loss normally began after the age of 65 and further at the age of 80 where the final cell count in this structure should a 40% decrease when compared to that of younger subjects (Brody , 1992).

Neurobiological changes in aging:

The aging process involved the formation of inclusion bodies as lipofusin or aging pigments which was the one of structure constantly reported in aging cells. It had been proven that lipofusin was harmless being primarily toxic but then isolated by the living cells. If the cells failed to isolate the toxin they would die as can be seen in the small sized cells of the cerebral cortex which decreased in amount and did not accumulate lipfusin. However, it was thought possible that lipofuscin decreased the branching of dendrites and caused a loss of function. The amount of lipfusin had been proven to be modified by dietary vitamin E. thus indicating that they were the product of peroxidation of structural elements (Brody, 1992).

Other inclusion bodies were lewy bodies appearing in melonin containing cells of the midbrain and brainstem. After the age of 60, there was loss of the normal microtubular structures which were rearranged forming neurofibrillary tangles. Which were a characteristic feature in cases of senile dementia of Alzheimer type. Around this age neuritic (senile) plagues, which represented interstitial degeneration starting to appear Mainly in the cortex. It had been suggested that after neuronal loss, the aging brain would undergo a process similar to that occurring after brain damage where the surviving neurones restored the connecting circuit by axonal sprouting (Kenney, 1989).

Soderberg et al. (1990) reported that the protein content decreased in the 90 year old in the hippocampas, gray matter and nucleus caudatus in the white matter, protein content decreased as age advanced. The phospholipid content decreased only (5.10%) in the oldest age group. Cholesterol was present in all areas of the brain where it might remain unchanged or decreased up to 40%.

Biochemical changes in the brain may be reflected by CSF analysis, the analysis of neuronal and synaptic proteins in CSF may function as biochemical Marker for the neuronal degeneration in aging. One such neuronal protein is Tau protein, a normal human brain phosphoprotein which bind to microtubules in the neuronal axon, thereby promoting microtubule assembly and stability, high CSF Tau protein concentration may be present before onset of clinical dementia so follow up studies will tell whether analysis of CSF Tau is useful as a biological

marker for early Alzheimer's disease and the result so far suggest that CSF Tau may help to differentiate Alzimer's disease from several problematic differential diagnosis such as age associated memory impairment **(Andreasen et al., 1998).**

Young et al. (1991) carried out immunoblotting analyses of G-proteins (Guanidine binding proteins which when activated by receptors activated a second messenger cascade that modulated ion channel activity) to estimate semi—quantitatively the G protein subunits **in** the parietal cortex of healthy subjects of a wide range. They detect a significant decrease of the Gs (Which activated the enzyme adenyl cycles) and Gi-alpha subunit immunoreactivities with advancing age.

This decrease in the abundance of the G protein subunits would affect the function and response of the receptor effector interection mediated by the G proteins which suggested the possibility of this importance in cerebral dysfunction and development of neuropsychiatric disease in older age.

In young adults perfusion of the brain occurred at a rate of 50-60 ml/min/100 gram of brain tissue where less then 40 ml/min/100 gram was considered the minimum requirement to maintain full neuronal function. The rate of blood flow decreased 20% over the age period from 30 to 70 years old. Studies have indicated that both cerebral oxygen and glucose consumption were relatively maintained compared to the blood flow with the advance of age **(Kenney, 1989).**

Using the single photo emission computed tomography (SPECT) to assess cerebral blood flow (CBF) in the healthy subjects revealed a selective decline of the CBF in the frontel cortex as well as subcortical regions with advancing age (**Waldemer et al., 1991).**

Marchal et al. (1992) recorded age related decline in the cerebral metabolic rate of oxygen all over the cortex and attributed this to morphological and functional changes of aging neurons.

Function in the aging brain could be maintained at effective levels in the absence of an actual disease process because of plasticity and redundancy. plasticity and redundancy were Mechanisms used by nerve cells to make up for any changes in the environment of the nervous system so that the organism could continue to function in the presence of such alterations e.g. in the normal aging brain the neurons had the capacity to produce thickened dendrites with increased branching in case of dendritic loss while in senile dementia, the brain does not show this potential **(Brody, 1992).**

Normal neurochemistry changes in aging brain:

Aging was more likely to affect certain neurotransmitter receptors system rather than certain brain areas this was based upon reports of changes **in** the metabolism of neurotransmitter substances with the advance of age which had marked influence on both behavioral and regulatory systems **(Rinne, 1987).**

Neuronal loss was reported to occur in the locus ceruleus which were secretors of norepinephrine and accordingly inhibitors of sertonin

secreting cells in the neighboring median raphe area decrease in the level of catecholamine was Also due to decrease in the level of enzymes concerned with their synthesis as well as increase of the monoamine oxidase enzymes involved in the breakdown of the catecholamines in several parts of the brain with the advance of age norepinephrine decreased in the hindbrain by 40% to 50% between young age and the age of 70 **(Brody ,1992).**

Monoamine oxides (MAO) is a key enzyme in the degeneration of monoamine neurotransmitters. Two subtypes of MAO are known: MAO-A and MAO-B. Since platelet MAO is almost entirely of the B-type and since many of the alterations in MAO activity in mental disorders are caused by MAO-B changes. The usefulness of this peripheral model is evident as a marker for possible changes in brain MAO- B activity. In the platelets MAO-B activity has been found to increase slowly with age **(Regland et al., 1988).**

Rinne et al. (1990) investigated dopamine D_1 and D, receptors binding in the caudate nucleus and putamen in healthy, elderly subject where they concluded that both receptors decreased with advancing age while their Ratio Dl :D2 remained unchanged. The result showed that the dopaminergic system degenerated in the aging striatum and might contribute to the frequent occurance of extrapyramidal symptoms in the elderly.

The cholinergic system played a major role in memory and disorders like Parkinson's disease (PD) and Alzheimer's disease (AD) in

the aging brain there would be reduction in the concentration of acetylcholine secondary to decrease of choline acetyltransferase activity and increase of acetylcholinesterase activity. Glutamic acid decarboxylase responsible for the formation of gama amino butyric acid also might slightly decreased mainly in the thalamus **(Rinne et al., 1990).**

Coffey et al. (1998) suggested that there are sex Difference in brain aging. The neurobiological bases for these sex difference in brain aging are not known neuro-endocrinological difference between sexes have been proposed as a possible explanation given that gonadal corticosteroid affect brain development and aging, and that age affect both the function and regional distribution of androgen and estrogen systems in the brain **Cowell et al. (1994).**

HIGH COGNITIVE FUNCTION IN ELDERLY:

Psychomotor performance in elderly:

One of the most commonly observed changes with increasing age was slowing down in performance, the study of reaction time was concerned with the speed of the individual response to some external or internal stimulus or events. it was not just a simple motor response but involved other factors such as perception, sensation, attention, short term memory, intelligence, decision making, personality and motor behaviour **(Hayslip & Panek, 1989).**

The decline began around the age of forty with a rapid course, the subjects at the age of seventy completed almost half as many items as did

the thirty year old. The failure to accelerate speed of performance was suggested to be a deliberate attempt to avoid error in the presence of impaired cognition **(Goggin and Meeuwsen, 1992).**

The primary case of slowdown in behaviour and performance with age has not yet been known. It was attributed to the impairment of sense organs and/or peripheral nervous system **(Botwinick,** 1984).Yet this was found not to be accurate, as upon overcoming such disabilities e.g. increasing the stimulus tone in an auditory task above the individuals threshold, reaction time was still found to be delayed. It had been suggested that the decrease in reaction time started during middle age usually around the age of 45, so the deficits in the sensory receptors caused not account for the decrease **(Hayslip & Panek, 1989).**

Central explanations for the slowing down in performance with age included delay in neural transmission and difficulty in establishing expectation set, preparation time, which was the inability or difficulty of older subjects to prepare their response to the stimulus, as the more prepared they were to respond, the better they were more likely to perform. The difficulty encountered as the stimulus information increased could be explained by the individual's information processing system becoming overloaded and so they would not be able to perform quickly and correctly **(Hayslip & Panek, 1989).**

Hamberger and Frideman (1992) stated that reaction times were faster with repetition than with first presentation of the stimulus, this character being uninfluenced by the advancing age.

Visuospatial functions:

Faulty perception of spatial aspects of visual experience might lead to a number of disorders grouped under the heading of visuospatial. Among these disorders were the difficulties in judging direction and distance or length of stimului; impairment of the angle of orientation of lines or the length of the lines; impaired perception of depth and defective topographic orientation, people with these difficulties were often lost, apparently being unable to appreciate their spatial location using prominent landmarks as cues **(Kolb and Whishaw, 1990).** Among the tests to assess this function was facial recognition, decline in facial recognition memory performance showed significant decline as early as the age of 50 **(Crook & Larrabee 1992).**

Attention:

Attention played an important role in almost all areas of daily functioning. It involved vigilance which was the ability to maintain attention to a task for a sustained period. This ability was very important in activities requiring prolonged attention such as driving, computer programs and others. In such cases, older subjects showed easier fatigability than the young **(Hayslip and Panek, 1989).**

Ferguson et al. (1992) suggested that elderly people when asked to hear words originating from two speakers and had to monitor the source of the spoken words, they would need distinctive cues e.g. the voices would be that of a male and a female. On the other hand, they would find

it difficult if they had to make use of multiple cues (perceptual and spatial). While young would be able to use multiple cuses to enhance their source monitoring performance.

Memory and learning:

During learning all stage operated simultaneously. Since learning depended on information storage, all types of learning were based on memory and so could be viewed as parts of the same process after initial registration of new information, it entered immediate or short term memory upon second presentation, the information was added to that already entered in short term memory, which was recalled as the information became familiar. At the same time, data relevant to the new information was retrieved from long term memory and so finally the new information interpreted in the light of previous experience would be consolidated and stored in long term memory **(Hayslip & Panek 1989).**

Petersen and Weingartner (1991) stated that there was a wide range of terminology used to describe various components of memory and that different aspects of memory were sensitive to the aging process to a variable extent.

Most of recent research on memory in old age has been conducted within an information processing framework which divides memory functioning into several components sensory, primary, secondary and tertiary memory stores.

Researches reported little difference between young and elderly subjects as regards sensory and primary memory favoring young adults.

The slowing experienced in elderly people in the processing of information in sensory memory had been attributed to relative difficulty encountered by older persons in shifting attention rather than defects in sensory memory perse **(Hayslip & Panek, 1989).**

There had been observations as regards slight decrease with age in digit span performance, where digits of different span lengths (2-7 digits) were read to the individual and then he repeated it either in the same or reversed order. age influence was more marked for digits backwards which required more processing and storage effort than digits forwards **(Hayslip & Panek, 1989).**

Working memory was a term first introduced by **Hitch (1984)** and was an elaboration of primary memory. It emphasized the role of short-term storage processes in other tasks. **Foos & Wright (1992)** showed increased age difference on the storage working memory but no difference on processing working memory.

The working memory limitations affected the ability of elderly adults in the comprehension of reading tests with complex syntactic (formation of phrases and sentences from words) constructions **(Norman et al., 1992).**

Age difference were commonly found in measures of secondary memory (immediate or delayed recall of longer spans of digits paired - associates where pairs of words to be associated are presented together for a certain number of trials and designs) however more highly educated adults might maintain more efficient memory systems **(Hayslip & Panek, 1989).**

There is minimal evidence for a decrement with age in tertiary memory **Kausler et al. (1992)** observed from long term memory results that successful short term recall enhanced later long term recall regard less of age level.

Kausler & Wiley (1991) reported that prior retrieval of actions appeared to enhance later recal regardless of age provided that retrieval required considerable cognitive effort. **Bolla et al. (1992)** added that if the material could not be remembered immediately after its presentation, poor retention (delayed recall) would also be expected.

Petersen et al. (1992) evaluated two aspects of memory function thought to be sensitive in elderly subjects. One was learning (a cguisition) and one was delayed recall (forgetting). They concluded that learning declined uniformly with advancing age, unrelated to education while delayed recal remained relatively stable. The importance of these results lied in the fact that in case learning performance decline more rapidly than expected or if delayed recall was significantly impaired, disorder of brain function should be suspected.

West et al. (1992) suggested that the age factor was consistently the most significant predictors of memory performance. **Dartigures et al. (1992)** one the other hand reported a strong correlation between lifetime occupation and memory performance in visual recognition (Benton visual retention test) and verbal induced recall (wechsler paired associates tests) in elderly subjects. Independent of the educational level, the risk of poor memory performance was two to three times greater for farmers.

Lichtenberg & Christensen (1992) reported that there was no correlation between the scores obtained by elderly subjects in the logical memory sub-tests of the wechsler memory scale-revised with age, sex, education or race.

Hartikainen et al. (1992) suggested a link between the cholinergic system, EEG slowing and memory problems in old age. This was based on a 2 year follow up study which indicated deterioration in the learning abilities of some and increased delta activity upon spectral analysis of the EEG which was inversely related to acetylcholinesterase activity of the CSF.

According to animal experiments there were two fundamental processes in memory one was suggested as the mechanism of short term memory which was facilitation at the cholinergic synapses while the other was long term memory involving synthesis of memory specific peptides. The memory changes with aging were related mainly to cholinergic neurotransmission impairment **(Ray et al., 1992)** while to a minimum extent to impairmed protein synthesis **(Kenney, 1989).**

DEMENTIA

DEFINITION AND CLASSIFICATION

Trethwan (1979) defined dementia as a collective term applied to a group of chronic mental states resulting from severe generalized damage to the brain and causing irreversible intellectual deterioration with its associated symptoms.

Lipowski (1980) defined dementia as the organic brain syndrome characterized by an acquired decrement of intellectual abilities sufficiently severe to impair social or occupational performance or both, a full developed case features impairment of memory, abstract thinking and judgement, and some degree of personality change that is either an accentuation or an alteration of the patient's habitual character traits, the disorder may be progressive, static or reversible and is caused by widespread cerebral damage or dysfunction.

Bowen and Davison (1983), suggested the term brain failure instead of dementia which is a major disability where there is a global mental impairment particularly of short term memory with declining self care.

Mckhann et al. (1984) stated that the term Alzheimer's disease (AD) is used to refer to the disorder proved by histologic means. The term dementia of the Alzheimer type (DAT) refers to the disorder diagnosed by clinical research criteria, not histologically verified. (By this terminology, AD is the equivalent of "AD" in the usage suggested by the National Institute of Neurological and Communicative Disorders

Alzheimer's Disease and Related Disorders Association Work Group and DAT is the equivalent of their "probable AD").

Berg (1985) defined Alzheimer's disease as a progressive disorder marked by dementia and the accumulation of cortical neuritic plaques and neurofibrillary tangles in excess of those found in normal aging.

Vascular dementia is easy to define but difficult to apply. Problems arise from both the term vascular and the word dementia. Most individuals would agree that vascular applies to any event leading to strock, whereas they will disagree on whether chronic ischemia exist and whether the white matter changes seen on brain scans are ischemic or the end Result of multiple processes. No agreement prevails as to whether dementia does or does not imply global intellectual involvement, progression and irreversibility **(Hachinski, 1992).**

Dementia carries so many and contradictory implications that a new term has been suggested: "dysmentia" defined by specific criteria **(Hachinski, 1987),** a more practical solution may be for a definition of dementia to carry a description e.g. such as multi- focal cognitive impairment" preferably expressed in term a standardized set of neuropsychological tests. in retaining the term dementia it should be understood to be one extreme of a spectrum encompassing asymptomless "brain at risk" and a warning pre- dementia stage. The brain at risk stage represents individuals in whom symptoms or signs may or may not develop. Patient in the predementia stage have some cognitive impairment that may be focal and may not add up to a conventional definition of dementia **(Hachinski, 1992).**

The California Alzheimer's disease diagnostic and treatment centers (ADDTC) define dementia as deterioration in intellectual function sufficient to interfere with customary affairs of life, which is not isolated to a single category of intellectual performance and is independent of level of conscionsness **(Chui et al., 1992).**

The national institute for neurological disorders and stroke define dementia as impairment of memory plans at least two other cognitive domains, sufficient to interfere with activities of daily living **(Roman et al., 1993).**

Vascular dementia can be broadly defined as a cognitive impairment caused by changes in the blood circulation of the brain **(Gersing et al., 1998).**

Classifications:

In I.C.D. -10 (1992) dementia is classified under the heading of organic, including symptomatic, mental disorders as follows:

F00 Dementia, in Alzheimer's disease

F00.0 Dementia, in Alzheimer's disease ,with early onset.

F00.1 Dementia in Alzheimer's disease, with late onset.

F00.2 Dementia in Alzheimer's disease, atypical or mixed type.

F00.9 Dementia in Alzheimer's disease, unspecified

F01 Vascular dementia

F01.0 Vascular dementia of acute onset.

F01.1 Multi- infarct dementia.

F01.2 Subcortical vascular dementia.

F01.3 Mixed cortical and subcortical vascular dementia.

F01.8 Other vascular dementia.

F01.9 Vascular dementia unspecified

F02 Dementia in other disease classified elsewhere.

F02.0 Dementia in Pick disease.

F02.1 Dementia in creutzfeldt- Jacob disease.

F02. 2 Dementia in Huntington disease.

F02.3 Dementia in Parkinson disease.

F02.4 Dementia in human immunodeficiency virus (HIV) disease.

F2. 8 Dementia in other specified disease classified elsewhere.

F3. Unspecified dementia

A fifth character may be used to specify dementia in F00-F03 as follow.

x 0 without additional symptom.

x 1 other symptoms, predominantly delusional .

x 2 other symptoms, predominantly hallucinatory.

x 3 other symptoms, predominantly depressive.

x 4 other mixed symptoms.

A sixth character may be used to indicate severity of the dementia

- mild - moderate - sever

In DSM IV (1994) Dementia in classified as follow

290. xx- dementia of Alzheimer's type.

290. xx- early onset (age 65 years or below).

290. 11 with delirium.

290. 12 with delusions.

290.13 with depressed mood.

290. 10 uncomplicated.

290. xx - late onset (After age 65 years).

290. 3 -with delirium.

290. 20 -with delusions.

290. 21 -with depressed mood.

290.0 - uncomplicated.

290. 4x- Vascular dementia

290. 41 - with delirium .

290. 42 - with delusions.

290. 43 - with depressed mood.

290. 40 - uncomplicated.

- Dementia due to general medical conditions

294. 1 - dementia due to Hiv disease.

294.1 - dementia due to head truma.

294.1 - dementia due to parkinson;s disease.

294. 1- dementia due to Huntington's disease.

294.10 - dementia due to pick's disease.

294.10 - dementia due to creutzfeldt- Jakob disease.

294.1 - dementia due to general medical condition. not listed above .

- Substance induced persisting dementia.

- Dementia due to multiple etiologies.

294.8 - Dementia not otherwise specified.

EPIDEMIOLOGY AND RISK FACTORS

The epidemiological study of mental disorders over the past 15 years has been dominated by the large population- based surveys using standardized diagnostic interviews, such surveys, reveal a much higher prevalence of mental disorders than many would expect. however, one of great surprise of the epidomiologic catchment area studies was that elderly people had the lowest prevalence for all mental disorders, other than severe cognitive impairment if these finding is real and not an artifact of the method of assessment , it says something very important about aging as being protective against mental disorders. On the other hand, there has been concern that the finding may lead to eradication in resources for psychogeriatric care, clearly, this finding needs to be followed up. its there for of epidemiological attention **(Jorm, 1998).**

The epidemic of studies on dementia prevalence shows no sign of abating however on interesting paper come from the canadian study of health and aging. **(ErkinJuntti et al, 1997)** showing that the prevalence of dementia is greatly affected by the diagnostic careteria used, with rates varying by a factor of 10 (over 1800 participents in the canadian study of health and aging were diagnosed for dementia according to six commonly used systems the proportion with dementia varied from 3% (with international classification of diseases- 10 criteria) to 29% with diagnostic and statistical manuel of diseases volume 3) only 20 persons were diagnosed as demented by all six systems.) these findings show that there is no true prevalence of dementia, the prevalence rate depends on the definition adopted; the finding is not new but illustrates the problem

of applying a categorical conception of dementia in epidemiological field studies **(ErkinJuntti et al., 1997).**

Alzheimer's Dementia (AD) is the most common cause of dementia in adult worldwide. In 1991 the canadian study of heath and aging documented prevalence rates of dementia (8.0% among people over age 65, 28.5% among those over 85 and 58% among those over 95) and found that AD was the cause in 64% of all cases of dementia, whereas vascular dementia was present in only 19% of all cases **(Ebly et al., 1994).** Surprisingly large number (16.8%) of people over 65 had cognitive impairment but not dementia **(Graham et al., 1997).** The main risk factors for AD were found to be a family history of dementia, and a lower level of education whereas the main protective factors was a history of arthritis **(Cnadian study of health and aging 1994).**

These results are similar to those from other epidemiological research on AD in countries with populations of western European origin **(Katzman and Kawas, 1994).** In Japan, the relative predominance of vascular dementia over AD as a cause of dementia may be due to the rarity of opo E.4 in this population **(Poirier 1994).** Studies of prevalence and incidence rates and of risk factors between different countries may gives an important clues about the multiple factors apparently at play in AD, particularly with regard to age at onset of symptoms. its likely that the incidence of dementia (including AD) is increasing, given the growing elderly populations (**Kokmen et al., 1993).**

Mccracken et al. (1997) studied the prevalence of dementia among elderly people in black and ethnic minorities, this study was

designed to identify all elderly people of ethnic minorities living in a defined geographical area (in inner- city Liverpool), they found that forty - two people were diagnosed as suffering from dementia (24 English speaking plus 12 Chinese and six African non English-speaking). levels of dementia appear consistent across all English-speaking ethnic groups, but there appear to be high rates of dementia among non English-speaking black Africans and Chinese. non English-speaking black Africans have a 19% higher prevalence of dementia than English-speaking—similarly non English-speaking Chinese have a 15% higher prevalence of dementia than English speaking, so they found a higher prevalence of dementia among non English speaking members of any ethnic group than among the English- speaking members of the same group given that any diagnosis of dementia rests heavily on symptoms of disorientation in time and place, these symptoms may be open to misinterpretation where these are language problems, and the high levels of dementia in the non English-speaking group can either be attributed to high levels of the condition or to an artefact of the interviewing methods or because of difficulties of communication or cultural differences in the presentation of symptoms.

It has been estimated that 10% of the population over 65 years suffer from mild to moderate dementia while 4-5% suffer from sever dementia. above the age of 80 years it may reach up to 30-40%. in Egypt those above 65 years are 4.5% of our population (60 million) so its expected to have about 250.000 suffering from dementia, Alzheimer constitute about 60% of cases of dementia (**Okasha, 1998).**

Rafaat (1998) studied the prevalence of Alzheimer's disease and other dementia in Assiut and upper Egypt this a 3 phase cross - sectional population based study was carried out to screen 2000 subjects residing eleven different locations representing the socioculture status of the area revealed that 90 demented subject yielding a crude prevalence ratio (case per 100 population over the age of 60) of 4-5. Diagnosis of subtypes of dementia was reached in 83 causes prevalence ratios for dementia subtypes were 2.2 for Alzheimer; disease, 0.95 for multi infarct dementia, 0.55 for mixed dementia and 0.45 for secondary dementia .age specific prevalence tends to be doubled every 5 years occupation, level of education and residence did not affect the prevalence or severity of dementia. comparison with other studies suggests that dementia of all types is as frequent in Assuit governorate as elsewhere.

Jorm (1997) studies the incidence of risk factors for Alzheimer's Disease he listed the only confirmed risk factors as follows: old age, family history, apolipoprotein E genotype and down's syndrome.

Evidence continues to accumulate that genetic factors are very important in Alzheimer's disease. Two Scandinavian twin studies **(Bergem et al, 1997)** and **(Gatz et al., 1997)** estimated the heritability of the disease to be 0.6 and 0.74 respectively several mutitions causing autosomal dominant forms of Alzheimer's disease are now known and apolipoprotein E (apo E) genotype is firmly established as a risk factor. A metaanalysis of apo E studies **(Farrer et al., 1997)** found that the E4 allele is a risk factor across all ages in both sexes and in all ethnic groups.

Several epidemiological studies have reported evidence that oestrogen replacement therapy is protective in women **(Henderson, 1997)** interest also continues in the possibility that Alzheimer's disease involves an inflammatory process and that anti inflammatory drugs are there fore protective, **Stewart et al. (1997)** reported that use of non steroidal anti-inflammatory drugs for 2 years or more halved the risk of the disease. evidence also continues to accumulate that a high level of education might be protective for Alzheimer's disease and dementia generally

Evons et al. (1997) reported that risk of the disease decreased by 17% for each year of education over the past year evidence has been presented that risk for the disease my be increased by diabetes mellitus, the insuline resistance syndrome and anemia and may be lowered by wine and fish consumption. It has also been reported that herpes simplex virus type **I** in the brain acts synergistically with the apo E 4 allele to increase risk for **(Jorm, 1998).**

Schoenberg (1986) stated that descriptive epidemiological studies demonstrate that the risk for dementia in general and of Alzheimer's disease in particular increasing with advancing age and the risk appear to the slightly greater among women.

The main risk factors for AD were found to be a family history of dementia and a lower level of education whereas the main protective factor was a history of arthritis, studies of prevalence and incidence rates and of risk factors between different countries may give us important clues about the multiple factors apparently at play in AD, particularly

with regard to age at onset of symptoms its likely that the incidence of dementia (including AD) is increasing, given the growing elderly populations, knowledge of risk factors may allow a preventive approach in the future. **(Gauthier et al., 1997).**

Cardiovascular disease and Alzheimer's disease are both common with increasing age but evidence is accumulating that there is more than a chance association, Alzheimer's disease and cardiovascular disease may share common risk factors such as hypertension **(Skoog et al., 1996),** non insulin dependent diabetes mellitus **(Libson et al., 1997),** smoking **(Ott et al., 1997),** and apo E4 Allele **(Noguchi et al 1993).**

Use it or lose it hypothesis proposes that higher educational and occupational levels have a protection effect against Alzheimer's disease. three mechanisms may mediate this one is the establishment of a cognitive reserve, perhaps as more synapses or more efficient synapses such that more have to be lost before, the disease is manifest so delaying onset. the second is that increased intellectual activity may enhance brain repair and recovery mechanisms so slowing the rate of progression finally other brain regions may take over the functions of those affected early in the disease **(Stern et al., 1995)** but **(Bowler et al., 1998)** concluded that neither the reported age of onset nor the rate of progression of Alzheimer's disease with or without coexisting cerebrovascular disease are influenced by education or occupation.

Letenneur et al. (1999) studied the age and educational level as a risk factors for dementia and concluded that women have a higher risk of developing dementia after the age of 80 then men and low educational

attainment is associated with a higher risk of Alzheimer's disease, however, the increased risk in women is not explained by a lower educational level.

The Canadian study of heath and aging by **Lindsay et al. (1997)** reported that risk factors for vascular dementia was associated with history of arterial hypertension, history of Alcohol abuse, history of heart condition, use of aspirin and occupation exposure to pesticides, herbicides, liquid plastic or Rubber.

Barba et al. (2000) concluded that dementia is frequent after ischemic or hemorrhagic stroke, age, nephropathy, atrial fibrillation, previous mental decline and stroke severity.

Geldmacher **and Withehouse (1996)** confirmed the importance of the following as a risk factor for vascular dementia.

- Auto immune vasculitis:

-Systemic (e.g. lupus erytheromatosus).

- Central nervous system (e.g. granulomatas angitis).

- Infections vasculitis:

Neuro syphilis.

Lyme disease.

- Non specific vaculopathy.

Binswangers disease.

-Posthemorrhagic obstructiv **hydrocephalus.**

- Recurrent small emboli.

-Endocarditis.

- Atrial myxoma.

-Recurrent intracerebral hemorrhages.

- Hypertension.

- Amyloid angiopathy.

- Stroke.

-Embolic (hemispheric large vessel).

-Thrombotic (lacunar, small vessel).

- Subarchnoid hemorrhage.

- Subdural hematoma.

-Other

- Diabetes mellitus

- Heart disease

-Hyperlipidemia.

- Atrial fibrillation.

- Hypotension.

-Genetic.

Apolipoprotein E.4.

-Environmental / Sociel.

-Smoking.

- Excessive Alcohol consumption.

- Exposure to fertilizer.

- Exposure to pesticides.

- Lower levels of education.

AETIOLOGY

Caine et al. (1986) hypothesised that Alzheimer's disease, Parkinson's disease **(PD),** and motorneurone disease are due to environmental damage to specific regions of the central nervous system and that the damage remains subclinical for several decades but makes those effected especially prone to the consequences of age-related neuronal attrition, this proposal is based on the association between environmental factors and certain neurodegenerative diseases (eg, methylphenyl, tetrahydropyridine and parkinsonism, poliovirus infection and post- poliomyelitis syndrome, chickling pea ingestion and lathyrism, an undientified environmental factor and amyotrophic lateral sclerosis-PD complex of Guam, and trauma and Pugilist's encephalopathy) and on the long latent period between exposure to environmental factor and the appearance of the symptoms in some of these disorders.

Dementing illnesses have been characterized clinically and pathologically, but most etiologies are not known. Silicon and aluminum have been linked to Alzheimer's disease by studies of senile plaques **(Nikaido et al., 1972 & Perl and Brody, 1980).** Aluminum has been found in elevated concentrations in brain by **Crapper et al., 1973,** but not by others **(Markesbery et al., 1981; McDermott et al., 1979).** Manganese toxicity causes a syndrome resembling parkinsonism **(Mena, et al., 1976),** and elevation has been reported in one case of dementia with extrapyramidal signs **(Banta and Markesbery, 1977).** Zinc deficiency has also been suggested as a cause of Alzheimer type dementia (ATD) **(Burnet, 1981).**

Hershey, et at 1983 said that the finding of elevated CSF silicon and zinc in some patients with ATD suggests several hypotheses. ATD may be a mixed syndrome; elevated CSF silicon could be a marker of one lesion, zinc of another, the second is that ATD patients have an inherited disorder of silicon metabolism, which is manifest as dementia according to the exposure of the patient to silicon, the third hypothesis is that CSF silicon becomes elevated only after sufficient progression of the disease, and finally, CSF silicon elevations may be more likely in ATD patients who experience a subsequent cerebral infarction.

Wells (1985) said that the cause of dementia is multi-factorial in the sense that Psychological and social factors influence its occurence, severity and course.

It is likely that the etiology of dementia is multifactorial; hence the majority of cases cannot attributed to genetic factors alone, indicating that environmental factors may modulate the onset and/or progression of the disease. Head injury and infectious agents are environmental factors that have been periodically implicated, with regard to infectious agents, speculation has often centered on the neurotropic herpes viruses, with herpes simplex virus- 1 (HSV- 1) considered a likely candidate (Cribbs et al., 2000).

The following list demonstrate the diseases and conditions that may produce dementia Asbury et al. (1992)

- Alzheimer's disease a – Vascular dementia b.

Varieties :

- Multiple infarcts (called multi infarct dementia).

- Lacunae.
- Binswanger'sdisease.
- Cortical microinfarction.

- Drugs and toxins including chronic alcoholic dementia).c
- Intracranial masses : c
  - Tumors.
  - Subdural masses.
  - Brain abscesses.
- Anoxic.
- Truma:-
  - Head injury c
  - Dementia pugilistica (Punch. drunk syndrome).
- Normal pressure hydrocephalous.c
- Neurodegenerative disorders.
  - Parkinson's disease d
  - Huntington's disease d
  - Progressive supranuclear palsy d
  - Pick's disease d.
  - Amyotrophic latral sclerosis.
  - Spino cerebellar degeneration.
  - Livo ponto cerebellar degeneration.
  - Ophthalmoplegia plus.
  - Metachromatic leukodystrophy (adult form).
  - Hallervorden. spatz disease.
  - Wilson's disease.

- Infections
    - Creutzfeldt - Jakob disease.
    - AIDS d
    - Viral encephalities.
    - Progressive multifocal leukoencephalopathy.
    - Behcet's disease.
    - Neurosyphities.
    - Chronic bacterial meningitis.
    - Cryptococcal meningitis.
    - Other fungal meningitides.
- Nutritional disorders:
    - Wernicke- korsakoff syndrome (Thiamine dificency).
    - Vitamin B12 deficiency.
    - Folate deficiency.
    - Pellagra deficiency.
    - Zinc deficiency.
- Metabolic disorders
    - Metachromatic leukodystrophy.
    - Adrenal leukodystrophy.
    - Hypo thyroidism.
    - Hyper Thyroidism.
    - Renal insufficiency (sever).
    - Cushing's syndrome.
    - Hepatic insufficiency.
    - Parathyroid disease.

- Chronic inflammatory disorders d

- Lupus.
- Other collagen- vascular disorders with intracerebral vasculitis.
- Multiple sclerosis.
- Whipple's disease.

N-8:

a Accounts for 50 to 60 percent of cases.

b Accounts for 10 to 20 percent of cases.

c Accounts for 1 to 5 percent of cases.

d Accounts for about 1 percent of cases.

No symbol: less then 1 percent of cases.

Other causes: Other causative theories have been proposed to explain the development of Alzheimer's disease. One theory is that an abnormality in the regulations of membrane phospholipid metabolism results in membranes that are less fluid- that is more rigid than normal .Aluminum toxicity has also been hypothesized to be a causative factor, because high level of Aluminum have been found in the brain of some patients with Alzheimer's disease but this is not considered a significant etiological factor **(Kaplian and Sadock 1997).**

Genetics:

Familial aggregation of Alzheimer's disease has been noted for decades and suggests a complex etiology that is composed of genetic and environmental factors several lines of evidence including twin studies,

family studies and population based epidemioloic surveys, support a genetic component in the etiology of Alzheimer's disease **(Scott, 1998).**

One method for determining whether atriat in genetic is to look for increased concordance rates in identical (monozygotic) versus fraternal (dizygotic) twins; concordance rates for monozygotec twins were two to four times greater than for dizygotic twins, supporting role for genes in the etiology of Alzheimer's disease. A second method of evaluating the genetic contribution to the etiology of a disease is to calculate a recurrence rate ratio (2) to compare the recurrence rates in the relative of patients sufferer from Alzheimer's disease with the general population prevalence, in general the higher the (A) the greater the evidence for familial risk of disease **(Scott, 1998).**

Many families in which Alzheimer's disease (AD) aggregates in an autosomal dominant fashion have been described. The initial approach to linkage studies in AD was to follow a candidate chromosome approach rather than a systematic genomic search, the reason for this was the frequent occurance of dementia with Alzheimer's pathology in aging down's syndrome (Trisomy 21). It therefore seemed reasonable that a gene on chromosome 21 present in triplicate in down's could be related to AD, **STgeorge-Hyslop et al. (1987)** reported linkage between the polymorphic loci D21 S 1/sll and D21S16 on the proximal long arm of chromosome 21 and AD in four early onset kindreds.

This finding hen been conformed in other studies **(Goat et al., 1989).** Two other studies however have found absence of linkage of

familial Alzheimer's disease to D21 S1/sll **(Pericak Vance et al., 1988)** and **(Schellenberg et al., 1988)** pooling of linkage data by a large collaborative study **(StGeorge-Hyslop et al., 1990)** suggested that AD is not a single entity. But result from genetic defects on chromosome 21 and from other genetic and/or non genetic factors.

Much excitement was generated by the cloning and localization of the B-amyloid precursor protein (B-APP) gene to the general region of chromosome 21 implicated in linkage studies **(Goldgaber et al., 1987).** Since the Alzheimer plague a key pathological feature of the disorder is principally composed of A4 amyloid derived from the product of this gene, the B APP gene was clearly a strong candidate gene for familial AD.

However the disease and B APP gene indicating that the AD gene and B APP were separated by a considerable genetic distance and apparently excluding B APP as the AD gene, at least in these families **(Walsh et al., 1992).**

However in a single family with Alzheimer's dementia at autopsy with chromosome 21 markers by **Goat et al. (1991).** Where a point mutation causing an amino acid substitution of isoleucine for valine was found. Close to the carboxy-terminus of the B-amyloicd gene (**Walsh et al., 1992).**

The greatest evidence that the disease has a complex genetic etiology is that four genes underlying the disease have already been identified. Mutation in three of these genes, those for amyloid precursor protein (APP) **(Goat et al., 1991).**

Presenlin-1 **(Shernington et al., 1995)** and presenilin-2 **(Levy-lahad et al., 1995),** case autosomal dominant early- onset (age of onset (AO) < 65 years) of Alzheimer's disease. Clinical research in autosomal dominant early onset Alzheimer's disease has recently focused on the phenotype associated with mutations at the three loci. The phenotype associated with presenilin-1 includes an early AO (25-65 years), rapid progression of disease (duration **2-17** years) and fairly consistent age at onset among members of the same family. In comparison, the age at onset in families with presenilin-2 mutations is often later (40-88 years) and more variable with significant interafamilial variation in age at onset and less severe course of disease (duration 5-23 years) **(Bird et al., 1996).**

Another study reported that the phenotype for Alzheimer's disease associated with two presenilin-1 mutation (A 290-319 and R 278T) included familial spastic paraparesis in some affected family members. Becouse one familial spastic paraparesis gene (SPG —3) and presenilin-1-gene both map to chromosome 14g, **(Kwok et al., 1997).**

Apolipoprotein (APO) E is the fourth Alzheimer's disease locus and is the single most significant biological risk factor identified for the disease. APO E is a susceptibility gene for Alzheimer's disease that is, neither necessary nor sufficient to cause disease. APOE has three common alleles (APOE-2, APOE-3 and APOE-4) and the APOE-3 allele is the most fregment in almost all population, studied the APOE E-4 allele acts in dose dependent manner to increase risk and reduce the age at onset in early—onset, sporadic and late — onset sporadic and familial Alzheimer's disease **(Corder et al., 1993).**

The APOE-2 allel exerts a protective effect on the risk of late onset Alzheimer's disease (Farrer et al., 1997), on observation supported by a recent neuropathologic, study that detected decreased B-amyloid deposition in patients suffering from Alzheimer's disease with an APO-E-2 allele. However, the effect of APOE-2 on risk of early onset sporadic Alzheimer's disease is unclear with some studies reporting an increase in risk due to APOE-2 (Van DuiJn et al., 1995) and other finding no such increase (Scott et al., 1997).

Variation in the APOE-4 associated risk by age ethnicity and sex has often been reported.several studies including a recent population based study of incident Alzheimer's disease in African,American suggest that its risk is only significantly elevated in African, American with two copies of the APOE-4 allele (e.g. the APOE-4/4 genotype) (Farrer et al., 1997). Also recent reports have supported that APOE-4 has its maximum influence on Alzheimer's disease risk before age 70 years (Bickeboller et al., 1997). Increased risk in women has been suggested to be caused by sex specific susceptibility to the disease in APOE-3/4 heterozygotes (Payami et al., 1996). But not all data support such a conclusion (Bickeholler et al., 1997).

The search for additional genes for Alzheimer's disease has resulted in an explosion of association studies (Table 1) of biologically plausible candidate genes, the large number of putative genes recently reported and the conflicting evidence for each requires that each association be examined critically before concluding a genetic effect

exists at that locus, compared with the widespread independent confirmation of the effect of APOE-4 allele, the evidence for each of these putative candidate genes should be regarded equivocal at best (Scott, 1998).

Table (A): Studies of selected candidate genes for Alzheimer's disease.

Gene	Association reported	No association detected
a-antichymotrypsin (ACT)	Kamo-H et al. (1995), Yoshiwa et al. (1997), Talbotc et al. (1996), Higuchi et al. (1997), Morgan et al. (1997)	Hainesetal (1996), Nacmias et al. (1996), Christie et al. (1996), Fallin et al. (1997), Didierjean et al. (1997), Murphy et al. (1997)
Presenilin (PSI)	Wragg et al. (1996), lose e al. (1996)	Scott et al. (1997), Korovaitseva et al. (1997)
Very low density lipoprotein receptor (VLDL-R)	oKuizumi et al. (1995)	Tang et al. (1996), Lendon et al. (1997), Pritchard et al. (1996), Fallin et al. (1997)
Low density lipoprotein receptyors related protein (LRP)	Lendon et al. (1997), Wavrant-Devrieze et al. (1997) and Kang et al. (1997)	Clatworthy et al. (1997), Scott et al. (1998)
Major histocompatibility complex (HLA)	Curran et al. (1997) and Payami et al. (1997)	
Dihydrolipoamide succinyl transferase (DLST)	Nakano et al. (1992)	
Serotonin transporter gene (SLC6A4)	Li et al. (1997)	
Butyrycholinesterase Kvariant (BCHE-K)	Lehmane et al. (1997)	
Mitochondrial polymorphisms	Changnon et al. (1996)	

An alternative approach to gene identification is to perform a genomic screen in families with Alzheimer's disease, identify regions with a high probability of harboring disease gene and perform candidate gene analysis only in those regions of interest. Such a genomic screen was recently completed and identified regions of interest on

chromosomes 4,6,12 and 20. The chromosome 12 region is located approximately 30 centim organs from low- density lipoprotein receptor—related protein (LRP.) one of the candidate genes for which evidence of association is conflicted **(Scott, 1998).**

The role of genetic factors has not been well defined for vascular dementia. This is not surprising because the role of genetic factors in stork has not been studied thoroughly **(Georelick, 1995).** Autosomal dominant hereditary cerebral hemorrhage with amyloidosis—Dutch type is uncommon as are familial vascular encephalopathies such as hereditary multi-infarct dementia and cerebral antosomel dominant arteriopathy with subcortical infarct and leuko-encephalopathy. **In** addition there is apaucity of information on the role of apolipoprotein E- polymorphism in vascular dementia **(Geore Lick, 1997).**

The gene frequency of APOE-4 allele has been show to have a threefold increase in late onset Alzheimer's dementia in addition there is a two-fold increase in the prevalence of APOE-4 allele in vascular dementia **(BenJamins et al., 1994).**

Wieringa et al. (1997) investigated the postulate that because the apoE-4 allele is a mediator of increased serum cholesterol and cholesterol fraction, low density lipoprotein (associated with atherosclerosis than high level of cholesterol) and low density lipoprotein levels were a risk factor for vascular dementia, weringea et al found that the evidence did not support this postulate and that the increased level, of apE-4 allel was not related to serum lipid levels.

KolmiJn et al. (1996) on the other hand found that the apo-E4 in combination with cerebral disease increased the risk of cognitive decline. In addition the risk for cognitive decline was found to be highest in patients with apoE-4 allele, and elevated cholesterol to high fibrinogen levels, Diabetes mellitus and normal blood pressure.

Bergem et al. (1997) concluded that heredity is a major factor in late onset Alzheimer's dementia, Where environmental or non — here ditary factors are most important in vascular dementia these finding do not rule out the possibility that susceptibility genes may have a role in vascular dementia.

PATHOLOGY

Dementia was once regarded as a unitary disorder of brain failure with homogeneous mental status alterations, but recent studies of intellectual changes in specific disease processes reveal that dementia has variable manifestations, and that the nature of the cognitive and behavioral alterations can be correlated with the distribution and severity of brain pathology, Alzheimer disease (AD) is the most common cause of dementia in the elderly, the clinical diagnosis of probable AD can only be confirmed at autopsy by the neuropathological demonstration of neurofibrillary tangles (NFTs) and senile plangues (sp) in the neocortex and hippocampus (**Gattaz et al., 1995).**

Cummings and Benson (1984) reported that anatomically, the cortical pattern is produced by diseases involving primarily, but not exclusively, the association cortex of the cerebral hemispheres and the medial temporal lobes whereas the subcortical pattern occurs in disorders, with predominant involvement of basal ganglia, thalamus and brain stem structures.

Alzheimer's disease and pick's disease are examples of cortical dementing processes; the dementia syndromes associated with the extrapyramidal disorders (Huntington's disease, parkinson's; disease, progressive supra nuclear palsy etc) exemplify the subcortical pattern of intellectual impairment.

McDuff and Sumi (1985) said that although Alzheimer's disease is generally considered a degenerative disease that primarily affects the

cerebral cortex, substantia innominata and certain brainstem nuclei may be involved, they found in a study of 28 patients with progressive dementia pathologically confirmed Alzheimer's disease, senile plagues and neurofibrillary tangles in the thalamus in 25 patients, in the hypothalamus in 22, and in the mamillary body in 17, and they concluded that the severity of these lesions seemed to be greater in those with presenile onset of dementia, they added also that Alzheimer's disease is a much more diffuse disorder than in usually appreciated.

Gibb (1989) said that pathology is present in subcortical regions in Alzheimer's disease and in cortical regions in Parkinson's disease. headed that in cortical or temporo —parietal dementia, the amnesia and cortical deficites are believed to result from hippocampal and neocortical pathology, comprising nerve cell loss with accumulations of neurofibrillary tangles and senile plagues and pathological changes also occur in the nucleus basalis of meynert, locus ceruleus, raphe nucleus and substantia nigra while searches for the pathological substrate of subcortical or fronto- limbic dementia have included the nucleus basails, ventral tegmental area, thalamus, and substantial Nigra.

Alzheimer's disease (AD) is a progressive Neurodegenerative disorder with characteristic clinical and pathological features .terms such as senility, retouren enfance and hardening of the arteries that had been used to describe this condition reflect the nature of Alzheimer's disease. It usually occurs in old age. It is associated with also of functional autonomy, and its often brought on by cerebrovascular changes

superimposed on synaptic and neuronal loss. The precise cause in the last category is still unclear, and it may differ greatly between early onset AD (occurring as early as age 40 and up to age 65 and late onset AD (occurring after age 65) **(Gauthier et al., 1997).**

The relative importance of the various neuropathological features of AD has been the subject of much debate **(Terry et al., 1994).** It is known that progressive synaptic and neuronal loss occurs in the cerebral gray matter, leading to cortical atrophy. This is most prominent in the temporal and hippocampal structures and leads to hippocampal atrophy, as detected by MRI. Other important pathological changes in the sequence of events leading to neuronal death include amyloid deposition in the extracellular space and around blood vessels, neurofibraillary tangle formation within neurons and localized inflammation associated with acute phase reactants, finally there is a significant loss of white matter, as demonstrated by subcortical atrophy in late stages of A.D. in part because of small vessels atherosclerosis (Leukoaraisosis) and cerebral amyloid angiopathy and in part because of loss of long axonal processes., the loss of neuronal cell bodies in the nucleus basalis of meynert **(Etienne et al., 1986)** had suggested the possibility of a nucleus specific illness (similar to the substantia nigra in Parkinson's disease) but more recent evidence indicates a diffuse pathological process involving medium Sized cortical neurons, particularly those using acetylcholine as a transmitter in the hippocamus and those found in associative temporal and parietal regions. The reason for this relative vulnerability is unknown but it may have to do with impaired plasticity or repair mechanisms,

which are to great extent driven by apolipoprotein E (apoE) gene type (Bireier, **1994).**

Berg et al. (1993) concluded that neocortical senile plague (sp) densities differentiate very old Alzheimer's disease subjects from non demented, but there is a need for more postmortem studies of old people demonstrated to be free of dementia, reports of numerous neocortical senile plague densities in the apparent absence of dementia had provided a case in point **(Crystal et al., 1988).**

In an study, the authors concluded that non demented old people whose brains have (sp) densities that exceed minimal criteria for AD should be considered to show pathological aging (but not AD) in contrast to "normal aging" i.e, not associated with cerebral amyloid deposition **(Dickson et al., 1992). Berg et al. (1993)** posited that some of those people with pathological aging may already have had very mild AD that might have been diagnosed by more sensitive methods. Their have since reported on the clinical indications of slight cognitive decline in some of control subjects shortly before their death and the replications of those minimal clinical changes for the finding of abundant neocortical amyloid containing sps, deposite the lack of overt dementia **(Morris et al., 1996).**

Berg et al. (1993) concluded also that among the microscopic lesions studied, densities of neocortical neurofibrillary tangles (NFTs) were most closely related to the degree and duration of dementia, Densities (counts per square millimeter) of total neocortical sp's., were not related to severity of dementia in the subjects with AD but cored neocortical plague densities were.

Berg et al. (1998) concluded that there was significant relationship between dementia severity and NFT, densities in all regions, the NFTS were less dense in neocortical compared with hippocampal regions, furthermore, the relation of NFTS to dementia severity varied for neocortical compared with hippocampal regions, the NFTs **in** the neocortex were substantially correlated with dementia severity, the correlations with dementia severity were more modest in the hippocmpal and entorhinal regions and the increase in NFTs occurred in the milder stages of the disease. Both total and cared SPs, were more prevalent in neocortical than hipocampal or entorhinal regions, carded plagues demonstrated a stronger, relation to dementia severity than did total or neuritic plagues, especially in neocortex. Neocortical cored SPS did not increase substantially until the severe stage of the disease, diffuse plagues were equally prevalent at all stages of severity. Neocortical NFT densities were significantly correlated with duration but those in hippocampal and entrohinal regions were not, total SPs, in temporal and parietal cortex were correlated with duration but not in frontal cortex or hippocampal or entorhinal regions.

In the last few years, there have been 2 major advances, the apolipoprotein E (apoE) genotype, especially the E4 allele, has been recognized as a major risk factor for late onset AD that lower, the age at onset and has been reported to increase the extent of B-amyloid deposition in brain parenchyma and in cerebral and meningeal blood vessels **(Olichney et al., 1996).**

The second recent advance is the recognition that cortical lewy bodies are often found in the brains of those older individuals with "plague only" or "plague predominant" AD (lewy body variant of AD) **(Hansen et al., 1993).**

Alzheimer disease (AD) is characterized neuropathologically by the presence of amyloid beta-peptide (A beta)-containing plaques and neurofibrillary tangles composed of abnormal Tau protein, **Naslund et al. (2000)** concluded that the level of (A beta) are elevated early in dementia and were strongly correlated with cognitive decline of particular interest, in frontal cortex, A beta was elevated before the occurrence of significant Tau pathology.

Dementia with lewy bodies **(Mckeith et al., 1996)** is a recently described condation in which autopsy examination of the brain of patients with dementia reveals diffusely distributed cortical and subcortical lewy bodies while some of these patients are found to possess only lewy body pathology, most have concomitant Alzheimer's disease (AD) pathologic features. Those patients with dementia and lewy bodies also manifest sufficient AD pathologic features are referred to as having the lewy body variant (LBV) of AD **(Hansen et al., 1990)** while senile plague distribution in LBV is similar to that in pure AD, Neocortical neurofibrillary tangles are absent or rare and entorhinal and hippocampal tangle count are intermediate between those of elderly controls and patients with pure AD, lewy bodies in LBV occur both neocortically and in the more common subcortical distribution (substanti nigra—locus ceruleus, substantial innominate and dorsalvagus nucleus) typically associated with Parkinson's disease **(Cannon et al., 1998).** controversy exists as to whether Parkinson's disease (PD) and dementia with lewy

bodies (DLB) including diffuse lewy body disease and lewy body variant of Alzheimer's disease (AD) (**Mekeith et al., 1996),** represent 2 distinct nosologic entities or whether they exist a long the spectrum of a single disorder, lewy body disease **(Perry, 1996)** such debate is the logical consequence of the considerable overlap of clinical and neuropathologic features in disorders associated with lewy bodies for example, extrapyramidal may be found in many patients with severe AD and dementia in many patients with PD **(Litvan et al., 1998).**

The demonstration a-synuclein, but not B-synuclein is major composition of lewy bodies (LBS) in sporadic PD and DLB **(Spillantini et al., 1997)** are likely to stimulate increased research on LB, and to prompt a reassessment of the role played by LBs in the pathogenesis of these disorder, since the mutation described in familial PD leads to an alanine to threonine substitution at position 53 (A 53t) in the a- synucline protein, this mutation could alter the biophysical properties of a synuclein, a poorly understood protein that is expressed primarily in neurons, where its localized predominantly at axon terminals or synapses, these the A53T mutation in asynuclein could predispose this normally soluble protein to aggregate or interact aberrantly with other protein (e.g. NF subunits)leading to the formation of LBs and the degeneration of affected neurons **(Goedert , 1997).**

Moreover, the report of the widespread presence of a synuclein in perikaryal LBS and in dystrophic neuronal processes of sporadic PD and DLB brain is highly significant for undestanding the pathogenesis of these disorder, because this finding implies that wild type a synuclein may aggregate alone or with other proteins into LB's and dystrophic neuritis. Nonetheless it remains to be determined if genetic or epigenetic

factors might perturb the metabolizes, solubility or interactions of a sunuclein in sporadic PD and synuclein in dystrophic neuritis. However its plausible that these lesions also could compromise the survival of affected neurones in those nonhereditary LB disorder, ultrastructural examination of LB, has revealed masses of aggregated 7 to 25mm diameter filaments that appear similar to neurofilaments (NFs) but the precise molecular composition of LBS, including the abnormal filaments in these intracytoplasmic neuronal inclusions, remains to be clarified, indeed the biological significance of LBS especially the role that they might play in the degeneration of neurons in LB disorders is still enigmatic **(Trojanowski and Lee, 1998).**

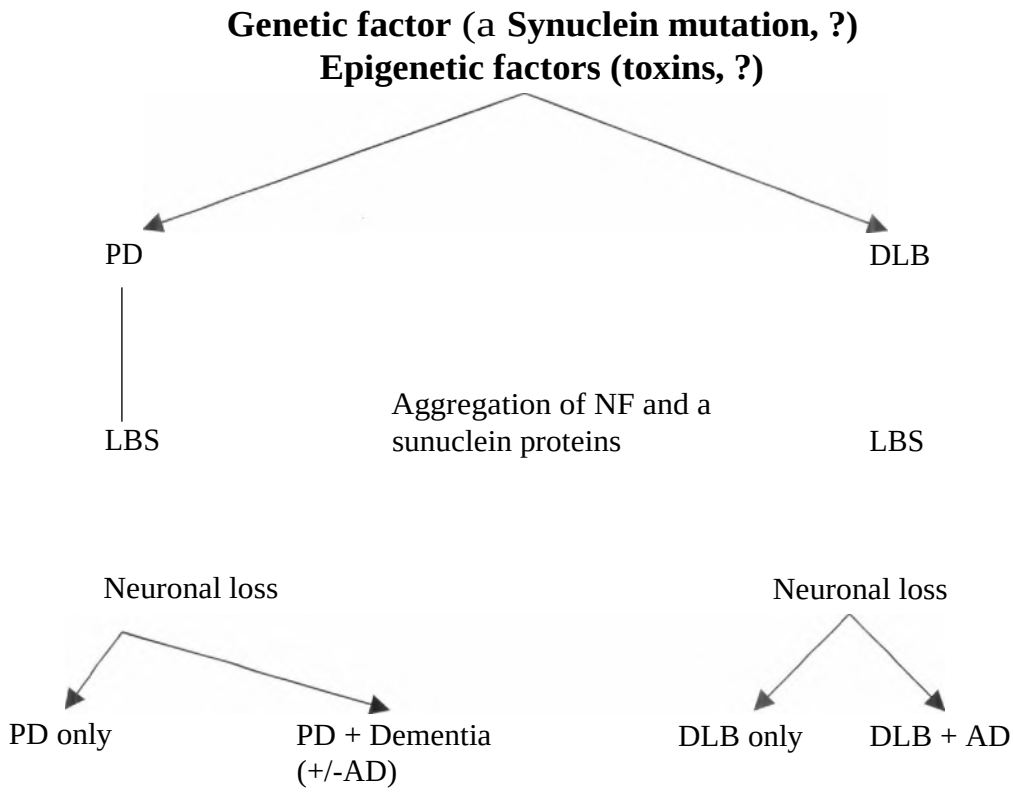

Fig. (1): Schematic summary of the spectrum of familial and sporadic lewy body (LB) disorder that may occur alone or in combination with other disease such as Alzheimer's disease (AD).

Although Alzheimer's pathology, has been a frequent finding in PD the neuropathologic and molecular basis of dementia in PD is less clear, recent advances in immunostaining of alpha-syunclein have suggested the possible importance of cortical lewy bodies (CLBs) in the brains of demented patients with PD. The CLBs positive for alpha-syunclein are highly sensitive and specific neuropathologic markers of dementia in PD and they are better indicators of dementia than neurofibrillary tangles, amyloid plaques or dystrophic neurities **(Hurtig et al., 2000).** Dementia in PD is likely to reflect interaction of the neuropathology of the basal ganglia and age related pathology **(Hughes et al., 2000).**

Patients fulfilling the clinical criteria for DLB also exhibit clinical features of possible vascular origin and a frontal profile. Subcortical vascular pathology, nigral degeneration and AD pathology could partly explain the clinical features used to define DLB **(Londos et al., 2000).**

Temporoparietal glucose hypometabolism, neuronal loss in the basal forebrain cholinergic structures and preferential accumulation of neurofibrillary tangles in the rhinal cortex (i.e in the entorhinal and perirhinal cortices) are three early characteristics of Alzheimer's disease. **Meguro et al. (1999)** assessed the remote metabolic effects of bilateral neurotoxic lesions of both entrohinal and perirhinal cortices. Using coronal PET coregistered with MRI, the cerebral metabolic rate for glucose (CMR_{glc}) was measured before surgery and sequentially for 2-3 months afterward (around days 30, 45 and 80). Compared with sham-

operted baboons, the lesined animals showed a significant and long-lasting CMR_{glc} decline in a small set of brain regions, especially in the inferior parietal, posterior temporal, posterior cingulate and associative occipital cortices, as well as in the posterior hippocampal region, all of which also exhibit glucose hypometabolism in Alzheimer's disease. Remarkably, the degree of CMR_{glc} decline in four of these regions significantly correlated with the severity of histologically determined damage in the rhinal cortex, strongly supporting the specificity of the observed metabolic effects. There were also differences between the metabolic pattern observed in the lesioned animals and that classically reported in Alzheimer's disease; for instance, the hypometabolism found in the stratum has not been reported in early Alzheimer's disease, although this structure can be affected in late stages of the disease and has direct anatomical connections with the rhinal cortex. Nevertheless, this study shows for the first time that the temporoparietal and hippocampal hypometabolism found in Alheimer's disease may partly result from neuroanatomical disconnection with the rhinal cortex. This, in turn, further strengthens the hypothesis that neuronal damage and dysfunction in the rhinal cortices play a major role in the expression of Alzheimer's disease.

Arima et al. (1998) Reported that the formation of astrocytic tubules (As-tbs) appear to be related to the duration of Alzheimer's disease and the intensity of histopathology, in these cases in which the disease was of extremely long duration As-Tbs were found in the frontal

and temporal neocortices, the temporal pole and hippocampus, two types of As-Tbs were observed, twisted tubules with periodic constrictions were seen, they were positively stained by anti- human Tau antibody, an antibody that does not recognize extracellular NFTS thus its most likely that As-Tbs are not the seguestration of extracellular NFTs and that they are of astascytic origin.

Dementia with grains also referred to as argyrophilic grain disease is a morphological condition in elderly individuals histologically characterized by the widespread occurrence of minute, spindle or come shaped argyrophilic, tau immuno reactive structures distinct from neuropil threads that are predominantly located in the hippocampus and related limbic areas including the amygdala, argyrophilic grain disease is considered to be a progressive disorder that may or may not be associated with dementia, they often occur in combination with neuritic Alzheimer's type lesion or other neurodegenerative disorders such as corticobasal degeneration, or pick's disease **(Jellinger, 1998).**

Fronto-temporal dementia is a disorder characterized by personality changes, deterioration of memory and executive functions as well as stereotypical behaviour, sometimes a Parkinsonian syndrome is prominent, Neuropatholgocially present with atrophy of frontal and temporal cortex as well as basal ganglia and substantia nigra. In the majority of cases these features are accompanied by neuronal loss, gliosis and microtubule associated protein Tau deposits which can be present in both Neurones and glial cells, no beta amyloid deposits are present. The

clinical and neuropathological features of the disease in these families suggest that fronto-temproal dementia and parkinsonism linked to chromosome 17 is a distinct disorder. The presence of abundant Tau deposits in the majority of these families define this disorder as a new tauopathy **(Spillantini et at 1998).**

Pick's disease, a rare dementing disorder that is sometimes familial, the cardinal features are circumscribed cortical atrophy most often affecting the frontal and temporal poles and argyrophilic, round intraneuronal inclusions (Pick bodies). Clinical manifestation, and personality deterioration and memory deficits are often more severe than visuospatial and apraxic disorders that are common in Alzheimer's disease, Neuronal loss and degeneration are usually maximal in the limbic system, including hippocampus, entorhinal cortex and a mygdala. Numerous pick bodies are often present in the dentate fascia of the hippocampus. Less specific features include leukoencephalopathy and ballooned cortical neurons (pickcells), tau immuno reactive glial inclusions are a recently recognized finding in pick's disease and neuritic changes have also recently been described, immunocytochemical studies have demonstrated that abnormal Tau proteins are the major structural components of pick bodies **(Dickson, 1998).**

The traditional assumption that there are two distinct forms of dementia vascular dementia and Alzheimer's disease receptively with and without evidence of vascular disease as a presumed causative factor has been called into question by recent epidemiological evidence which raises

the possibility that vascular risk factors may be important in the etiology not only of dementia in general but also specifically for Alzheimer's disease **(Stewart, 1998).**

There is overwhelming evidence to suggest that the neuropathology of Alzheimer disease extends beyond amyloid plaques and neurofibrillary tongles, review of various consortium data shows that more than 30% of AD cases exhibit cerebrovascular pathology. However, certain vascular lesions such as cerebral amyloid angiopathy, microvascular degeneration and periventricular white matter lesions are evident in almost all cases of AD. Whether these vascular lesions are coincidental or causal in the pathogenic processes of AD remains to be defined **(Kalaria and Ballard, 1999).**

Sever coronary artery disease has been associated with increased senile plague counts and hypertension with increased plaque and neurofibrillary tangle densities in a necropsy series of subjects without dementia **(Sparks et al., 1995),** suggesting that the burden of Alzheimer's pathology may be increased by systemic vascular disease, possibly to a threshold beyond which it becomes progressive and self generating. Increased amyloid precursor protein activity and B-amyloid production have been found in the hippocampi of rodents after severe but transient ischeamia **(Hal et al 1995).** A process which is probably a non specific response to cerebral trauma (**Kogure and Kato, 1993),** these sub clinical processes may involves small areas of cortical or subcortical infarction or may be related to disturbances in cerebral perfusion possibly

exacerbated by pre-existing Micro Vascular abnormalities associated with Alzheimer's disease (dela torre and Mussivand, 1993).

In one of the most publicized studies (the nun study) Snowdon et at 1997 found an important association between clinical symptoms of Alzheimer's Disease and infarcts specifically, subcortical lacunar infarcts were associated with significant increased levels of cognitive decline. The lacunar infarcts had a strong association with Atherosclerosis in the circle of willis. The number of infarcts was not associated with the number of neurofibrillary tangles or senile plagues, neuritic plagues and suggests an independent role.

One means of ascertaining whether the origins of amyloid in Alzheimer's disease is neuronal or vascular has been to examine its distribution relative to neurones or blood vessels, a recent study attempting to resolve this problem by examining amyloid deposition in white matter, has reported distribution of amyloid to be particularly related to blood vessels, suggesting a vascular rather than neuronal source (Iwamoto et al., 1997).

The relevance of vascular amyloid disposition (Cerebral amyloid angiopathy) in the pathogenesis of Alzheimer's disease remains uncertian but may play apart in interactions with cerebrovascular pathology, cerebral amyloid angiopathy may be a consequence of cerebrovascular disease via effects of ischemia and secondary amyloid deposition or, on other hand it may cause vascular disease through toxic effects (possibly mediated by free radical damage) of B amyloid on the vascular endothelium (Sutton et al., 1997).

Alzheimer gave the first convieing description of the pathological changes in a vascular dementia **(Alzheimer, 1899).** Over the ensuring seven decades the view that gradual narrowing of cerebral blood vessels starved the neurons and caused dementia has prevailed, the view that mental senility resulted from slow strangulation of the brain blood supply proved logical compelling and wrong, **Hachinski et al. (1975)** crystallised the concept, introduced the term and proposed a standered method of diagnosing multi-infarct dementia, to emphasise that the vascular process in guantal and episodic rather than continuous and chronic.

Hypoxic ischemic disorders have been invoked as a possible underlying mechanism for a form of vascular dementia termed "hypoperfusion dementia" a syndrome in which the metabolic demands of the brain exceed the available cerebral blood supply, resulting in supply failure, Although most discussions of the pathogenesis of vascular dementia have emphasized the role of atherosclerosis and thrombo embolism, supply failure may be an important additional pathogenic mechanism in certain subgroups of patients **(Wallin and Blennow, 1993).**

Brun (1994) found that the predominant pathological features in the hypoperfusion was incomplete infarction of the white matter, with completed interaction of the border zone territories, no occlusions were noted in the hypoperfusion group but atherosclerotic narrowing of the penetrating cerebral arterioles was common.

Fluctuations in the systemic intra-arterial pressure combined with atheromatous changes of the deep penetrating vessels were proposed to account for the white matter changes.

Cooper and Mungas (1993) found that a history of general anaesthesia was significantly associated with vascular dementia and proposed apathophysiological role for hypertension resulting from anasthesia in the development of vascular dementia.

Hypertension was also associated with vascular dementia ,chronic hypertension results in the delivery of higher pressure loads to the cerebral vascular bed forcing structural remodeling, Accelerating atherogensis and impairing autoregulatory efficiency **(Zhanq et al., 1994).**

Sulkava and ErkinJuntti (1987) in their description of patients who developed new dementia in temporal association with hypotensive episodes and cardiac arrhythmias noted that all of their patients had been receiving anti hypertensive medications. Thus the elderly may be at higher risk for cerebral hypoperfusion from antihypertensive medications due to blunted baroreceptor compensatary reflexes impaired cerebral autoregulation and Atheromatous disease of the deep perforating end arteries thus, overzealous treatment of hypertension in elderly stork patients, especially those known or suspected to have intracranial atherosclerosis is potentially harmful **(Moroney et al., 1996).**

Recognition of the importance of white matter disease in vascular dementia has stemmed from the study of binswanger's disease, both binswanger's and the role of periventricular white matter lesions in

dementia however have aroused controversy. Recent studies describes leukoaraiosis (Raerefaction or thinning of the white matter) which appears as patchy zones of lucency in the periventricular areas on cranial C.T. or decreased signal on the T1 phase of MRI. The spectrum of subcortical white matter change has been defined pathologically **(Erkinjuntii et al., 1996).** Clinical studies have shown that the presence of periventricular white matter lesions does not always correlate with dementia, additional studies are needed to define malignant and more benign forms of stages of periventricular white matter lesion **(Gorelick, 1997)** and the microvascular deep white and grey matter lesion, but not macroscopic infarction, were significant in vascular dementia **(Esiri, 2000).**

White matter changes are often associated with stroke, risk factors for stroke and dementia, they may be associated with an increased risk of pre- or poststroke dementia because (i) they are linked with subtle cognitive decline, which may add to the consequences of the stroke lesions and of associated Alzheimer pathology and (ii) they indicate on increase risk of stroke recurrence **(Pasquier et al., 2000).**

Although theoretical mechanisms exist by which cerebrovascular and Alzheimer's pathologies may interacts its also possible that the two processes may be parallel and unrelated at a pathological level but interacting in their clinical effects as cerebrovascular disease acts to precipitate clinical Alzheimer's disease at pathological stages where it would not otherwise become clinically apparent **(Stewart, 1998).**

NEUROCHEMISTRY

There are several reasons to consider biological markers for AD, including strengthening the certainty of the clinical diagnosis, distinguishing AD from cognitive symptoms attributable to aging, and from other dementias, allowing early and even presymptomatic diagnosis and providing an index of disease activity **(Galasko et al., 1998).**

Today diagnosis of sporadic Alzheimer's disease is based on clinical exclusion criteria and diagnosis is only definite at necropsy, therefore, both in clinical routine and in view of emerging therapeutic compound. There is a great need for biochemical diagnostic markers of Alzheimer's disease especially to help in the diagnosis early in the course of the disease, moreover biochemical markers might also be useful to monitor the effects of new potential therapeutic compounds during treatment trials **(Andreasen et al., 1998).**

Relation to Acetylcholine:

An association between Alzheimer's disease and cholinergic activity has been noted several years age. When scopalamine (an Anti-cholinergic agent) was shown to cause impairment of memory storge and retrieval **in** normal subjects and choline acetyltransferase deficiency has been postulated in those patients with Alzheimer's dementia. A correlation between the severity of dementia and the degree of choline acetyl transferase deficit has been found **(Wilcock et al., 1982).**

The distribution of regional cerebral blood flow (RCBS) and regional cerebral oxygen metabolism (Rcm ko2) is negatively correlated

with the distribution of maximal cholinergic abnormality **(Procter et al., 1988).**

Administration of physostigmine (a cholinesterase inhibitor) in patient with early Alzheimer's dementia increased total recall and retrieval in some patients related to the degree of cholinesterease inhibition in the cerebrospinal fluid, suggesting that the degree of improvement was related to the amount of physostigmine that reached the brain **(Thal et al., 1983).**

Trial with the use of tetra- hydro- amino acridine (THA) (a cholinesterease inhibitor) for Alzheimer's patient, however gave no satisfactory beneficial clinical effects **(Van GooL et al., 1991).**

Despite marked reduction in choline acetyl transferase (CAT) is the most consistent neurochemical finding in Alzheimer's disease, yet it was also found that it is deficiency could be found also in other demented patients as those with parkinsonism making it a sensitive but non specific marker for Alzheimer's disease **(Perry et al., 1985).**

Antemortem CSF acetyl cholinesterease (AchE) studies revealed conflicting results, despite post- mortem brain tissue studies found it to be decreased. Such variation may be due to contamination with pseudo cholinestrease or due to the fact that CSF AchE is derived from subcortical Nuclei that are not primarily affected in Alzheimer's disease **(MC Donald and Nemeroff, 1991).**

The colinergic theory of Alzheimer's disease was confirmed in histological studies. Cell necrosis was found in the basal nucleus of menyert. Experimental studies in animals have demonstrated that

anticholinergic drugs leads to deficits in learning and behaviour. .consequently therapeutic trials were started with substitutional drugs (percursors of Acetyl choline, cholinergic agonist such as choline and a number of cholinasterase blockers such as physiostigmine or tetrahydro-amino acridine) with the result that the postsynaptic cholinergic system was almost completely spared from degeneration. This paved the way for the application of cholinesterase blockers in order to increase cholinergic input **(Ruther et al. 1994).**

More recent evidence indicate a diffuse pathological process involving medium sized cortical neurones particularly those using acetylcholine as atransmitter in the hippocampus and those found in associative temporal and parietal regions, the reason for this relative vulnerability is unknown. But it may have to do with impaired plasticity or repair mechanisms which are to a great extent driven by apoE. gentype **(Gauthier et al., 1997).**

Relation to glutamate and other amino acid:.

Recently there has been considerable interest in excitatory amino acids theories of neuro-degenerative disease or Alzheimer's disease **(Olney, 1989).** Excitatory amino acid in general and glutamate in particular have been hypothesized to contribute to a neurotoxic process involved in the pothogenesis of Alzheimer's disease **(Maragos et al., 1987).**

Lawler and Davis (1992) postulated that the neurotoxic and excitatory effects of glutamate can occur via activation of both N. methyl D. aspartate (NMDA) and non NMDA receptors (as guisgualate and

kainate receptors) thus both sites should be targeted by pharmacological modulation in glutaminergic therapeutic strategy of Alzheimer's disease.

In addition to higher glutamate levels, CSF taurine levels were also found to be lower in Alzheimer's disease with increased proline levels. Taurine is an inhibitory neuromodulator. Hence its lower level might reflect decreased inhibitory tone which might facilitate greater glutaminergic activity although proline like taurine is thought to have inhibitory effects. It might also effect glutamate levels because it is a potential substrate for glutamate synthesis and is believed to modulate N-methyl D-aspartate (NMDA) receptors which is a type of glutamate receptors **(Mc Geer et al., 1987).**

Relation to neuro-peptides:

Tamminga et al (1987) studies the somatostatin concentration in CSF of Alzheimer's disease patients correlated with the degree of cognitive functional impairment and cerebral metabolism (by positron emission tomography), they found significantly lower levels of somatostatin in CSF of those patients; the degree of reduction being correlated with intellectual impairment and with decline in glucose utilization. There was a close association between reduction in CSF somatostatin concentration and under utilization of glucose in the parietal and temporal lobes.

Bed et al. (1986) found marked reduction in neuropeptide y-immuno-reactivity in the brain of Alzheimer's disease patients especially in frontal, temporal and occipital cortex as well as hippocampus and locus

ceruleus. Because neuropeptide y is localized with somatostatin in a large portion of cortical neurons, the loss of γ-immuno- reactivity may partially reflect degeneration of these neurons.

Reduction in corticotropin releasing factor (CRF) immuno-reactivity is one of consistently reported neuropeptides alteration in Alzheimer's disease. **Desouza and Battaglia (1986)** demonstrated an increase in the density of post synaptic CRF receptors. CSF CRF concentration were found to be decreased in some studies (**Mouradian et al., 1986 and May et al., 1987).**

Vasopressin has generally been found to be reduced in Alzheimer's disease; however this finding has been observed also in other condition as depression and schizophrenia **(Rashind et al., 1986).**

Mazurek et al. (1987) found an increase in oxytocin concentration in hypothalamas and temporal cortex of Alzheimer's patients although **Rashind et al. (1986)** found no changes. studies of beta endorphins (Which are known to facilitate memory storage) revealed either no change **(Rashind et al., 1986)** or decreased CSF level **(Jolkkonen et al., 1987)** however a similar decrease has been also reported in patients with multi infarct dementia and Huntington's disease **(Jolkkonen et al., 1987).**

Nemeroff et al. 1989) found decreased neurotensin in the amygdala. other studies could found no difference **(Farrier et al., 1985).**

Parnetti et al. (1990) found that dexamethasone suppression test is of no diagnostic value in differentiating Alzheimer's disease from patients with cerebro-vascular insult; although the test can differentiate both groups from normal age matched controls.

Lawler et al. (1991) studies the relation between the level of post dexamethasone cortisol and behaviour as well as progression in Alzheimer's disease and found significant correlation between post dexamethasone level and agitation scores in those patients (DST non suppressors were significantly more disturbed than suppressors) however no relation with the rate of progression was found. The authors concluded that hypothalamic pituitary adrenal axis hyperactivity may reflect specific aspects of behavioural change in Alzheimer's disease.

Roelandt (1989) carried out CSF Adrenocorticotrophic hormone (ACTH) estimates in demented patients compared to age and sex matched control and found no significant difference between both groups.

Christie et al. (1987) studies the plasma concentration of pituitary hormones and found selective changes in level of thyroid stimulating hormone (TSH), growth hormone (GH) and oestrogen-stimulated neurophysion (ESN).

(Relation to serotonin) and platelet activation:

Although principally a disease of the brain, Alzheimer's disease (AD) has also been associated with peripheral manifestations; platelets has received particular attention in this regard with reported abnormalities including, increased membrane fluidity **(Piletz et al., 1991),** increased a_2 adrenoreceptor binding **(Adunsky et al., 1989),** increased mono amine oxidase activity **(Smith et al., 1982),** reduced cytochrome oxidase activity **(Parker et al., 1994)** increased protein kinase c activity **(Matsushima et al., 1994)** and reduced phospholipase C activity **(Matsushima et al., 1995),** platelets have also recently been shown to be

the principal source of both amyloid precursor protein and B-amyloid peptide in human blood **(Chen et al., 1995).**

Additionally, alterations **in** platelet serotonin levels and uptake have been reported in patients with AD **(Kumar et al., 1995).**

Sevush et al. (1998) concluded that the platelets of patients with Alzheimer's disease exhibit greater unstimulated activation than those of controls, potential causes of such activation include possible stimulation of platelets by damaged cerebral endothelial cells or platelet activation induced by membrane abnormalities which previously reported to be present in platelets of patients with AD. In light of recent evidence that platelets are the principal source of both amyloid precursor protein and B-amyloid peptide in human blood is possible that AD platelet activation may reflect or even contribute to the pathogenesis of disease.

In addition to potential relationships between platelet activation and serotonin and membrane fluidity changes, it is also possible that AD platelet activation related directly to the cerebral component of AD pathophysiological features, particularly inviting in the possibility that endothelial cell damage in the cerebral microcirculation induced by amyloid angiopathy might cause platelet activation by local stimulation or by secretion of a platelet activating factor in the general circulation. The report of increased circulating von willebrand factor in patient with AD (**Mari et al., 1996)** is consistent with this possibility; since activated platelets have been reported to bind to injured endothelial cell through a mechanism involving von willebrand factor **(Sevush et al., 1998).**

An additional possibility that platelet activation is not merely a result but may also relate to the cause of the AD pathological process, must also be considered this platelets store amyloid precursor protein (APP) in a-granules (Von-Nostrand et al., 1990) incroporate it in platelet and platelets micro-particles (PMP) membranes (Nomura et al., 1995) and secrete it on platelets activation in guantities sufficient to make platelets a principal source of circulating APP. Platelets have also been reported to secrete and be a principle source of circulating B-amyloid peptide (Chen et al., 1995) plasma level of which have been reported to be elevated in AD (Scheuner et al., 1996).

Sevush et al. (1998) provides a possible mechanism whereby increased level of APP and B- amyloid peptide secretion by activated AD platelets could conceivably contribute directly to the AD pathological process.

Relation to CSF Tau protein:

As the intercelluler space in the brain is in direct contact with the CSF, biochemical changes in the brain may be reflected by CSF analysis. Besides an increased number of senile plagues and neurofibrillary tangles, the central neuro-pathological finding in AD consists of a degeneration of the neurons and their synapses (Blennow et al., 1996) thus analysis of neuronal and synaptic proteins in CSF may function as biochemical markers for the neuronal degeneration in A.D, one such neuronal protein is tau protein, a normal human brain phosphoprotein which binds to microtubules in the neuronal axons, thereby promoting microtubule assembly and stability (Goedert, 1993). Abnormal

phosphorylation of the tau-protein is regarded as a crucial step in the formation of neurofibrillary tangls in the neuronal cell bodies and neuropil threads in dendrites **(Thal et al., 2000).**

Several studies have found an increase in CSF tau protein (CSF tau) in A.D **(Vandermeeren et al., 1993 and Galasko et al., 1997).** However the specificity of CSF tau has not been well established as an increase in CSF tau has also been found in some studies in vascular dementia **(Blennow et al., 1995).**

Andreasen et al. (1998) confirmed the high sensitivity of CSF tau for the diagnosis of Alzheimer's disease. But high CSF tau was also found in vascular dementia resulting in a lower specificity, however the high CSF tau concentration found in vascular dementia may in part be explained by the fact that these patient may in addition to cerebro-vascular pathology have concomitant AD pathology which is impossible to exclude clinically, more even an increase in CSF tau was only found in the group without progressive leukoaraiosis, a possible theory is that patient with vascular dementia with progressive leukoararosis may define more pure form of vascular dementia with normal CSF tau concentration however results so far suggest that CSF tau may help to differentiate AD from several problematic differential diagnosis such as age associated memory impairment, depressive psudodementia, parkinson's disease and frontal lobe dementia.

Andreasen et al. (1998) found the CSF tau concentrations were stable between baseline and follow up, and there was no correlation between CSF tau and duration of dementia , these finding suggest that

high CSF tau concentrations are present during the whole course of the disease. It is possible that the same high CSF tau concentration are also found before the onset of clinical dementia if so, CSF Tau may be useful for selection of patient with early memory disturbance for clinical drug trial; **Andreasen et al. (1998)** found no correlation between CSF tau and severity or rate of progression of dementia.

In vitro studies have shown that apolipoprotein E3 (APO E3) binds to the microtubule associated protein tau with high avidity whereas APO E.4 does not bind tau, suggesting that APO E3 but not APO E4 by binding to tau, slows the degree of tau Phosphorylation and self assembly into paired helical filaments **(Strittmatter et al., 1994).** It has also been suggested that intraneuronal APOE, by interaction with tau protein, may influence the neuronal pathology in Alzheimer's disease from early in the disease **(Han et al., 1994).**

Galasko et at (1998) studied the CSF level of amyloid B protein ending at amino acid 42 (AB42) and tau as a markers for A.D and concluded that the CSF levels of AB42 decreased and CSF levels of tau increased in A.D, also found that APOE4 had a dose dependent relationship with CSF levels of AB42 but not Tau, after combined analysis of CSF AB42 and Tau levels can discriminated patients with AD including patients with mild dementia from the cognitively normal elderly control subjects supporting use of these proteins to identify AD and to distinguish early AD from aging.

Relation to monoamine oxidase (MAO):

Many psychiatric and neurological disease and personality disorders are claimed to be associated with a change of platelet monoamine oxidase (MAO) activity **(Schalling et al., 1987).**

The underlying theory posits the involvement of MAO in monoaminergic metabolism and in possible genetic link between MAO activity and psychopathology or neurological illness, a defective neurotransmitter balance might induce change in MAO activity and altared MAO activity might cause imbalance between neurotransmitter, its therefore assumed that both mechanisms are able to provoke psychopathological symptoms **(Danielczyk et al., 1988).**

Mono amine oxidase (MAO) is a key enzyme in the degradation of monoamine neurotransmitters. MAO activity is divided into two types A and **B** based on sensitivity to the selective MAO-A inhibitor clorgyline. Brain MAO-B activity increases with age and is further increased in patients with dementia of the Alzheimer type, analysis of MAO activity in platelets has been performed in an attempt to find a peripheral marker of dementia in the blood. In platelets MAO- B activity has been found to increase although very slowly with age **(Oreland and Gottfries, 1986).** In patients suffering from primary degenerative dementia of the Alzheimer type, platelet MAO activity has been found to be increased in comparison with age matched control **(Alexopoulos et al., 1984).**

Danielczyk et al. (1988) studied the monoamine oxidase (MAO-B) activity of platelets of an age and sex matched group of controls was compared with several groups of patients having non familial dementia of

Alzheimer type (DAT), parkinson's disease (PD), multi- infarct dementia (MID), mixed type of these 3 disease and a group of other central nervous system (CNS) organic Disorders. They concluded that a statistically significant enhancement of MAO - activity could be observed in DAT patients and in PD patients where the MID group showed a mean activity similar to that of control group and the group with other organic CNS disorders, in DAT patients the degree of dementia and the enhancement of MAO activity were positively correlated, but PD did not show such a correlation, it is concluded that the increase of MAO activity in PD and in DAT might be due to a disease related enhanced affinity to oxygen and to such oxygen derived radicals as superoxide or hydroxyl radicals. However a possible drug induced enhancement of MAO activity in PD cannot be excluded furthermore the MAO-B activity values in platelets of individual patients or controls are not indicative of diagnosis or prognosis of any of these diseases and are of no disease related specificity.

Neurotoxic factors especially radicals, combined with genetic predisposition might cause parkinson's disease (PD) and or Dementia of Alzheimer's type (DAT). Cell damage of DAT and PD could be trigered by a change in membrane fluidity, as shown for platelets of DAT patients **(Zubenko et al., 1987)** which is generated through the production of toxic radical, preliminary data suggest that, in familal froms of DAT, the gene of superoxide dismutaze is linked to the amyloid protein gene **(van Broeckhoven et at 1987),** whose products are found in the senile plaque of DAT patients, abuse of 1-Methyl-4 phenyl- 1,2,3,6. Tetra-hydropyridine (MPTP) derived radicals and highly reactive metabolites is

also known to produce a degenerative brain disorders with parkinson like symptoms, the discovery that hydrogen peroxide is able to enhance MAO-B activity **(Konradi et al., 1986)** in coherance with enhanced MAO- B-activity in the platelets of the DAT and PD patients seems to suport a radical hypothesis for the pathophysiology of both diseases (Danielczyk **et al., 1988).**

i**Hara et al. (1997)** measured hydroxyl radical (OH) levels in blood and superoxide dismutase (SOD) activity in red blood cells (RBC) in DAT and VAD group and found that (OH) in DAT and VAD groups was significantly higher whereas SOD level significantly lower, so concluded that oxidative stress plays a role in the brain damage seen in both groups. **Meszaro et al. (1998)** studied the effect of age, medication, and disease on platelet MAO -B activity and serotonin content in patients with dementia they found that platelet serotonin content and platelet count was increased in patients with dementia compared to controls and found also a positive correlation between platelet MAO-B activity, platelet serotonin content and age. Platelet MAO- B activity, was higher in the haloperidol treated group, compared with patient treated with anxyolitics and the platelet serotonin content is increased in demented patients with delusions compared to dementia without complications, it seems that platelet MAO-B activity is influenced mainly by drug therapy while serotonin content rather reflects clinical characteristics in dementia.

A 4 year follow up study of platelet MAO-B activity and mini-mental state (MMS) was performed in patients with probable dementia of the Alzheimer's type (DAT), and age matched controls, the MAO-B

activity of DAT patient increased significantly 2 years after the beginning of the study as compared with controls and remained significantly higher for the entire period of examination, the decrease of the MMS scores did not correlate with the time course of the increase of platelet MAO-B activity, the decline of the MMS scores of DAT patients preceded the elevation of MAO -B activity. Since degenerative processes in brain areas which are responsible for cognitive function and are reflected by the MMS scores rather affect cerebral cholinergic than monoaminergic neurotransmitter systems and degeneration of the latter at late stages of DAT might be reflected by increased platelet MAO-B activity **(Gotz et al., 1998).**

Relation to Vit B12 and folate:

Low vit B12 levels in the serum are known to be quit common in patients with senile dementia and confusion even in the absence of haematological changes **(Gross et al., 1986).**

Although there have been several case report of cognitive improvement after treatment with vit B12, it has not been definitely verified that treatment with vitamin B12 is of significant value for dementia disorders **(Regland et al., 1988).**

There are indications that vitamin B 12 has an etiological role in the genesis of dementia, in the 1940s brain autopsies from patients with pernicious anemia, revealed cerebral white matter changes that were related to psychiatric symptoms of dementia **(Ferraro et al., 1945).** These cerebral changes described as demyelinating subacute degeneration, which is in agreement with the finding of spinal cord

lesions reproduced in experiments on vitamin B 12 deficient rhesus monkeys **(Scott et al., 1981).**

Patients with Alzheimer's disease (AD) with subnormal vitamin **B** p levels show more frequent behavioural and psychological symptoms of dementia than Alzheimer's disease patients with normal vitamin $_{B12}$ levels, vitamin **B** $_{12}$ could play a role in the pathogenesis of behavioural changes in AD (**Meins et al., 2000).** So all patients with cognitive impairment should be investigated for $_{B12}$ deficiency. However, vitamin B $_{12}$ treatment may improve frontal lobe and language function in patients with cognitive impairment but rarely reverse dementia **(Eastley et al., 2000).**

Homocysteine (Hcy) may represent a metabolic link in the pathogenesis of atherosclerotic vascular diseases and old age dementias, Hcy, is a reliable marker of vitamin B12 deficiency, a common condition in the elderly which is known to induce neurological deficits including cognitive impairment, high prevalence of folate deficiency has been reported in psychogeriatric patients suffering from depression and dementia. Both these vitamins occupy a key position in the remethylation and synthesis of S-adenosylmethionine (SAME) a major methyl donor **in** CNS; therefore deficiencies in either of these vitamins lead to a decrease in SAME and increase in Hcy which can be critical in the aging brain, another pathogenetic mechanism linking high Hcy levels to reduced cognitive performances in the elderly might be represented by excitotoxicity **(Parnetti et al., 1997).**

Vitamin B 12 and folate are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethioine.

S-adenosylmethionine is involved in neumerous methylation reaction involving proteins phospholipids, DNA and neurotransmitter metabolism. Both folate and vitamin B 12 deficiency may cause similar neurologic and psychiatric disturbance including depression and dementia, the defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies, folate deficiency may specifically affect central monoamine metabolism and aggrevate disorders **in** addition the neurotoxic effects of homocysteine may also play arole in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency **(Bottiglieri, 1996).**

Cobalamin/Folate deficiency in elderly subjects may lead to psychiatric symptoms, but more often it increases the severity of various organic and non organic mental disease. A major clinical problem, however is the uncertainty and contraversy concerning biochemical markers of cobalamin/folate deficiency to be used in diagnostic evaluation, **Nilsson et al. (2000)** concluded that plasma Hcy is the best marker to investigate suspected tissue deficiency of cobalamin/folate.

Regland et al. (1988) found vitamin B12 concentrations below the lower limit of referance value and described a significant negative correlation between MAO- B level and vitamin B 12. in a recent study **Regland et al., 1991** found low vitamin B12 level with significant decrease of MAO- B levels 4 weeks after intramuscular injection of

hydroxycobalamino, **Parnetti et al. (1992)** also found a significant negative correlation between MAO- B and vitamin B12, contrasting to this reports, **Fischer et** al. (1994) did not find any correlation between low vitamin B12 and high MAO-B activity, the source of the discrepancy between **Fischer et at (1994)** study and previous studies in not known but may be related to diet balance **(Fischer et at 1994).**

Relation to monoamino metabolites

Wallin et al (1996) studied the levels of the CSF monoamine metabolites; 5 hydroxy indoleacetic acid (5 HiAA), homovanillic acid (HAV) and 4- hydroxy-3 methoxy phenylglycol (HMPG) in patients with vascular dementia and found a significant lower mean concentration of monoamine metabolites in CSF of vascular dementia patients.

Studies on other disease, such as Alzheimer's disease (AD), parkinson's disease and depression have also revealed decreased CSF monoamine metabolite concentrations, indicating that these changes are not specific to vascular dementia, the decreased concentrations of CSF 5-HiAA and CSF HVA found in AD **(Blennow et al., 1991)** probably reflect nerve tissue damage in this disorder, the CSF monoamine metabolite finding in AD may interpreted in the same way as in vascular dementia that may reflect not only primary nerve cell involvement but also energy depletion and vascular disturbances, the low CSF 5 HIAA and HVA level found in VAD appear to be a phenomenon that reflect central serotoninergic and dopaminergic function but is unspecific to the disease, these low level may be attributable to subcortical white matter changes that creat atransependymal barrier effect with central

accumulation of monoamines or to a decreased production of monoamines which are dependent on oxygen for their synthesis **(Wallin et al., 1996).**

Relation to phospholipase:

Phospholipase A2 (PLA2) is a key enzyme in the metabolism of membrane phospholipids. In cholinergic neurons PLA2 controls the physico-chemical properties of neuronal membranes as well as the break down of phosphatidyl choline to produce choline for acetylcholine synthesis, morever PLA2 influences the processing and secretion of amyloid precursor protein, which give rise to the B-amyloid peptide the major component of the amyloid plague in AD; in AD Brains PLA2 activity was significantly decreased in the parietal and to a lesser degree in the frontal cortex, the lower PLA2 activity is correlated significantly with an earlier onset of the disease, higher counts of neurofibrillary tangles and senile plaques and an earlier age at death, indicating a relationship between abnormally low PLA2 activity and amore sever form of illness, this results provide new evidence for a disordered phospholipid metabolize in AD brains and suggest that reduced PLA2 activity may contribute to the cholinergic deficit and to the production of amyloidogenic peptides in the disease **(Gattaz et al., 1995).**

DIAGNOSIS OF DEMENTIA

Alzheimer's disease (AD) is an illness that at this time is estimated to afflict 15 million people around the world **(Khachaturian, 1997).** This illness has recognized clinical and pathologic manifestations. Although the etiology is unknown, there are known risk factors such as age, Down's syndrome and genetic predisposition. The manifestations of the illness evolve continuously as the disease progresses, these include prominently neuropsychological features, neuropsychiatric manifestations and disturbance in dialy living **(Reisberg et al., 1997).**

There have been a number of consensus statements regarding the clinical and pathological diagnosis of AD over the last 15 years **(American Psychiatric association, (DSM III) 1980, (DSMIII-R) 1987, (DSM VI) 1994; Khachaturian, 1985; Mckhann et al., 1984; Mirra et al., 1991; World Health Organization, 1992).** There was agreement that AD is a clinicopathologic syndrome. Traditionally, the diagnosis of AD has been said to be a process of exclusion. In this way, AD differed from most other medical diagnosis in that doctors were to arrive at this diagnosis only after exhaustive work-up. However, research during recent decads has indicated that AD has clear clinical manifestations at all points in the manifest progression of the disease additionally. AD has physical manifestations that may be evident using neuroimaging and other methods and AD has evident brain changes upon postmortem examination **(Reisberg et al., 1997).**

Clinical diagnosis of Alzheimer disease (AD) typically requires history from the patient and ideally an informant and results of mental status testing, physical and neurological examinations, a panel of laboratory tests and a neuro-imaging study to rule out other causes of dementia, the work up may include additional laboratory tests in atypical cases and more detailed psychometric testing and follow up to increase the confidence of the diagnosis, especially when a patient presents with mild dementia **(Galasko et al., 1998).**

History and physical examination:

The history and physical examination remains the essential elements of assessment of the older patients with dementia, as well as the principal means of establishing a diagnosis of dementia. The physician must derive information from a range of sources, which will incorporate information from caregivers and integrate biological, psychological and psychosocial factors (Geldmacher **and Whitehouse, 1996),** further, the initial evaluation not only provides information, but begins a process of intervention **(Finkel and Woodson, 1997).**

It is best to begin the interview with the patient by asking nonthreatening questions, which are easily answered questions about parents, brothers and sisters, early educational experiences, and work history are usually answered in accoperative manner and set the stage for more detailed cognitive evaluation, a chronically suspicious patients may be reluctant to answer questions relating to cognition, but in the process will facilitate your evaluation of his or her personality.Some investigators

prefer to evaluate cognition earlier on in the interview when the patients is more alert **(Jarvik and Wiseman, 1991).**

Commonly the patient will answer questions superficially and without the depth that might be expected from his or her educational back ground and history. Many may also respond but with answers that do not fit the questions. Social skills generally remain until cognitive dysfunction is moderate. Other helpful questions relate to the speed of usual activities that may slow significantly: for example, personality changes, relationship with grand children and previous history of coping strategies in response to loss, which help to predict the response to the current cognitive and functional losses **(Finkel and Woodson, 1997).**

Any history should include the present illness, past medical history, medications, eating and nutritional status and social history (including family and employment). Mental status evaluation would include appearance, speech and language, affect, pereciption, thought content, insight and judgment, memory and orientation, in primary care practice rating scales are generally not used. However, they should be strongly encouraged, particularly to establish a base line from which subsequent measurements can be compared, placing the patient in a helpful role generally elicits his or her cooperation. It is important to provide positive feedback to the answers in order to increase the chances of continued cooperation **(Finkel and Woodson, 1997).**

The physical examination serves both to determine the etiology of dementia and to determine the existense of other illness that can

contribute to excess disability, attention to gait, balance, sensory deficits and other neurological changes are described elsewhere in this issue. Evidence of physical trauma, as the result of falls or abuse, must be evaluated and followed up-dehydration and malnutrition occur commonly, particularly in those living alone and also contribute to excess disability. Poor self cure as well as evidence of food or dried faces, neglect of hair and evidence of non compliance with medication.

In conclusion, the history and physical examination are evaluation tolls in establishing a diagnosis of dementia. The evaluation process serves as the begining of therapeutic interventions and management and includes the evaluation of medical and psychiatric contributory factors, providing information and referal to family members and the development of a treatment plain **(Finkel and Woodson, 1997).**

Mental status and neuropsychological assessment:

Mental status and/or neuropsychological assessment is presently used nearly universally to establish the presence of dementia. Because these assessments are sometimes misused and/or misunderstood, it is important to emphasize that a low score on any of these measures conveys no information on the etiology of a dementing disorder. In conjunction with a premorbid history, however, including an educational, social, cultural, and medical history, comprehensive mental status and/or neuropsychologic assessments can establish the presence of dementia i.e.

a generalized decline in intellectual and cognitive capacities from permorbid levels **(Reisberg et al., 1997).**

Neuropsychology contributes greatly to the diagnosis of dementia. Cognitive deficits can be detected several years before the clinical diagnosis of dementia. The neuropsychological assessment at an early stage of dementia has two goal (a) to determine a memory disorder (b) to characterize the memory disorder in light of the cognitive neuropsychology and to asses other cognitive (and non-cognitive) functions toward integrating the memory disorder in a syndrome **(Pasquier, 1999).**

Mental status assessment has along tradition in the evaluation of dementia, the mini-mental status examination (MMSE) is the most widely used mental status test and includes assessment of orientation, memory, attention and calculation, language, ability to follow commands, reading comprehension, ability to copy a drawing **(Folstein et al., 1975).**

Folstein has suggested acutoff score of 23 or less for the presence of dementia on this measure in persons with at least 8 years of education. However, normal educated elderly persons commonly score 29 or 30 on this 30 point screening measure. It should be noted that education, occupation and cultural and background factors can strongly influence MMSE scores **(Tangalos et al., 1996).**

The MMSE permits considerable flexibility in administration and the mode of administration and the versions utilized have also been shown to strongly influence scores (**Molloy et al., 1991).** Within the

conventional dementia range in well educated subjects, mean changes in MMSE scores of approximately 2 to 5 points per year have been found in AD subjects however, the correlation of MMSE change scores with the temporel progress of AD has been found to be only approximately 3, indicating wide variability even in selected populations **(Reisberg et al., 1996).** Because of the wide variability in MMSE scores depending upon the mode of administration, a standardized MMSE has been suggested (**Molloy et al., 1991).** However in any version, additional well known limitations of the MMSE, apart from those already noted include (a) floor effects, which preclude the ability to track the latter portion of AD entirely with this measure (rendering diagnostic assessment of course impossible in patients with sever AD) (b) ceiling effects, which limit dementia detection in well educated populations and (c) variable sensitivity over the optimal range of this widely utilized screening measure (**Reisberg et al., 1997).** Neuropsychological measures can over come some of these assessment problems for example, the Alzheimer's disease assessment scale (ADAS) **(Rosen et al., 1984)** is widely used in many pharmacologic trials, partly because its believed to have improved sensitivity over a particular range of dementia. Similarly, the sever impairment battary **(Saxton et al., 1990)** and the modified ordinal scales of psychological development (M-OSPD) **(Auer et al., 1994)** assess dementia severity in ranges where the MMSE scores are low or at bottom. Many neuropsychologic tests have been shown to be useful in identifying dementia, possible due to AD, at ranges in which mental

status scores are generally normal. Another nuropsyologic test battery that appear to be guiet useful for dementia diagnosis and guite sensitive to change with dementia evaluation is the SKT (Erzigkeit, 1989).

Global and Functional assessment:

Global assessments can outline the characteristic cognitive, functional and behavioral causes of AD. These outlines can be very useful in affording clinicians a rapid and comprehensive overview of AD. (Reisberg et al., 1982).

Two independently developed globale staging procedures have come into wide usage, the global deterioration scale (GDS) (Hughes et al., 1982) and the clinical dementia rating (CDR) (Risberg et al., 1982). These procedure divide normal brain aging and progressive AD into seven stages in the case of the GDS or five stages in the case of the CDR, these staging procedures have been shown to be at least as reliable in the categorization of AD severity as the best mental status or psychometric measures (Morris et al., 1997) more importantly, staging procedures may be superior to mental status and neuro-psychological assessments in the long-term longitudinal tracking of the courses of AD, there is also considerable evidence for the utility of global staging procedures in the identification of generally benign, normal aged subjective forgetfulness and boundary states that may be associated with incipient AD (Morris et al., 1996).

Functional assessments are useful in the identification of the existence of a dementing condition additionally, certain functional

measures of dementia may be very useful in the tracking the course of AD and even in the diagnosis, differential diagnosis and assessment are available for documenting these functional deficits. There include the disability assessment for dementia (DAD) **(Gelinas et al., 1995).**

The interview for deterioration in daily living activities in dementia **(IDDD) (Lawton and Brody 1969),** the Cleveland scale for activities of daily living **(Patterson et al., 1992).** The instrumental activities of daily living **(IADL)** scale (Sclan **and Reisberg 1992).** The physical self maintenance scale (PSMS) and the functional assessment staging (FAST) procedure **(Teunisse et al., 1991)** in conjunction with a premorbid history.

Each of these procedures can be useful in documenting the presence of functional deterioration, which may be due to dementia or an incipient dementing disorder (**Reisberg et al., 1997).**

Neuropsychological assessment:

Neuropsychological assessment involves the observation and measurement of an individual behaviour in relation to a given stimulus that has been selected for its likelihood to provoke an abnormal response in the presence of neurological damage **(Ritchie, 1994).**

Memory:

Neuropsychologists refer to two major memory systems: implicit memory and declarative memory. These are considered to be directed by the striatal and limbic systems respectively **(Ritchie et al., 1997).** Implicit memory refers to indirect or incidental learning due to prior exposure, of

which the subject is often unaware. Declarative memory on the other hand, involves a conscious process of information acquisition and is usually conceived in terms of a primary and secondry store. Primary memory or working memory is an initial stimulus registry with a retention period of approximately 30 seconds, the secondary memory system permits longer term retention through semantic processing and is conventionally divided into semantic and episodic stores. Semantic memory is a system for receiving, revising, and transmitting information about wards, facts and concepts, whereas espisodic memory is concerned with events relating to the individual **(Ritchie et al., 1997).**

In both normal aging and AD, implicit memory does not appear to be affected studies of primary memory also suggest that in normal aging the subsystems of working memory are relatively spared (**Kaszniak et al., 1986).** In contrast, studies of working memory in senile dementia indicate that although there is little evidence of impairment of either the articulatory rehearsal mechanism **(Morris 1987)** or the phonological store **(Morris 1984),** significant deficits may be observed in central executive functioning (**Morris 1986)** and in primary visuospatial memory **(Morris 1989).**

Whereas impairment of episodic memory is reported frequently by normal elderly persons, semantic memory remains intact **(Perlmutter, 1978),** in contrast problems in episodic and semantic memory appear central to the memory impairment associated with AD **(Huff et al., 1986).**

Previous research has demonstrated that explicit recognition of dot patterns is impaired in amnesic patients with damage to the limbic-diencephalic memory system, while implicit categorization of the same kind of stimuli is preserved. But **Keri et al. (1999)** revealed that the explicit recognition of dot patterns was significantly impaired in Alzheimer's disease. However, implicit categorization function were also disrupted. This was selective for the prototype stimuli, the categorization of non category learning is likely to reflect the damage of modality-specific neocrotical areas in Alzheimer's disease.

Language:

Although its generally considered that there is little change **in** language skills during normal aging they are cited consistently as diagnostic indicators of senile dementia, **Bayles (1982)** suggest that although the range and progression of language disorder, appear variable, they may be commonly characterized by a reduction in vocabulary and attendency for speech to become repetitive, circumlocutory and concrete with an amnesic aphesia that may show dissociation for naming and conversational skills.

The abnormalities that are most commonly reported in AD are morphological-lexical (naming difficulties) and metemorphological (reduction in verbal fluency on tasks demanding organizational and conceptual skills). In AD, word naming difficulties have been found to be a function of both response latency and word frequency **(Ritchie, 1997).**

Visuospatial organization:

Visuospatial organization concerns the skills required by the individual to perceive and evaluate within a spatial domain. Two aspects of visuospatial functioning are found to be impaired in AD:

1- Visuospatial analysis:

Which is primarily concerned with the perception, localization and visual analysis of material.

2- Visuospatial performance:

Which refers to the individual's acquired capacity to carry out goal-oriented tasks whithin a spatial domains independently of language, motor or sensory deficits. Disabilaities in this area (apraxias) are conventionally classified as constructional, ideomotor or ideational apraxia **(Ritchie 1997).**

A number of neuropsychological studies of AD have noted early deterioration of visuoconstructive abilities **(Rosen 1983),** other researchers however, cited cases in which visuoconstructive abilities have remained intact despite progressive deterioration in other cognitive capacities (**Martin, 1987)** a dissociation strongly suggestive of an AD subtype.

Attention:

Within the field of cognitive psychology "attention" has been generally defined as the capacity to allocate processing resources to a select stimulus.

Schneider et al. (1984) has identified two types of attention: divided and focused, divided attention reters to the capacity to simultaneously process multiple sources of independent information whereas focused attention refers to the capacity to ignore irrelevant information.

Studies conducted on elderly patients with AD suggest that although they can use context cues as effectively as normal elderly subjects in order to focus attention, reaction time is slowed considerably **(Cossa et al., 1989)** with regard to divided attention AD subjects show significantly greater decrement than normal elderly individuals which increases proportionally with the number of stimuli **(Nebes and Brody, 1989).** Visual attention impairment in AD has been related to degeneration of the locus coeruleus and basal forebrain nuclei and subsequently production of acetylocholine and norepine phrine **(Sahakian et al., 1989).**

Current evidence suggests that after an initial amnesic stage in Alzheimer's disease, attention is the first non memory domain to be affected, before deficits in language and visuospatial functions. This is consistent with the possibility that difficulties with activities of daily living, which occur in even midly demented patients, may be related to attentional deficits. It appears that divided attention and aspects of selective attention such as set-shifting and response selection, are particularly vulnerable while sustained attention is relatively preserved in the early stages. The neuropathological basis of these attentional deficits remains unsettled, with two competing hypotheses: spread of pathology

from the medial temporal to basal forebrain structures versus corticocortical tract disconnection Perry and Hodges (1999).

Neu roimaging:

Most neurologists, geriatricians and psychiatrists agree that structural imaging to the brain should be performed at least once in the evaluation of a dementing illness, even though most imaging studies do not alter the subsequent management of the illness, the main aim of the investigation is to exclude any remediable structural causes of cognitive impairment and obtaining early and more accurate diagnosis of neuro-degenerative causes of dementia (Walker, 1997).

Computed tomogrophy scan (C.T scan):

Benson (1986) said that the most troublesome aspect of the use of C.T.scans in the diagnosis of dementia concerns cerebral atrophy. A CT scan reading of "cerebral atrophy" cloud not be trusted to indicate dementia. Non demented individuals of the same age often show considerable cerebral atrophy may prove useful as a confirmatory diagnostic finding, although this finding is often relatively late, demonstrating pathognomonic C.T. findings only after the disorder is well established.

Kinkel et al. (1985) reported that leucoencephalopathy appearing as areas of varying extent symmetrically involving the periventricular whites matter, has been described.

Hershey et al. (1987) added that the pathologic correlates of white matter lesions include demyelination, loss of axons, astrogliosis and have been attributed to incomplete infarction, extensive hyalinization, intimal

fibrosis and obliterative atherosclerosis of small arteries and arterioles have been identified in and near periventricular white matter lesions in these patients.

Burns et al. (1991) studied clinical and radiological associations in patients with Alzheimer's disease and found significant correlation between cognitive functions and cortical atrophy as well as ventricular size especially with temporal lobe atrophy.

Anatomical imaging studies in the future most likely will focus on specific brain structure rather than on gross features for example a recent investigation used C.T scan to examine dilatation of hippocumpal fissure in controls, Alzheimer's patients and in patients with minimal memory dysfunction and found an enlarged tissue in all group except controls. It has been concluded that no atrophic hippocampus could be an early marker for Alzheimer's disease **(De Leon et al., 1989).**

The hippocampal formations are parts of the brain particularly affected in **AD,** resulting in prominent memory impairment, although radiological evidence of hippocampal atrophy on C.T. or major scan supports the diagnosis of AD, there trends to be an overlap between atrophy associated with early stages of AD and atrophy associated with normal aging (Walker 1997).

Volumetric measurements of the hippocampal formation showed that a symmetrical atrophy (>5% difference) developed Before the appearance of cognitive symptoms, verbal and visual memory measures declined in parallel with hippocampal loss **(Walker, 1997).**

In an attempt to improve the reliability of clinically based criteria for vascular dementia, **Pullicino** et al. (1996) recently published criteria designed to grade the likelihood of vascular dementia using computed tomographic (C.T) images alone. Based on an assumption that there is relationship between the severity of vascular Brain damage and the severity of cognitive impairment, **Pullicino et al,** predicted that higher imaging grades would be more to be associated with vascular dementia, large infarct volume, extensive white matter disease and presence of atrophy have all been shown to relate to the presence of vascular dementia and these can be measured on hard copy C.T. images with acceptable reliability, these imaging criteria combine infarct volume, severity of white matter disease and presence of atrophy to delineate 4 grades of increasing Severity of vascular brain damage.

Table (B): imaging criteria.

Grade	Description	Criteria
0	VaD absent	No infarcts; wms <3; vi, any Dimension.
1	VaD unlikely	Single infarct; vol, < 100m1; vi, any dimension Multiple infarcts; vol < 100m1; vi<60
2	VaD possible	Multiple infarcts; vol < 100m1; vi≥ 60 Infarct (s); Vol, ≥ 100 ml; vi, < 60 Wms, 3 ; vi, ≥ 60 Wms, 4; vi, < 60
3	VaD probable	Infarct (s): vol, ≥ 100 ml; vi; ≥ 60 wms , 4; vi ≥ 60.

- VaD, vascular dementia; vol, infarct volume; vi, ventricular index; and wms, white matter scale.
- Each line gives different allowable combination for that particular grade.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging due to it is high resolution is preferable to C.T in observing the morphological changes in dementia. The finding of generalized atrophy is not specific to Alzheimer's disease as it occurs in many other disorder (**McGeer et al., 1986).**

Mri-T2 weighted images have been used in Alzheimer's disease to evaluate white matter hyperintensities (WMHI). But the clinical significance of the result remain controversial. **Bondareff et al., (1990)** reported a correlation between the magnitude of WMH1 and the severity of dementia. But **Hunt et al., (1989)** found elderly subjects with extensive WMHI and normal neurologic status and neuro-psychologic performance.

MRI measurement, of hippocampal formation size significantly predicted a decline in memory performance, these result indicate that hippocampal atrophy may be a risk factor for accelerated memory dysfunction in normal aging (**Walker 1997).**

Although hippocampal atrophy is very sensitive marker for A.D. it can not be used at present as an absolute diagnostic test as emphasized by **Laakso et al., (1996)** they compared hippocampal atrophy detected by volumetric **MRI** in a group of patients with mild to moderate AD with that in patients with VaD and with that in patients with parkinsons disease with and without dementia in the parkinsons's disease patients with dementia, the absolute volume of hippocampal formation were even smaller than those in the AD group.

Studies with magnetic resonance imaging (MRI) show multiple white matter lesions (WMLs) in patients with vascular dementia, but none in those with SDAT or pick's disease. The white matter changes seen on MRI in vascular dementia were similar in location to those seen on C.T but they were better visualized on T2-weighted images of MRI. **Hershey et al. (1987)** suggested that an MRI could differentiate non Alzheimer's dementia patient from age matched control, and that the likelihood of dementia in any given patient increased as of the number and location of WMLs. However there have been no controlled studies comparing the MRIs of demented and non demented patients with known ischemic cerebrovascular disease.

Brown et al. (1989) used in vivo phosphorus 31 Nuclear magnetic resonance (31p NMR) spectroscopy to study regional high energy phosphate and phospholipid metabolism in brain of patient with dementia associated with probable Alzheimer's disease (AD) and multiple subcortical infarct dementia (MSID). The MSID patients demonstrated elevations of the (phosphocreatine (PCK). inorganic or thophosphate **(PI)** ratio in both the temproparietal and frontal regions. Phosphomonosters (PME) and the ratio of PME to phosphodiesters were elevated in the temporoparietal region of AD. PI was also elevated in the frontal and temporoparietal regions of AD, findings from 31p NMR were accurate in distinguishing MSID from AD.

Regional cerebral blood flow

- Positron emmission tomography (PET)

And single photon emission computed tomography (SPECT).

Hoyer (1982) provided a review of global changes in regional cerebral blood flow. CBF oxidative metabolism and glucose metabolism in abnormal brain aging. He concluded that early in the onset of Alzheimer's disease cerebral blood flow and cerebral metabolic rate for oxygen ($CMRO_2$) are found to be normal while cerebral metabolic rate for glucose (CMR gl) is reduced contrary to multi-infarct dementia where glucose metabolism is abnormally increased.

As the course of the disorder advances blood flow, oxygen metabolism and glucose metabolism follow similar degeneration to reduced levels. The severity of dementia was found to be correlated to reductions in perfusion and metabolisms.

Gustafson et al. (1984) and Risberg (1985) studied 4 subcategories of dementia using two-dimensional probe system and Xe-133 i.e. Presenile Alzheimer's disease, senile Alzheimer's disease. Pick's disease and multi-infarct dementia. They found significant differences among the four groups as follows:

Alzheimer's disease patients had significant flow reductions in parietal, Perieto-occipital and parietotemporal regions, while Picke's disease patients had lowest flow values in premotor, supplementary motor and prefrontal regions.

In both groups rCBF. Reductions were symmetric across hemispheres.

Presenile and senile subtypes of Alzheimer's disease were similar in most aspects, although presenile patients had a more localized post-central flow reductions. While senile patients showed more widespread reduction, involving the frontal lobes to a greater extent.

Patients with multi-infarct dementia had large variations in the mean CBF i.e. flow patterns were heterogenous with no systematic patterns. Patients with small and /or deep infarcts showed normal flow levels. While in more advanced stages right-left asymmetries were observed with "spotty" flow paterns **(Risberg, 1985).**

After a 1 year prospective study **Rogers et al., (1986)** concluded that patients at risk for multi-infarct dementia have patchy reductions of cerebral blood flow levels, at least 2 years before the onset of signs of symptoms, but in Alzheimer's disease patients rCBF levels were maintained immediately prior to the symptoms, but decreased rapidly and diffusely as cognition declined.

Reed et al. (1989) studied the relation between memory deficits and regional cerebral blood flow in mildly symptomatic Alzheimer's disease patients and found that memory deficits tended to precede metabolic /blood flow abnormalities in those patients.

Prohovnik et al. (1989) using Xe-133 inhalation, found that there is greater grey matter degeneration in presenile Alzheimer's disease than in the senile form.

Rapoport et al. (1984) examined cerebral metabolic rate for glucose (rCMR gl) in patients with Alzheimer's disease in comparison to healthy controls and found no correlation between parameters of cognitive function and resting glucose metabolism in healthy subjects. While in Alzheimer's patients. rCBF was reduced throughout the brain in relation to the severity of the disease with specific declines in temporo-parietal cortex in later stages.

Of particular interest is a study that compared PET, performance on neuropsychological tasks and brain volume in AD patients with and without sever abnormality of white matter on MRI, the AD without severe abnormality of white matter on **MRI** group showed the typical parietal- temporal metabolic deficit and correlation between neocortical metabolism and neuropsychological performance in contrast the AD with sever abnormality of white matter on **MRI** group had a pattern of cerebral metabolism significantly different from that of the AD without sever abnormality of white matter on **MRI** patients as well as no significant correlation between metabolism in the neocortex and neuropsychological performance, and that differences reflected superimposed pathology possibly of vascular origin in the white matter **(Decarli et al., 1997).**

Reiman et al. (1996) used PET to investigate the cerebral glucose metabolism in 11 cognitively normal apolipoprotein E4 homozygotes and in 22 individuals without the apolipoprotein E4 allale, they found significantly reduced rates of glucose metabolism in the posterior

cingulate, parietal, temporal and prefrontal region as previously found in patients with AD, providing preclinical evidence that the apolipoprotein E4 allele is a risk factor for AD.

SPECT perfusion studies show in accord with PET studies that the most characteristic abnormality in patients with **AD** is a bilateral reduction of brain perfusion in the temproparietal cortex although the findings in both scanning techniques are similar, SPECT and PET may show different sensitivity and specificity values because of the different resolution and count density **(Walker 1997).**

Lehtovirta et al. (1998) concluded that cerebral perfusion ratios measured with SPECT for all patients with AD were significantly reduced in temporo- parietal regions compared with control subjects. Moreover, some differences were evident in the perfusion ratios for subgroups of A.D. the homozygous E4 allele subgroup had the lowest ratios at the basline in the parietal and occipital cortices and at the follow up in the temporal, parietal and occipital cortices. The difference was significant at the follow up in the right and left occipital cortices compared with the no E4 allele subgroup and control subjects, also at the follow up, the one E4 allele subgroup, had a significantly reduced perfusion ratio in the left occipital cortex compared with the no E4 allele subgroup, asignificant interaction effect of time and different apolipoprotein E groups was found in the right occipital cortex and the left parietal cortex. In the right occipital cortex, the perfusion ratio was significantly reduced in the homozygous E4 allel subgroup compared

with the no E4 allele subgroup and in the left parietal cortex in the one E4 allele subgroup compared with the control subjects.

The development of PET methodologies has made it possible to study the in vivo brain metabolic correlates of human cognitive and behavioral functions. Moreover, as PET scan examinations can be repeated, the progression of the neuropathological process and its relation to cognitive dysfunction can be followed over time **(Piertrini et al., 2000).**

Imran et al. (1999) concluded that bilateral parieto- temporal deficit of CBF along with a definite decrease in blood flow in the frontal region were established in patients with Alzheimer's disease with normal control and significant correlation of left parietal CBf values with patient age and severity of dementia was found, this suggest that metabolic images not only provide diagnostic and prognostic information but also help in determination of the stage of disease.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dementia, is complex and usually made in two stages, diagnosis of dementia syndrome and diagnosis of the underlying etiology **Byrne (1997).**

Differential diagnosis of the dementia syndrome:

Table (C) lists conditions that are considered to mimic the dementia syndrome or that can confuse diagnosis, the first three (delirium depression and aging) are the most common, a part from the obvious difference between delirium and dementia in terms of onset and progression, one source of diagnostic uncertainty between the two syndrome lies in the belief that delirium of short duration with florid symptomatology, chronic delirium (lasting more than 6 months) or prolonged subacute confussional states (with less florid symptoms) may mimic dementia and seem to have been overlooked for example, **Lishman (1987)** writes a prolonged subacute delirious state due to anoxia, uremia or hepatic disorder can simulate dementia very closely although this clinical pictures resembles any chronic toxic psychosis, the fluctuations differentiate it from the progressive organic dementia **(Byrne 1997).**

Dementia and depression are the two most common mental illnesses in late life and its therefore probable that they will coexist in many patients this.

Table (C): Differential diagnosis of the dementia syndrome

Feature
- Delirium Depression
- Aging
- Focal cerebral syndrome Personality disorder
- Schizophrenia
- Lack of educational experience
- Anxiety.

Coexistence is complicated by the fact that both illnesses can be mistaken for each other, its of course, necessary to correctly differentiate between these tow diagnosis, if depression is the cause of the cognitive impairment, full recovery is possible its also important to recognize depression in patient with AD, because the depression represents a treatable source of additional disability not only as a result of the affective symptoms but because depression also causes functional impairment **(Reiner, 1997).**

A simple scheme for classifying mixed cognitive affective symptoms depends on categorizing the affected patients into two groups. Type I patients have only depression, whereas in patients of type **II** there are two diagnosis comprising depression and AD the differentiation is based largely on clinical examination table (D).

	Type I	Type II
Primary disorder	Depression (with secondary memory changes)	Dementia (with superi mposed depression)
- onset	Subacute (weaks to months)	Gradual (years) in AD, abrupt in multi-infarct dementia
-initial course	Depressive symptoms usually appear first	Congitive impairment usually appear first
-Cognitive status	Memory loss often entirely snbj ective and not substantiated by testing	Cognitive impairment clearly apparent on testing
- Prognosis	Treatment may relieve all symptoms	Treatment can relieve depression, memory loss usually unchanged.

Selected Differential etiologies:

Dementia of frontal lobe type (DFT). Onset is usually before the age of 65 years; the characteristic clinical features is early prominent personality and behavioral changes (non cognitive features) whereas cognitive function is only mildly and patchily impaired early in the courses even in advanced disease, orientation is preserved in the early stages patients may score within the normal range on standard tests of intelligence and as noted by **Neary and Colleagues (1994),** the verbal-performance scale discrepancy noted in AD is not present in DFT.

In the early stages of DFT, language disorder is predominantly frontal in type with perseveration and reduced speech production, neurological signs are not feature of DFT only in the late stages do primitive reflexes and varying degrees of rigidity and atonia appear **(Byrne, 1997).**

Among these cardinal features of DFT are two of the five feature that **Klatka and Colleagues (1996)** have flagged as clues to an alternative diagnosis to AD namely absence of visuospatial impairment and early personality changes.

- **Dementia with lewy bodies (DLB).** The characteristic clinical features of DLB are progressive cognitive decline which shows extreme variability within a day and from day to day as well as early and complex visual hallucinations and spontaneous parkinsonism, Autonomic features (such as orthostatic hypotension) may be prominent and about 15% of causes have myoclonus **(Byrne 1997).**
- **Creutzfeldt- Jakob disease (CJD):**

CJD Belongs to a group of degenerative brain disease, known as the prion dementia or spongiform encephalopathies, the onset of dementia is seen around the age of 60 years rapidly progressing with myoclonus, motor dysfunction, visual disturbances and a characteristic EEG with periodic sharp wave complexes, pathologically confirmed cases of CJD have been misdiagnosed as AD **(Byrne 1997).**

The Aids Dementia Complex:

The acquired immune deficiency syndrome (AIDS) is frequently complicated by a clinically distinct and generally progressive encephalopathy in which dementia and motor dysfunction predominate, the precise incidence of this AIDS dementia complex is uncertain, but it may eventually afflict the majority of AIDS patients **(Epstein et al., 1985).**

Nuerological diseases affecting the brain during the late stages of HIV infection cause considerable morbidity and are associated with a poor prognosis. These late complications can be due to diffuse HIV related pathology such as in HIV dementia (also called AIDS dementia complex, HIV-1- associated cognitive motor complex) or due to focal lesions caused by opportunistic pathogens.

The group of opportunistic brain diseases consists mainly of progressive multifocal leukoencephalopathy, cerebral toxoplasmosis and primary CNS lymphoma **(Baldeweg et al., 1998).**

The brains of patients with AIDS with dementia or cerebral atrophy show varying degree of demyelination, neuronal loss, gliosis, microglial activation, multinucleated gaint cells and detectable HIV antigen or RNA. Probable mechanisms responsible for the non-specific neuropathological changes are as follows (a) the gliosis results from a strocyte proliferation in response to tumornecrosis factor- a (tnf a) (b) the myelin pallor may be due to S-adenosyl methionine (SAM) deficiency or the production of TNF a or other cytokines and oxygen radicals and

(c) the neuronal loss may be due to local production of neurotoxins such as guinolinic acid, arachidonic acid metabolites, free radicals and nitric oxide (NO)-NO- produced by certain types of neurons as macrophages, microglia and astrocytes **(Tan and Guiloff, 1998).**

subjects and Methods

SUBJECTS AND METHODS

The study was carried out over a six months period (May-October 1998) and conducted at Psychiatry and Medical Biochemical Department, Faculty of Medicine, Zagazig University.

Subjects:

Sixty subjects were participated in this study:

"40" patients with dementia disorder with established diagnoses according to DSM IV attending the outpatient psychiatric clinic of Zagazig University Hospital, 20 degenerative dementia patients include 13 males and 7 females of age range 65 to 85 years, with mean age 71.7±6.1 and 20 vascular dementia patients include 10 males and 10 females of age range to 60 to 80 years with mean age 66.8±5.4, the Hachinski cerebral ischaemia scale was carried out to differentiate between degenerative and vascular dementia patients, the severity of dementia was carried out by using the mini-mental state examination.

- "20" control subjects consisted of "10" non demented healthy subjects include 6 males and 4 females of age range 60 to 75 years with mean age 67.0±5.05 and "10" non demented depressed control diagnosed according to DSM IV include 5 males and 5 females of age range 60 to 73 years with mean age 64.1±4.3 years

4- Main groups were assigned:

1- Degenerative dementia group.

2- Vascular dementia group.

3- Non demented depressed control.

4- Non demented healthy control.

Methods:

1-A semistructured psychiatric interview designed for the study, derived from the psychiatric case record sheet of the psychiatric department of Zagazig University Hospital was applied to all patients for the purpose of collecting clinical and socioeconomic data occupation were classified according to **Barker (1985)** and diagnosing patients according to DSM IV criteria (appendix I).

2- Full medical and neurological examination to exclude any other causes of dementia (appendix II) each selected case was examined clinically for pulse rate, blood pressure, temperature also complete chest, cardiac, abdominal, thyroid and neurological examination was carried out to exclude other causes of dementia and the only controlled hypertensive patients was participated in this study.

3 **Radiological assessment:** This was carried out by the computerized axial tomographic scanning (CAT scan) of the brain. The one used was that of Zagazig University Hospital, Faculty of Medidcine. contrast enhancement by intravenous administration of iodine-containing x-ray contrast agents such as urographin was performed.

4- Neuropsychological assessment:

1- **Mini-mental (MMS) examination** mini-mental state examination **(Folstein et al., 1975)** (Appendix **III).**

It assess:

- Subject's orientation to time and place (visuospatial orientation).
- Instantaneous recall.
- Short-term memory.
- Serial substraction.
- Constructional capacities (copying a design).
- Use of language.

The total score is 30. The score of 24 is used to distinguish the normal from the abnormal.

2- **Hachinski ischaemic scale (Appendix IV).**

It is a scoring system to differentiate between vascular from degenerative dementia, a total score of 4 or less speaks against a vascular form of dementia and in favour of a primary degenerative dementia. Total score of 8 or more suggest a vascular dementia **(Hachinski et al., 1975).**

3- **Hamilton scale for depression (HSD) (Hamilton, 1960)** (Appendix V)

The Hamilton Rating Scale for Depression is a widely used depression scale with up to 24 items, each of which is rated 0 to 4 or 0 to 2, with a total score of 0 to 76, the clinician evaluates the patient's answers to questions about feelings of guilt, thoughts of sucide, sleep

habits and other symptoms of depression and the ratings are derived from the clinical interview.

4- The Zagazig depression scale (ZDS) (Fawzi et al., 1983). (Appendix V1)

This is a self rating instrument for measuring depression. Presented in the form of 52 questions written in Arabic, the answer for each question is either "Yes" or "No" and the questions cover 17 items involving the symptoms and signs of depression: These are:

1. Depressive mood.
2. Guilty feelings.
3. Suicidal tendency.
4. Early insomnia.
5. Interrupted sleep.
6. Late insomnia.
7. Work and interests.
8. Retardation.
9. Irritability.
10. Psychic tension.
11. Somatic tension.
12. Gastrointestinal symptoms.
13. General somatic symptoms.
14. Libido.
15. Hypochondriasis.
16. Loss of insight.
17. Loss of weight.

These items, and the weight of their scores are modelled of Hamilton scale for depression (HSD), but rated by the patient himself. It has been suggested that investigations using both instrument together are more soundly based **(Shaheen and Fawzi, 1985)**

5- Biological investigation (Biochemical tests)

A- Routine laboratory test:

Which include the following:

1- Complete urine analysis.

2- Complete blood picture.

3- Blood sugar (fasting and postprandial) the patients participated in this study with controlled blood sugar.

4- Renal function test.

5- Liver function test.

6- Thyroid function test.

7- Serum cholesterol and triglycerides

B- Biochemical assessment of:

A-Serum vitamin B 12 level.

B-Platelet mono amine oxidase activity

1- Determination of vitamin B_{12}

Vitamin B_{12} was quantified by IMX automoted system using the commercial kits, supplied from abbott laboratories, diagnostic division. IMX vitamin B_{12} assay is based on microparticles enzyme immunoassay (MEIA) technology in which the substrate 4-methyl-umbelliferyl

phosphate, was added to the matrix cell and the fluorescent product was measured by MEIA optical assembly according to **Lee and Griffiths (1985).**

Procedure:

10 ml of venous blood from every subject were withdrawn and divided into two tubes, the first portion as collected into anticoagulant free tube for serum determination of vitamin B_{12} and the second portion was collected on EDTA acid (5%) for platelet monoamine oxidase B activity.

2- Determination of platelet monoamine oxidase activity:

Platelet monoamine oxidase B activity was determined according the method described by **Tipton and yaudimi(1976)** based on the oxidation of benzlamine followed by benzladehyde extraction by cyclohexan.

Platelet rich plasma was prepared by centrifugation at 170 g for 10 minutes. The platelet rich plasma was then centrifugated at 2700 g for 15 minutes and the supernatent was discarded and the platelet pellet was resuspended in 500 ul of ammonium hloride (0.87%) to destory erythrocytes. After centrifugated at 1500g for 10 minutes, the pellets were washed once with 0.9% saline solution, resuspended in 500 ul of 0.25M sucrose, and finally frozen at -70°C and untill the assay time of platelet monoamine oxidase B activity.

Prior to the assay, the platelets pellets were left at room temperature till complete thawing then thawed pellets were shaked by

sonication with a microprobe with 30 pulses at 5 w. 225 ul of 0.1 M phosphate buffer, pH 7.4 were added to each platelet pellet then incubated for 7 minutes at 37°C in a borosilicate glas tubes. The amount of protein in pellets were determined according to the method of **Bradford (1976)** with bovine serum albumin as a standard.

Procedure:

- 600 ul of platelets extract samples were pipetted into tubes.
- 750 ul of 0.2 M phophate buffer, pH 7.4 were added to each tube.
- 150 ul of 0.008 M (1.2 mole) benzlamine in phosphate buffer were also added to each tube.
- The reaction mixture tubes were then incubated at 37°C in electric shaker for 3 hours.
- After incubation, 150 ul of 60% perchloric acid were added to each tube.
- 1.5 ml of cyclohexane were added after that to each tube.
- All tubes were the shacked vigrously by vortex for 2 minutes.
- The tubes were allowed then to stand at room temperature for 15 minutes and then shacked another time.
- All tubes were centrifuged of 10 minutes at 2000 rpm.
- The optical denesties of cyclohexane extract were measured at spectrophotometer at wavelength 242 nm.
- The optical densties were multiplied by 100 to convert to enzyme unites.

STATISTICAL ANALYSIS

The data were entered to an EPI.INFO file using EPI [6.03] software computer package **(WHO, 1994).**

Measures of central tendency were computed for all variables tested and correlation were used.

$$\text{Mean, } = \frac{EX}{n} \quad \frac{\text{Sum of the values}}{\text{Number of the values}}$$

$$\text{Standard deviation, S.D.} - \sqrt{\frac{E\,(X - X)^2}{(n - 1)}}$$

$$\text{Standard error SE} - \frac{SD}{}$$

t test when comparing two means:

$$t = \frac{- x2}{\sqrt{\frac{SD_1^2}{n_1} \quad \frac{SD_2^2}{n2}}} \qquad d\,F = n_1 + n_2 - 2$$

Where X_1, X 2= The sample mean for group l& 2 respectively

SD_1, SD_2 =The corresponding standard deviation of the two groups

$n_1, n2$ = number of observation in group 1,2

ANOVA analysis of variance:

Is used to compare the means of several groups.

$$F \quad \frac{\text{Between groups MS}}{\text{Within groups MS}}$$

$$\text{Mean of squares, MS} = \frac{SS}{d.f}$$

SS = sum of squares.

Between groups SS = $\Sigma ni\,(Xi - X)^2$

d.f. between groups = K-1

where K = The number of groups

Within groups SS $= \Sigma n_i (n_i - 1)S,^2$

$df = (N-K)$

where N = The total number of observations

Correlation:

Measures the closeness of the association

$$r = \frac{\Sigma(X - \bar{X})(y - \bar{y})}{\sqrt{\Sigma(X - \bar{X})^2 \Sigma(y - \bar{y})^2}}$$

where X denotes one variable and Y the other variable

X and Y are the corresponding means

"**r**" is positive if X and Y tend to be high or low together.

Conversely, the "r" is negative if high values of Y tend to go with low values of X.

The Chi-squared test is used to test whether there is an association between the row and column variable.

$$X^2 = \Sigma \frac{[O - E]^2}{E}$$

D.f. = [r —1] [C-1]

Where: 0 = Observed Value.

E = Expected value — $\frac{\text{Column total} * \text{Row total}}{\text{Overall total}}$

Kruskal-Wallis equivalent to Chia-squared used in non parametric result.

Results

RESULTS

The results of this study could best be described under 5 headings:

A- Comparison between demented patients and control subjects. Tables (la-lb).

B- Comparison between degenerative dementia, vascular dementia patients and control subjects (Tables 2a-2b).

C-Comparison between degenerative and vascular dementia. Tables (3a-3 b).

D- Comparison between degenerative dementia and vascular dementia as regards the influence of selected variable on other variables (Tables 4 - - - 15).

E- Correlation between platelet mono amine oxides and vitamin B 12 in different patient groups. Table (16).

A- Comparison between demented patients and control subjects:

(A) As Table (la) demonstrate that:

1- Platelet monoamine oxidase: (Plat MAO) the mean of plat MAO of demented patients is 2.4, depressed patients is 1.85 and healthy control is 1.86 with statistical significant difference was found which by direct analysis revealed that a highest plat-MAO activity was found in demented patients.

2- Vitamine B12 (vit B12): The mean of Vit B12 of demented patients is 246.6, depressed patients is 294.7 and healthy control is 329.2 with significant difference was found which by direct analysis revealed that a lowest vit. B12 activity was found in demented patients.

3- Mini-mental state (MMS): The mean of MMS of demented patients is 11.6, depressed patients is 29.9 and healthy control is 29.8 with highly statistically significant difference which by direct analysis revealed that lowest MMS was found in demented group.

4- Zagazig depression scale (ZDS): The mean of ZDS of demented patients is 10.3, depressed patient is 31.0 and healthy control is 6.6 with highly significant difference was found which by direct analysis of result revealed that a highest ZDS score was found in depressed patients.

6- Hamilton depression scale (HDS): The mean of HDS of demented patients is 12.1, depressed patients is 31.6 and healthy control is 6.7 with highly significant difference was found which by direct analysis revealed that a highest HDS score was found in depressed patients.

Table (la): Comparison between demented patients and control subjects.

	Dementia group (n=40)		Depressed control(n=10)		Healthy control(N=10)			
	X	SD	X	SD	X	SD	t	P
Plat. MAO	2.4	0.65	1.8 5	0.29	1.86	0.6	5.88	0.005*
Vit. B12	246.6	74.6	294.7	80.1	329.2	109.5	4.68	0.012*
MMS	11.6	3.1	29.3	1.25	29.8	0.4	311.6	0.001* HS
ZDS	10.3	4.1	31.0	3.7	6.6	1.35	141.01	0.000* HS
HDS	12.1	4.6	31.6	1.7	6.7	1.3	125.8	0.000* HS

Table (la) showing comparison between demented patients and control groups that revealed a significant difference between demented patients and control groups as regards, plat.MAO and vit B12 and a very highly significant difference as regards MMS, ZDS and HDS.

X = mean SD = Standard deviation
P=P-value T= test
Plat MAO = Platelat monoamine oxidase.
Vit B12 = Vitamin B12. MMS = Min. mental state
ZDS = Zagazig depression scale. HDS = Hamilton depression scale.

(B) As Table (lb) demonstrate that:

(1) Sex: males represented 57.5% of demented patients, 50% of depressed control and 60% of healthy control; females represented 42.5%, 50% and 40% respectively and no significant difference was found.

(2) Smoking: non smokers represented 40% of demented patients, 60% of depressed control and 50% of healthy control; smokers, represented 60%, 40% and 50% respectively and no significant difference was found.

(3) Family history: negative family history represented 75% of demented patient, 100% of depressed control and 100% of healthy control; positive family history represented 25%, 0% and 0% respectively and significant difference was found.

(4) Psychotic symptoms: subjects without psychotic symptoms represented 52.5% of demented patients, 100% of depressed control and 100% of healthy control; subjects with psychotic symptoms represented 47.5, 0.0% and 0.0% respectively and highly significant difference was found.

(5) Hypertension: non hypertensive represented 27.5 of demented patients, 40% of depressed control, and 50% of healthy control; hypertensive represented 72.5%, 60% and 50% respectively and no significant difference was found.

(6) Diabetes: non diabetics represented 45% of demented patients, 70% of depressed control and 60% of healthy control; diabetics represented 55%, 30% and 40% respectively and no significant difference was found.

Table (lb): Comparison between demented patients and control subjects:

	Dementia group (N=40)		Depressed control (No=10)		Healthy control (No=10)			
	No	%	No	%	No	%	X2	P
Sex								
Male	23	57.5	5	50	6	60	0.24	0.8
Female	17	42.5	5	50	4	40		
Smoking								
Non smokers	16	40	6	60	5	50	1.41	0.49
Smokers	24	60	4	40	5	50		
Family history								
Negative	30	75	10	100	10	100	6.0	0.04*
Positive	10	25	0	0.0	0	0.0		
Psychotic symptoms								
Without psych. symptoms	21	52.5	10	100	10	100	13.9	0.001'
With psych. symptoms	19	47.5	0	0.0	0	0.0		
Hypertension								
Nonhypertensive	11	27.5	4	40	5	50	2.06	0.35
Hypertensive	29	72.5	6	60	5	50		
Diabetes								
Non diabetics	18	45	7	70	6	60	2.34	0.3
Diabetics	22	55	3	30	4	40		

Table (lb) showing comparison between demented groups and control subjects that revealed a significant difference in relation to family history and a very highly significant difference in relation to psychotic symptoms.

X^2 = Chi- sugared test.

B- Comparison between degenerative dementia, vascular dementia and control subjects:

(A) As Table (2a) demonstrate that:

(1) Plat. MAO: The mean of plat.MAO of degenerative dementia is 2.57, vascular dementia is 2.27, depressed control is 1.85 and of healthy control is 1.86 with significant difference was found which by direct analysis revealed that a highest plat.MAO activity was found in degenerative and vascular dementia.

(2) Vit.B12: The mean of Vit B12 of degenerative dementia is 208.4, vascular dementia is 246.7, depressed control is 294.7 and of healthy control is 329.2 with highly significant difference was found which by direct analysis revealed that the lowest vit B 12 activity was found in degenerative dementia and higher activity in depressed control.

(3) ZDS: The mean of ZDS of degenerative dementia is 10.1, vascular dementia is 10.55, depressed control is 31.0 and of healthy control is 6.6 with highly significant difference was found.

(4) HDS: The mean of HDS of degenerative dementia is 11.95, vascular dementia is 12.25, depressed control is 31.6 and of healthy control is 6.7 with highly significant difference was found.

(5): MMS: The mean of mms of degenerative dementia is11.3, vascular dementia is 11.75, depressed control is 29.3 and of healthy control is 29.8 with highly significant different was found.

Table (2a): Comparison between demented groups and control subjects

	Dementia				Depressed control		Healthy control			
	Degenerative N=20		Vascular N=20		N=10		N=10			
	X	SD	X	SD	X	SD	X	SD	t	P
Plat. MAO	2.57	0.6	2.27	0.68	1.85	0.296	1.86	0.59	4.87	Sig.
Vit. B12	208.4	60.9	248.7	68.0	294.7	80.1	329.2	109.5	6.97	HS
MMS	11.3	3.1	11.75	3.15	29.3	1.25	29.8	0.42	206.1	HS
ZDS	10.1	4.1	10.55	4.2	31.0	3.7	6.6	1.3	92.6	HS
HDS	11.95	3.94	12.25	5.2	31.6	1.7	6.7	1.3	82.5	HS

Table (2a) showing comparison between dementia (degenerative and vascular), depressed control and healthy control that revealed a significant difference as regards Plat.MAO and a highly significant difference as regards Vit. B12, MMS, ZDS and HDS.

(B) As Table (2b) demonstrate that:

(1) Sex: Male represented 65% of degenerative dementia, 50% of vascular dementia, 50% of depressed control and 40% of healthy control, female represented 35%, 50%, 50% and 40% respectively and no significant difference was found.

(2) Smoking: Non smokers represented 35% of degenerative dementia, 45% of vascular dementia, 60% of depressed control and 50% of healthy control; smokers represented 65%, 55% 40% and 50% respectively and no significant difference was found.

(3) Family history: Negative family history represented 80% of degenerative dementia 70% of vascular dementia 100% of depressed control and 100% of healthy control, positive family history represented 20%, 30%, 0.0% and 0.0% respectively and no significant difference was found.

(4) Psychotic symptoms: subjects without psychotic symptoms represented 50% of degenerative dementia, 55% of vascular dementia, 100% of depressed control and 100% of healthy control; subjects with psychotic symptoms represented 50%, 45%, 0.0% and 0.0% respectively with significant difference was found.

(5) Hypertension: non hypertensive represented 40% of degenerative dementia, 15% of vascular dementia, 40% of depressed control and 50% of healthy control; hypertensive represented 60%, 85%, 60% and 50% respectively with no significant difference was found.

(6) Diabetes: non diabetics represented 50% of degenerative dementia, 40% of vascular dementia, 30% of depressed control and 40% of healthy control; diabetics represented 50%, 60%, 70% and 60% respectively with no significant difference was found.

Table (2b): Comparison between demented groups and control subjects

	Dementia				Depressed control (N=10)		Healthy control (N=10)			
	Degenerat. (N=20)		Vascular (N=20)							
	No	%	No	%	No	%	No	%	X2	P
Sex										
Male	13	65	10	50	5	50	6	60	1.15	0.76
Female	7	35	10	50	5	50	4	40		
Smoking										
Non smokers	7	35	9	45	6	60	5	50	1.82	0.6
Smokers	13	65	11	55	4	40	5	50		
Family history										
Negative	16	80	14	70	10	100	10	100	6.72	0.08
Positive	4	20	6	30	0	0.0	0	0.0		
Psychotic symptoms										
Without psych. symptoms	10	50	11	55	10	100	10	100	14.02	0.002*
With psych. symptoms	10	50	9	45	0	0.0	0	0.0		
Hypertension										
Nonhypertensive	8	40	3	15	4	40	5	50	4.88	0.18
Hypertensive	12	60	17	85	6	60	5	50		
Diabetes										
Non diabetics	10	50	12	40	3	30	4	40	2.24	0.4
Diabetics	10	50	8	60	7	70	6	60		

Table (2b) showing comparison between dementia (degenerative and vascular), depressed control and healthy control that revealed a significant difference as regards psychotic symptoms.

C- Comparison between degenerative dementia and vascular dementia:

(A) As Table (3a) demonstrate that:

(1) Age at onset: The mean of age at onset of degenerative dementia is 66.95 and of vascular dementia is 64.4 with no significant difference was found.

(2) Plate MAO: The mean of plat .MAO of degenerative dementia is 2.57 and of vascular dementia is 2.27 with no significant difference was found.

(3) Vit. B12: The mean of vit $_{B12}$ of degenerative dementia is 208.4 and of vascular dementia is 246.7 with highly significant difference was found which by direct analysis of results revealed that the lowest vit B_{12} activity was found in degenerative dementia.

(4) Mini–mental state (mms): The mean of mms of degenerative dementia is 11.3 and of vascular dementia is 11.75 with no significant difference was found.

(5) ZDS: The mean of ZDS of degenerative dementia is 10.1 and of vascular dementia is 10.55 with no significant difference was found.

(6) HDS: The mean of HDS of degenerative dementia is 11.95 and of vascular dementia is 12.35 with no significant difference was found.

Table (3a): Comparison between degenerative and vascular dementia:

	Degenerative N=20		Vascular N=20		T	P
	X	SD	X	SD		
Age at onset	66.95	5.95	64.4	6.15	1.33	0.18
Plat. MAO	2.57	0.61	2.27	0.68	1.49	0.13
Vit. B12	208.4	60.9	246.7	68.0	3.73	0.0001* HS
MMS	11.3	3.1	11.75	3.15	0.6	0.55
ZDS	10.1	4.1	10.55	4.2	0.34	0.73
HDS	11.95	3.94	12.25	5.2	0.39	N.S

Table (3a) showing comparison between degenerative and vascular dementia that revealed a highly significant difference as regards vit. B_{12},

(B) As Table (3b) demonstrate that:

(1) Sex: males represented 65% of degenerative dementia and 50% of vascular dementia ;females represented 35% and 50% respectively and no significant difference was found.

(2) Smoking: non smokers represented 35% of degenerative dementia and 45% of vascular dementia, smockers represented 65% and 55% respectively with no significant difference was found.

(3) Family history: subjects with negative family history represented 80% of degenerative dementia and 70% of vascular dementia, subjects with positive family history represented 20% and 30% respectively and no significant difference was found.

(4) Psychotic symptoms: subjects without psychotic symptoms represented 50 of degenerative dementia,and 55% of vascular dementia; subjects with psychotic symptoms represented 50 and 45 respectively with no significant difference was found.

(5) Hypertension: non hypertensive represented 40% of degenerative dementia and **15%** of vascular dementia, the hypertensive represented 60% and 85% respectively and no significant difference was found.

(6) Diabetes: non diabetics represented 50% of degenerative dementia and 40% vascular dementia; the diabetics represented 50% and 60% respectively with no significant difference was found.

Table (3b): Comparison between degenerative and vascular dementia:

	Degenerative N = 20		Vascular N = 20		X^2	P
	NO	%	NO	%		
Sex						
Male	13	65	10	50	0.92	0.33
Female	7	35	10	50		
Smoking						
Non smokers	7	35	9	45	0.42	0.51
Smokers	13	65	11	55		
Family history						
Negative	16	80	14	70	0.53	0.46
Positive	4	20	6	30		
Psychotic symptoms						
Without psych. symptoms	10	50	11	55	0.1	0.75
With psych. symptoms	10	50	9	45		
Hypertension						
Nonhypertensive	8	40	3	15	3.3	0.07
Hypertensive	18	60	17	85		
Diabetes						
Non diabetics	10	50	12	40	0.4	0.52
Diabetics	10	50	8	60		

Table (3b) showing comparison between degenerative dementia and vascular dementia that revealed no statistically significant difference.

(D) Comparison between degenerative dementia and vascular dementia as regards influence of selected variable on other variables:

(1) Age at onset:

As Table (4) shows that the comparison between degenerative and vascular dementia as regards the influence of age at onset on other variables; the correlation coefficient of plat.MAO is 0.16, vit B12 is 0.45, MMS is 0.15, ZDS is 0.02, HDS is 0.17, family history is 0.22, psychotic symptoms is 0.01, diabetes is 0.15 and hypertension is 0.17 with significant difference was found as regards vit.B12 level.

(2) Sex:

1-As Table (5a) shows that the influence of sex on other variables in degenerative dementia which by direct analysis of results and T-test revealed no statistically significant difference was found.

2-As Table (5b) show that the influence of sex on other variables in degenerative dementia, in male patients, positive family history represented 15.4%, smokers 100%, psychotic symptoms, 46.2% diabetics 53.8% and hypertensive 61.5% in female patients represented 28.6%, 0.0%, 57.1%, 42.9% and 57.1% respectively with highly significant difference was found as regards smoking.

3- As Table (5c) shows that the influence of sex on other variables in vascular dementia which by direct analysis of results and T-test revealed no statistically significant difference was found.

4- As Table (5d) shows that the influence of sex on other variables in vascular dementia; in male patients, positive family history represented 30%, smokers 100%, psychotic symptoms 20%, diabetics 70% and hypertensive 80%; in female patients represented 30%, 10%, 70%, 50% and 90% respectively with significant difference was found as regards psychotic symptoms and highly significant difference as regards smoking.

(3) Duration of illness:

As Table (6) shows that the comparison between degenerative and vascular dementia as regards the influence of duration of illness on other variables; the correlation coefficient of plat.MAO is 0.19, vit B12 is 0.03, MMS is 0.54, ZDS is 0.04, HDS is 0.31 and pyschotic symptoms is 0.22 in degenerative dementia, but in vascular dementia is 0.17, 0.35, 0.35, 0.19, 0.05 and 0.15 respectively with significant difference was found as regards MMS.

(4) Family history:

As table (7) show that the comparison between degenerative dementia and vascular dementia as regards the influence of family history on other variables, and by direct analysis of results and the "T" test revealed no significant difference.

(5) Occupation:

As Table (8a) shows that the influence of occupation on other variables in degenerative dementia which by direct analysis of results and "r test revealed no significant difference was found.

As Table (8b) shows that the influence of occupation on other variables in vascular dementia which by direct analysis of results and "f" test revealed no significant difference was found.

(6) Education:

As Table (9a) shows that the influence of education on other variables in degenerative dementia which by direct analysis of results and "T" test revealed no significant difference was found.

As Table (9b) show that the influence of education on other variables in vascular dementia which by direct analysis of results and "T" test revealed no significant difference was found.

(7) Smoking:

As Table (10) shows that the comparison between degenerative dementia and vascular dementia as regards the influence of smoking on other variables which by direct analysis of results and "T" test revealed a significant difference as regard the Vit. B12 in which the mean of vit. B12 of non smokers in degenerative dementia is 227.7 and in vascular dementia is 272.6 and the mean of vit. **B12** of smokers is 198.1 and 294.7 respectively and also revealed a significant difference as regard the duration of illness in which the mean of duration of illness of non smokers in degenerative dementia is 5.4 and in vascular dementia is 4.1 and the mean of duration of illness of smokers is 6.1 and 3.46 respectively.

(8) Mini-mental state (MMS):

As Table (11a) shows that the correlation between severity of dementia and levels of plat.MAO and Vit. B12; The correlation coefficient of plat. MAO is 0.41 and of vit. B12 is 0.34 with highly significant difference.

As Table (11b) shows that the correlation coefficient of plat. MAO is 0.18, vit. B12 is 0.01, ZDS is 0.45, HDS is 0.21 and psychotic symptoms is 0.02 in degenerative dementia group and 0.12, 0.04, 0.14, 0.18 and 0.12 respectively in vascular dementia group with significant difference was found as regard ZDS.

(9) Depression:

As Table (12a) shows that patients, were divided according to Zagazig depression scale to, no depression, mild depression, moderate depression and severe depression, and a highly significant difference was found by X^2 ($P<0.0001$).

As Table (12b) shows that patients, were divided according to hamilton depression scale to no depression, mild depression, moderate depression and severe depression, and a highly significant difference was found by X^2 ($P<0.0001$).

As Table (12c) shows that the correlation coefficient of plat.MAO is 0.17, vit.B12 is 0.2 and MMS is 0.45 in degenerative dementia and 0.24, 0.28 and 0.14 respectively in vascular dementia with significant difference as regard MMS.

As Table (12d) shows that the correlation coefficient of degenerative dementia is 0.45, vascular dementia is 0.78, depressive control is 0.77 and healthy control is 0.01 with highly significant difference was found.

(10) Psychotic symptoms:

As Table (13a) shows that by direct analysis of results and "**T**" test revealed no significant difference was found in relation to psychotic symptoms between the two patients groups.

As table (13b) shows that a significant difference was found in relation to sex in which male patients without psychotic symptoms represented 70%, and with psychotic symptoms represented 60% in degenerative dementia, and male patients without psychotic symptoms represented 72.7% and with psychotic symptoms represented 22.2% in vascular dementia; female patients represented 30%, 40%, 37.3% and 27.8% respectively.

(11) Diabetes:

As Table (14a) shows that a significant difference was found as regard vit **B12** level in which the mean of degenerative dementia patients without diabetes is 240 and with diabetes is 176.9 and of vascular dementia is 271.9 and 243.3 respectively.

As Table (14b) shows that by direct analysis of results and "t" test revealed no significant difference was found .

(12) Hypertension:

As Table (15a) shows that by direct analysis of results and "T" test revealed no significant difference was found.

As Table (15b) shows that a significant difference was found as regard psychotic symptoms in which the psychotic symptoms in non hypertensive represented 12.5% and in hypertensive represented 75% of degenerative dementia and in vascular dementia is 33.3% and 47.1% respectively.

Table (4): Age at onset.

	Degenerative(n=20)		Vascular(n=20)	
	r	**P**	**r**	**P**
Plat.MAO	0.16	>0.05	0.24	>0.05
Vit. B12	0.45	<0.05*	0.22	>0.05
MMS	0.15	>0.05	0.12	>0.05
ZDS	0.02	>0.05	0.1	>0.05
HDS	0.17	>0.05	0.1	>0.05
Family history	0.22	>0.05	0.08	>0.05
Psychotic symptoms	0.01	>0.05	0.26	>0.05
Diabetes	0.15	>0.05	0.36	>0.02
Hypertension	0.17	>0.05	0.38	>0.05

Table (4) showing comparison between degenerative and vascular dementia as regard the influence of age at onset on other variables that revealed a significant difference as regard vit. B12.

Table (5a_b): Sex and degenerative dementia.

	Male(n=13)		Female(n=7)			
	X	**SD**	**X**	**SD**	**t**	**P**
Plat.MAO	2.5	0.6	2.6	0.6	0.32	0.7
Vit.B12	198.1	53.9	227.7	72.6	1.03	0.31
MMS	11.4	2.7	11.3	3.99	0.06	0.94
ZDS	9.2	3.4	11.9	4.98	1.43	0.16
HDS	11.3	4.2	13.1	3.2	0.99	0.66

Table (5a) showing comparison of the influence of sex on other variables in degenerative dementia that revealed no significant difference.

	Male(n=13)		Female(n=7)			
	No	**%**	**No**	**%**	**X^2**	**P**
Family history	2	15.4	2	28.6	0.49	0.48
Smoking	13	100	0	0.0	20	0.0001**
Psychotic sympt.	6	46.2	4	57.1	0.22	0.63
Diabetes	7	53.8	3	42.9	0.22	0.63
Hypertension	8	61.5	4	57.1	0.04	0.84

Table (5b) showing comparison of the influence of sex on other variables in degenerative dementia that revealed a highly significant difference as regards smoking.

Table (5c_d): Sex and vascular dementia.

	Male(n=10)		Female(n=10)			
	X	**SD**	**X**	**SD**	**t**	**P**
Plat.MAO	3.4	0.7	2.2	0.6	0.6	0.56
Vit.B12	295.6	80.7	273.9	54.7	0.7	0.5
MMS	12.1	3.4	11.8	3.1	0.2	0.83
ZDS	9.9	4.1	11.2	4.3	0.68	0.5
HDS	12.6	3.9	11.9	6.4	0.29	0.76

Table (5c) showing comparison of the influence of sex on other variables in vascular dementia that revealed no significant difference.

	Male(n=10)		Female(n=10)			
	No	**%**	**No**	**%**	**X2**	**P**
Family history	3	30	3	30	0.0	1.0
Smoking	10	100	1	10	16.36	0.0001**
Psychotic sympt.	2	20	7	70	5.05	0.024
Diabetes	7	70	5	50	0.83	0.36
Hypertension	8	80	9	90	0.39	0.53

Table (5d) showing comparison of the influence of sex on other variables in vascular dementia that revealed a significant difference as regard psychotic symptoms and a highly significant difference as regards smoking.

Table (61: Duration of illness.

	Degenerative (N=20)		Vascular (N=20)	
	r	P	R	P
Plat.MAO	0.19	>0.05	0.17	>0.05
Vit. B12	0.03	>0.05	0.35	>0.05
MMS	0.54	<0.01	0.35	>0.05
ZDS	0.04	>0.05	0.19	>0.05
HDS	0.31	>0.05	0.05	>0.05
Psychotic symptoms	0.22	>0.05	0.15	>0.05

Table (6) showing comparison between degenerative and vascular dementia as regard the influence of duration of illness on other variables that revealed a significant difference as regard MMS.

Table (7): Family history.

	Degenerative						Vascular					
	-ye family H (n=16)		+ve family H (n=4)				-ve family H (n=16)		+ve family H (n=4)			
	X	SD	X	SD	t	P	X	SD	X	SD	t	P
Plat.MAO	2.6	0.6	2.3	0.6	0.99	0.6	2.32	0.7	2.13	0.74	0.56	0.58
Vit. B12	210.4	57.8	200.7	81.9	0.27	0.78	274.3	70.3	309.2	61.0	1.05	0.3
MMS	11.3	2.9	11.2	4.3	0.07	0.9	11.8	3.4	12.2	2.8	0.195	0.84
ZDS	10.3	4.5	9.2	2.6	0.45	0.6	10.5	4.2	10.7	4.5	0.07	0.93
HDS	12.1	4.3	11.5	2.6	0.24	0.8	11.8	3.7	13.3	8.1	0.59	0.56
Age at onset	66.3	5.9	69.5	6.1	0.95	NS	64.7	6.99	63.7	3.9	0.34	0.73
Duration of illness	5.6	1.9	7.0	2.4	1.26	0.21	4.1	1.6	2.8	0.98	1.88	0.07

Table (7) showing comparison between degenerative and vascular dementia as regard the influence of family history on other variables that revealed no significant difference.

Table (8a): occupation and de enerative .

	Professional N=4		Semiprof N = 4		Skilled worker N=4		Unskilled worker N = 4		Labrour N = 4			
	X	SD	X	SD	X	SD	X	SD	X	SD	F	P
Plat.MAO	2.8	0.4	3.0	0.5	2.2	0.7	2.3	0.4	2.55	0.8	1.27	0.32
Vit. B12	220.5	31.9	200.2	44.7	226.2	85.3	237.5	65.1	157.7	61.1	1.07	0.4
MMS	11.7	2.9	9.5	1.9	12.5	4.2	11.5	3.7	11.5	3.3	0.45	0.76
ZDS	11.7	5.7	7.3	0.5	12.2	4.3	8.7	2.9	10.5	5.1	1.03	0.42
HDS	12.7	5.3	11.7	2.9	15	5.1	10.2	3.4	10	1.4	1.09	0.39
Age at onset	71	8.3	65.5	6.6	63.7	4.3	66.3	2.9	68.2	6.5	0.84	0.51
Duration of illness	7.2	2.1	4.5	1.7	4.5	1.7	5.7	1.5	7.2	2.1	2.26	0.11

Table (8a) showing comparison of the occupational levels of degenerative dementia group. That revealed no statistically significant difference.

Table (8b): Occupation and vascular dementia.

	Professional N=3		Semiprof N = 4		Skilled worker N=5		Unskilled worker N = 5		Labrour N = 3			
	X	SD	X	SD	X	SD	X	SD	X	SD	F	P
Plat.MAO	2.5	1.1	1.8	0.7	2.3	0.6	2.5	0.5	2.1	0.7	0.64	0.6
Vit. B12	286	129.3	283	55.8	244.2	60.3	291.4	25.3	342.3	69.5	0.99	0.55
MMS	12	3	11.7	3.4	11.6	3.1	11.6	4.3	13.3	2.9	0.147	0.95
ZDS	9.3	2.5	14.5	5.3	11.2	4.8	9.6	2.7	7	1	1.41	0.15
HDS	11.3	3.2	16.7	10.5	11	2.3	11.8	2.5	10	1.7	0.99	0.55
Age at onset	62.7	2.5	65.7	3.6	67	11.4	61.6	3.2	64.7	3.1	0.53	0.71
Duration of illness	3.0	1.7	3.5	1.3	4	1.2	4.4	2.1	3.3	1.5	0.47	0.73

Table (8b) showing comparison of the occupational levels of vascular dementia group that revealed no statistically significant difference.

Table (9a): Education and degenerative dementia.

	Iliterate N= 7		Read and write N=5		Pre/secondary N=4		University N=4			
	X	SD	X	SD	X	SD	X	SD	T	P
Plat.MAO	2.5	0.65	2.2	0.7	2.9	0.4	2.8	0.5	1.33	0.29
Vit. B12	201	77.5	194	31.9	227.5	89.5	220.5	31.9	0.27	0.84
MMS	11.7	3.5	12	3.8	9.5	1.9	11.8	2.9	0.561	0.65
ZDS	9.8	4.2	10.2	4.4	8.8	2.9	11.7	5.7	0.32	0.8
HDS	10.5	4.2	12.8	5.6	18.5	3.3	12.75	5.3	0.4	0.75
Age at onset	67.8	4.8	64	3.4	65	7.1	71	8.3	1.27	0.31

Table (9a) showing comparison of the educational level of the degenerative dementia group that revealed no statistically significant difference.

Table (9b): Education and vascular dementia.

	Iliterate N= 8		Read and write N=7		Pre/secondary N=2		University N=3			
	X	SD	X	SD	X	SD	X	SD	T	P
Plat.MAO	2.4	0.6	2.1	0.6	2.1	1.1	2.5	1.1	0.25	0.8
Vit. B12	310.5	49.4	253.7	54.1	288.5	88.3	286.0	129.3	0.84	0.5
MMS	12.3	3.7	11.8	2.5	11.0	5.6	12	3.0	0.07	0.9
ZDS	8.6	2.5	13.4	5.4	10	1.4	9.3	2.5	2.09	0.14
HDS	11.1	2.3	15.1	7.6	8	1.4	11.3	3.2	1.4	0.27
Age at onset	62.7	3.3	67.4	9.3	63	2.8	62.7	2.5	0.85	0.51

Table (9b) showing comparison of the educational level of the vascular dementia group that revealed no statistically significant difference.

Table (10): Smoking.

	Degenerative N = 13		Vascular N = 11			
	X	SD	X	SD	t	P
Plat.MAO	2.5	0.6	2.3	0.7	0.75	0.53
Vit. B12	198.1	53.9	294.7	76.6	3.61	0.001*
Age at onset	66.9	6.5	63.5	3.1	1.57	0.12
MMS	11.4	2.7	12.4	3.3	0.79	0.56
ZDS	9.1	3.4	9.6	4	0.31	0.75
HDS	11.3	4.25	12.3	3.9	0.57	0.57

Table (10) showing comparison between degenerative and vascular dementia group as regards the influence of smoking on other variables that revealed a significant difference in relation to Vit. B12.

Table **(11a-b):** Severity of dementia.

	r	P	Sig
Plat.MAO	0.41	<0.001	HS
Vit. B12	0.34	<0.01	HS

Table (11 a) showing correlation between severity of dementia and levels of plat. MAO and vit. B12 that revealed a highly significant difference.

	Degenerative		Vascular	
	r	P	r	P
Plat.MAO	-0.18	>0.05	-0.12	>0.05
Vit. B12	0.01	>0.05	0.04	>0.05
ZDS	0.45	<0.05*	0.14	>0.05
HDS	0.21	>0.05	0.18	>0.05
Psychotic symptoms	0.02	>0.05	0.12	>0.05

Table (11b) showing comparison between degenerative and vascular dementia as regard the influence of severity of dementia on other variables that revealed a significant difference in relation to ZDS.

Table (12a): Incidence of depression according to ZDS.

	Degenerative dementia		**Vascular dementia**		**Dep. control**		**Healthy control**	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
No depression	14	70	10	50	0	0.0	10	100.0
Mild depression	6	30	10	50	0	0.0	0	0.0
Moderate depression	0	0.0	0	0.0	3	30.0	0	0.0
Sever depression	0	0.0	0	0.0	7	70.0	0	0.0

$X^2 = 69.26$ P<0.0001 HS

Table (12a) showing compression of depression according to Zagazig depression scale among studied groups that revealed a highly significant difference.

Table (12b): Incidence of depression according to HDS.

	Degenerative dementia		Vascular dementia		Dep. control		Healthy control	
	No	%	No	%	No	%	No	%
No depression	7	35.0	7	35.0	0	0.0	10	100
Mild depression	12	60.0	11	55.0	0	0.0	0	0.0
Moderate depression	1	5.0	2	10.0	1	10.0	0	0.0
Sever depression	0	0.0	0	0.0	9	90.0	0	0.0

$X^2 = 71.07$ $P<0.0001$ HS

Table (12b) showing compression of depression according to hamilton depression scale among studied groups that revealed a highly significant difference.

Table (12c): Correlation between depression and other variables.

	Degenerative dementia		Vascular dementia	
	r	P	r	P
Plat.MAO	0.17	>0.05	0.24	>0.05
Vit. B12	0.2	>0.05	0.28	>0.05
MMS	0.45	<0.05	0.14	>0.05

Table (12c) showing comparesion between degenerative and vascular dementia group as regard the influence of depression on other variables that revealed a significant difference in relation to MMS.

Table (12d): Correlation between ZDS and HDS.

	Degenerative dementia		Vascular dementia		Dep. control		Healthy control	
	r	P	r	P	r	P	r	P
	0.54	<0.001 HS	0.78	<0.001 HS	0.77	<0.001 HS	0.01	>0.05

Table (12d) showing a correlation between Zagazig depression scale and homilton depression scale among studied groups that revealed a highly significant in relation to degenerative dementia, vascular dementia and depressive control groups.

Table (13a - b): Psychotic symptoms.

	Degenerative dementia						Vascular dementia					
	Without psychotic symptoms(n=10)		With psychotic symptoms (n=10)				Without psychotic symptoms (n=11)		With psychotic symptoms (n=9)			
	X	SD	X	SD	t	P	X	SD	X	SD	T	P
Plat.MAO	2.6	0.5	2.56	0.7	0.06	0.9	2.5	0.7	1.98	0.5	1.79	0.08
Vit. B12	222.9	42.5	194	74.7	1.06	0.3	298.6	81.5	267.8	45.9	1.0	0.32
MMS	11.4	3.0	11.3	3.3	0.07	0.9	12.3	3.5	11.6	2.9	0.49	0.63
ZDS	10.8	4.75	9.4	3.5	0.7	0.5	9.7	3.9	11.6	4.5	0.97	0.67
HDS	13.4	4.2	10.5	3.2	1.75	0.09	11.3	4.1	13.4	6.3	0.92	0.6
Age at onset	70.6	5.6	72.8	6.8	0.79	0.5	63.0	2.8	66.1	8.6	1.13	0.27
Duration of illness	4.5	1.8	6.3	2.3	0.97	0.6	3.5	1.5	4.0	1.6	0.65	0.52

Table (13a) showing comparison between degenerative and vascular dementia groups as regard the influence of psychotic symptoms on other variables that revealed no statistically significant difference.

	Degenerative dementia						Vascular dementia					
	Without psychotic symptoms (n=10)		With psychotic symptoms (n=10)				Without psychotic symptoms (n=11)		With psychotic symptoms (n=9)			
	No	%	No	%	X2	P	No	%	No	%	x2	P
Sex												
Male	7	70	6	60	0.22	0.6	8	72.7	2	28.2	5.05	0.02*
Female	3	30	4	40		N	3	27.3	7	77.8		
Positive Family history	1	10	3	30	1.25	0.26	2	18.2	4	44.4	1.63	0.2
Smokers	7	70	6	60	0.22	0.6	8	72.7	3	33.3	3.1	0.07
Diabetics	4	40	6	60	0.8	0.37	8	72.7	4	44.4	1.65	0.19
Hypertensive	3	30	9	90	75	0.006*	9	81.8	8	88.9	0.19	0.65

Table (13b) showing comparison between degenerative and vascular dementia groups as regards the influence of psychotic symptoms on other variables that revealed a significant difference in relation to sex and hypertension.

Table (14a-b): Diabetes.

	Degenerative dementia						Vascular dementia					
	Without diabetes (n=10)		With diabetes (n=10)				Without diabetes (n=12)		With diabetes (n=8)			
	X	SD	X	SD	t	P	X	SD	X	SD	t	P
Plat.MAO	2.5	0.5	2.6	0.7	0.11	0.9	2.2	0.7	2.3	0.7	0.12	0.9
Vit. B12	240	57.7	176.9	48	2.65	0.015	271.9	47	293.3	79.9	0.68	0.51
MMS	12.1	3.3	10.6	2.8	1.08	0.29	13.1	3.1	11.2	3.0	1.39	0.17
ZDS	11.3	4.7	8.9	3.3	1.32	0.19	12.2	4.7	9.4	3.5	1.54	0.13
HDS	12.1	4.2	11.8	3.9	0.16	0.86	14.3	6.5	10.8	3.8	1.5	0.13
Age at onset	66.1	6.1	67.8	5.9	0.62	0.54	61.7	44	66.2	6.7	1.64	0.11
Duration of illness	5.6	1.9	6.1	2.3	0.53	0.6	3.9	1.5	3.7	1.6	0.29	0.76

Table (14a) showing comparison between degenerative and vascular dementia groups as regards the influence of diabetes on other variables that revealed a significant difference in relation **to** vit. B12.

	Degenerative dementia						Vascular dementia					
	without diabetes (n=10)		with diabetes (n=10)				without diabetes (n=12)		with diabetes (n=8)			
	No	%	No	%	X^2	P	No	%	No	%	X2	P
Sex												
Male	6	60	7	70	0.22	0.6	3	37.5	7	58.3	0.83	0.36
Female	4	40	3	30			5	62.5	5	41.7		
Smokers	6	60	7	70	0.23	0.6	3	37.5	6	66.7	1.65	0.19
Hypertensive	5	50	7	70	0.83	0.36	7	87.5	10	83.3	0.07	0.79

Table (14b) showing comparison between degenerative and vascular dementia groups as regards the influence of diabetes on other variables that revealed no statistically significant difference.

Table (15a-b): Hypertension

	Degenerative dementia						Vascular dementia					
	non hypertensive (n=8)		Hypertensive (n=12)				non hypertensive(n=3)		Hypertensive (n=17)			
	X	SD	X	SD	t	P	X	SD	X	SD	t	P
Plat.MAO	2.3	0.4	2.7	0.7	1.71	0.09	2.5	0.7	2.2	0.7	0.77	0.54
Vit. B12	220.7	47.9	200.2	69.1	0.72	0.5	302	123.0	281.7	59.5	0.46	0.65
MMS	12.1	3.3	10.8	3.0	0.9	0.62	10.7	2.3	12.2	3.3	0.75	0.53
ZDS	12.1	5.3	8.7	2.6	1.91	0.06	10.7	6.4	10.3	3.9	0.49	0.63
HDS	13.5	4.4	10.9	3.4	1.48	0.15	11.3	3.2	12.4	5.5	0.32	0.74
Age at onset	65.7	4.4	67.7	6.8	0.72	0.5	5.9	3.6	65.3	6.1	1.73	0.09
Duration of illness	5.0	2.4	6.4	1.7	1.56	0.13	3.7	1.5	3.8	1.6	0.1	0.9

Table (15a) showing comparison between degenerative and vascular dementia groups as regards the influence of hypertension on other variables that revealed no statistically significant difference.

	Degenerative dementia						Vascular dementia					
	Non hypertensive n=8)		Hypertensive (n=12)				Non hypertensive n=3)		Hypertensive (n=17)			
	No	%	No	%	X2	P	No	%	No	%	X2	P
Sex:												
Male	5	62.5	8	66.7	0.04	0.8	2	66.7	8	47.1	0.34	0.53
Female	3	37.5	4	33.3			1	33.3	9	52.9		
Smokers	5	62.5	8	66.7	0.04	0.8	2	66.7	9	52.9	0.39	0.53
Diabetics	3	37.5	7	58.3	0.83	0.36	2	66.7	10	58.8	0.07	0.79
With Psychotic symptoms	1	12.5	9	75	7.5	0.006*	1	33.3	8	47.1	0.19	0.65

Table (15b) showing comparison between degenerative and vascular dementia groups as regards the influence of hypertension on other variables that revealed a significant difference in relation to psychotic symptoms.

E- Correlation between plate MAO and vit B_{12} in different patient groups:

As table (16) demonstrate that the correlation coefficient of dementia (total) is 0.03, degenerative dementiais 0.3 and vascular dementia is 0.08 with no statistically significant difference was found.

Table (16): Correlation between plat MAO and vit B12.

	r	P
Dementia (total)	0.03	>0.05
Degenerative dementia	0.3	>0.05
Vascular dementia	0.08	>0.05

Table (16) showing a correlation between plate MAO and vit **B12** in different patient groups, that revealed no significant difference.

SUMMARY OF RESULTS

A- The comparison between dementia and control subjects revealed a significant difference as regards, plot.MAO, vit.B12 and family history and a highly significant difference as regards MMS, ZDS, HDS and psychotic symptoms (Tables la-lb).

B- The comparison between degenerative dementia, vascular dementia and control subjects revealed a significant difference as regards, plot.MAO and psychotic symptoms and a highly significant difference as regards vit.B12, MMS, ZDS and HDS (Tables 2a-2b).

C- The comparison between degenerative and vascular dementia revealed a highly significant difference as regards vit B_{12} (Tables 3a-3b)

D- The comparison between degenerative and vascular dementia as regards the influence of selected variable on other variables.

1- Age at onset: a significant difference was found as regards vit.B12 level Table (4).

2- Sex: a highly significant difference as regards smoking in degenerative and vascular dementia and a significant difference as regard psychotic symptoms in vascular dementia (Tables 5a,b,c,d).

3- Duration of illness: a significant difference was found as regard MMS (Table 6).

4- No significant difference was founds as regards the influence of family history, occupation and education on other of variables (Tables 7, 8a-b, 9a-b).

5- Smoking: a significant difference was found as regards the vit.B12 and duration of illness (Table 10).

6- Mini-mental state: a significant difference was found as regard. The ZDS and a highly significant difference was found as regard the correlation between severity of dementia (MMS) and the levels of plat.MAO and vit.B12 (Tables 11 **a-1 lb).**

7- Depression: a significant difference was found as regard the MMS, and a highly significant difference was found between patients groups and control groups as regards the severity of depression by both ZDS and **HDS** with a high correlation coefficient between two scales in degenerative dementia, vascular dementia and depressed control groups (tables 12a,b,c,d).

8- Psychotic symptoms: a significant difference was found in relation to sex Tables (13a-b).

9- **Diabetes:** a significant difference was found as regard vit.B12 level (Tables 14a-b).

10-Hypertension: a significant difference was found as regard psychotic symptoms (Tables 15a-b).

E- The correlation between plate. MAO and vit B12 in different patient groups revealed no significant difference was found (Table 16)

Discussion

DISCUSSION

Psychiatric research is uniquely difficult; the human brain, the organ on which psychiatric research must focus is the most complex structure in all of biology **(Hyman and Nestler, 1993)** not only complexity but also the in availability of the living human brain tissue for scientific research, together with our insisting need to find etiology or pathophysiology that accounts for mental disorders with the hope that it well help us to find more effective methods of treatment and even preventive measures, for these and other reasons indicators of the metabolism of the brain which could be measured in body fluids received much attention by psychiatric researchers.

During the past two decades many evidence have accumulated suggesting a link between mental disorders and the metabolism of biogenic amines, one of the most extensively studied subjects here is the enzyme involved in their metabolism monoamine oxidase (MAO), platelet monoamino oxidase-B activity has been found to increase significantly in geriatric patients with alzheimer's disease with and without depression (Dainelczyk et **al., 1988).** Recent evidence suggests that this increase is due to vitamin B_{17} deficiency **(Parnetti et al., 1992).** Low vitamin B_{12} levels in the serum are known to be quite common in patients with senile dementia and confusion, even in the absence of haematological changes there as indications that vitamin B_{12} has an etiological role in the genesis of dementia, brain autopsies from patients with pernicious anemia revealed cerebral white matter changes that were

related to psychiatric symptoms of dementia, these cerebral changes were described as a demyelinating subacute degeneration, which is in agreement with the finding of spinal cord lesions reproduced in experiments on vitamin B12 deficient rhesus monkeys (**Regland et al., 1988).**

Monoamine oxidase (MAO) is a key enzyme in the degeneration of monamine neurotransmitters, two subtypes of MAO are known: MAO-A and MAO-B with different affinities to several substrate and inhibitors. Since platelet MAO is almost entirely of the B-type and since many of the alterations in MAO activity in mental disorders are caused by MAO-B changes, the usefulness of this peripheral model is evident as marker for possible change in brain, as there is little possibility of measuring MAO activity in human brain in vivo **(Danielczyk et al., 1988).**

High platelet monoamine oxidase activity has been reported in dementia **(Adolfsson et al., 1980; Alexopoulos et al.,1984, 1987; Danielczyk et al., 1988)** and also vitamin B12 deficiency reported in dementia **(Reglond et al., 1988, 1991; Oreland et al., 1990; Parnetti et al., 1992)** however there is a considerable overlap in values between patients and normal control subjects, moreover, the findings of these studies were contradicting as regarding the relation of MAO activity and vitamine B12 levels to dementia subtypes or to a certain factors e.g balanced nutrition.

This study provides, in addition to complete sociodemographic and clinical data of patients and control; a biochemical trial to link platelet

MAO activity with vitamin B_{12} level and with a plenty of symptoms and variables.

Patients on whom the study was carried out were:

Mostly chronic patients, receiving the classic psychotropic or neurotonic, available in an zagazig university hospital and out patients clinic, consequently we were not able to have patients on and off medication as we washed. To have patients on and off medication, is important for excluding the treatments effects on the MAO activity and also we were not able to have patients with the same diatery intake, which is important to exclude the malnutrition as a common cause of vitamin B_{12} deficiency.

The data presented in this study indicate that certain features are shared by a high proportion of patients. The findings demonstrate a number of important points.

A) Patients versus control subjects:

- When the platelet monoamine oxidase (plat. MAO) level of dementia patients was compared to that of the control subjects, a significant difference was found as the plat. MAO activity is significantly higher in demented patients than control subjects. Our finding agrees with the reports of **Alexopoulos et al. (1984), Oreland and Gottfries (1986), Regland et al. (1988), Danielczyk et al. (1988), Fischer et al.**

(1994), Meszaro et al. (1998), Gotz et al. (1998) and **Soto et al. (1999).**

The increase of mono amine oxidase activity might be due to a disease related enhanced affinity to oxygen and to such oxygen derived radicals as superoxide or hydroxyl radicals, neurotoxic factors especially radicals, combined with genetic predisposition might cause dementia of Alzheimer's type. Cell damage of demented patients could be trigered by a change in membrane fluidity as shown for platelets of demented patients which is generated through the production of toxic radical, the discovery that hydrogen peroxide is able to enhanc MAO activity **(Konradi et al., 1986)** in coherance with enhanced MAO activity in the platelets of the dementia of Alzheimer type seems to support a radical hypothesis for the pathophysiology of disease (Danielczyk **et al., 1988).**

-The vitamin B 12 level is significantly decreased in demented patients than control subjects, a finding that is going with several previous studies of **Scott et al. (1981), Gross et al. (1986), Regland et al. (1988), Fischer et al. (1994), Bottiglieri et al. (1996), Parnetti et al. (1992-1997), Eastley et al. (2000)** and **Meins et al. (2000).**

The vitamin **B_{12}** deficiency is more common in the elderly than in younger patients. This is because of the increased prevalence of cobalamine malabsorption in this age group, which is mainly caused by autoimmune atrophic body gastritis, elderly individuals with cobalamin deficiency may present with neuropsychatric disorders without frank macrocytic anaemia **(Nilsson, 1998).** Vitamin B12 is required in the

methylation of homocysteine to methionine and in the synthesis of s-adenosylmethionine. S-adenosylmethionine is involved in neumerous methylation reactions involving proteins, phospholipids, DNA and neurotransmitter metabolism. Vitamin B_{12} deficiency may cause neurologic and psychiatric disturbance including dementia. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of this vitamin deficiency in addition the neurotoxic effects of homocysteine may play a role in the neuropsychatric disturbances that are associated with vitamin B_{12} deficiency **(Bottiglieri, 1996 and Parnetti et al., 1997).**

-A highly significant difference was found between the demented patients group and control subjects as regards the mini-mental state score, which by direct analysis; it became apparent that mini-mental state score is much lower in patients group than in control subjects, this was expected because it is well established clinically that the mini-mental state score is low in demented patients **(Kaplan et al., 1997).** This finding is consistent with the findings of all discussed previous studies in field of dementias (Alexopoulos **et at (1984), oreland and Gottfries (1986), Regland et al (1988),** Danielczyk **et at (1988), Fischer et at (1994), Meszaro et al (1998) and Gotz et al (1998).**

-As regards the depressive symptoms the comparison between patient groups and control groups showed that there is a highly significant difference was found which by direct analysis of results, the score of depression by both Zagazig depression scale or hamilton depression scale

is much higher in depressed control than demented patients and healthy control ,with a higher score in demented patients than healthy control. This finding agrees with the reports of **Fischer et al. (1994).**

Dementia and depression are the two most common mental illnesses in late life, and it is therefore probable that they will coexist in many patients. This coexistence is complicated by the fact that both illnesses can be mistaken for each other, so that many patients with Alzheimer's disease (AD) may initially be diagnosed as depressed, whereas depression is a recognized cause of cognitive impairment and a source of additional disability not only as a result of the affective symptoms but because depression also causes functional impairment **(Reifler 1997).**

-A significant difference was found between patient groups and control groups as regards family history, this finding agrees with the reports of Canadian study of health and aging, 1994, **Jarm (1997),** and **Gauthier et al. (1997).** As they found that the family history is the main risk factor for Alzheimaer's dementia.

-As regards the psychotic symptoms the comparison between patient groups and control subjects showed that there is a highly significant difference was found as the psychotic symptoms is much higher in demented patients than control subjects this finding in consistent with the finding of **Alexopoulos et al. (1984) and Hirono et al (1998).**

The psychotic symptoms are common in patients with dementia, the underlying mechanism for psychosis in dementia is not well understood. Although psychosis have been reported to be associated with many clinical and biological factors such as sex, age, duration of illness, education level and apolipoprotein E (APOE) genotypes the associations were variable. So possible explanation for this findings is that a particular subtype of dementia has a distinctive clinical and neuropathological features. an alternative explanation is that characteristics including genetic, psychosocial and environmental factors may affect development of psychosis. **(Hirono, et al. 1998).**

B) Patients versus patients:

-When the platelet mono amine oxidase activity of degenerative dementia patients was compared to that of vascular dementia patients, no significant difference was found, a finding that is going with previous study of Regland **et al. (1988).** But disagrees with the finding of **Danielczyk et al. (1988).**

There is overwhelming evidence to suggest that the neuropathology of Alzheimer disease (AD) extends beyond amyloid plaque and neurofibrillary tangles, review of various consortium data shows that more than 30% of AD cases exhibit cerebrovascular pathology. However, certain vascular lesions are evident in almost all cases of AD, whether, these vascular lesions are coincidental or causal in the pathogenic processes of AD remains to be defined. Although systemic

vascular influences may be responsible for such pathology in AD, its equally intriguing that about one third of patients diagnosed with vascular dementia will have AD type pathology at autopsy. We also consider pathological findings in relation to genetic influences such as apolipoprotein E. That may shed light on the link between AD and VaD **(Kalaria and Ballared, 1999).** In view of these commonalities, its reasonable to consider the same platelet monoamine oxidase activity in both AD and VaD.

-When the vitamin **B12** level of degenerative demenita patients was compared to that of vascular dementia patients a highly significant difference was found, as the vitamin $_{B12}$ level is significantly lower in degenerative dementia patients, than vascular dementia patients, a finding that disagrees with previous studies of **Regland et al. (1988, 1991)** and **Parnetti et al. (1992).**

The source of the discrepancy between our study and that of **Regland et al. (1988, 1991)** and **Parnetti et al. (1992)** is not known but may be related to imbalanced nutrition between degenerative and vascular dementia patients.

-No significant difference was found between two patients groups as regards severity of dementia by MMS score a finding that agrees with the finding of **Danielczyk et al. (1988).**

Our explanation for this finding is that the mini- mental state examination can be used as a simple measure of overall abnormality for symptomatic diagnosis but not for etiological diagnosis.

-As regards the level of depression, by comparison between degenerative dementia group and vascular dementia group there is no significant difference was found, a finding that agrees with previous study of Danielczyk et al. (1988).

.The low Zagazig depression scale (ZDS) and hamilton depression scale (HDS) scores in degenerative and vascular dementia groups provides that depression was not a cousal or a determining factor of any importance in the dementia of the whole patient group.

C) Relating platelet mono-amine oxidase and vitamin B_{12} to different parameters:

*By direct analysis of results there is a significant difference as regards the vitamin B_{12} level in relation to age at onset with higher vitamin B_{12} level in degenerative dementia than in vascular dementia, a finding that agrees with the results of Regland et al. (1988).

*No significant difference between plat. MAO activity or vitamin B_{12} level and type of sex both in degenerative or vascular dementia was found in our study, a finding that disagrees with the previous studies of George et al. (1984) and Danielczyk et al. (1988).

*No correlation between plat. MAO activity or vitamin B_{12} level and duration of illness both in degenerative dementia or vascular dementia was found in our study. This finding agrees with finding of Regland et al. (1986).

*A highly significant difference was found as regards the platelet mono-amine oxidase activity in relation to severity of dementia (MMS), this finding is consistent with the findings of **Danielczyk et al. (1988)** and **Fischer et al. (1994).** But disagrees with finding of **Alexopoulos et al. (1984)** and **Gotz et al. (1998).**

The significant positive correlation between monoamine oxidase activity and the severity of illness suggests that monoamine oxidase activity may be a state-dependent marker of neurodegeneration, it may be that dementia involves some central biochemical changes that are reflected in certain peripheral tissues (e.g platelets) or a systemic derangement that also affect the brain **(Bonqioanni et al., 1997). Gotz et al. (1998)** concluded that the decline of the MMS scores preceded the elevation of MAO activity, since degenerative processes in brain areas which are responsible for cognitive function and are reflected by the MMS scores rather affect cerebral cholinergic than monoaminergic neurotransmitter system, degeneration of the latter at late stages of dementia might be reflected by increased platelet MAO activity.

*As regards the vitamin B_{12} level a highly significant difference was found in relation to severity of dementia (MMS), a finding that disagrees with the finding of **Fischer et al. (1994).** But agrees with the findings of **Small et al. (1997), Meins et al. (2000)** and **Nilsson et al. (2000).**

Vitamin B_{12} deficiency in elderly subjects may lead to psychiatric symptoms, but more often it increases the severity of various organic and

non organic mental diseases **(Nilsson et al., 2000).** Vitamin B_{12} is required in the methylation of homocysteine to methionine and in the synthesis of S adenosylmethionine which is involved in neumerous methylation reactions involving proteins, phospholipids, DNA and neurotransmitter metabolism, the defect in methylation processes in addition to the neurotoxic effects of homocysteine may play a role in the neuropsychatric disturbance that are associated with vitamin Bp deficiency **(Parnetti et al., 1997)** and also increased plasma homocysteine concentration associated with low vitamin $_{B12}$ in demented patient was correlated with severity of dementia **(Nilsson et al., 2000).**

*As regards the correlation between plat.MAO activity and vit. B_{12} level there is no significant differences was found in different patient groups our finding is consistent with the findings of **Fischer et al. (1994), Fischer et al.** did not find any correlation between low vitamin B_{12} level and high MAO.activity, but disagrees with the finding of **Regland et al. (1988, 1991), Oreland et al. (1990)** and **Parnetti et al. (1992).**

.Regland et al. (1988) found vitamin B_{12} concentrations below the lower limit of the reference value in demented patients and described a significant negative correlation between platelet MAO levels and vitamin B_{12} levels, in a further study (1991) patients with low vitamin B_{12} levels, a significant decrease of platelet MAO levels 4 weeks after intramuscular injection of hydroxycobalamin was found, **Parnetti et al. (1992)** also found a significant negative correlation between MAO and vitamin B_{12} levels in demented patients. The source of discrepancy between our

results and that of **Regland et al. (1988, 1991)** or **Parnetti et al. (1992) is** not known but may be related to nutritional factors.

*In an trial to find a relationship between educational and occupational characteristics of our patients and different parameters, no significant difference was founds as regards age at onset, duration of illness, plat.MAO, vit B_{12} and severity of dementia our findings are consistent with finding of **Beard et al. (1992), Cobb et al. (1995)** and **Bowler et al. (1998).** But disagrees with the findings of **Canadian study of health and aging (1994), Sterny et al. (1995), Evons et al. (1997), Gauthier et al. (1997)** and **Letenneur et al. (1999).**

Our findings provide evidence against the **use it or lose it** hypothesis. This hypothesis proposes that higher educational and occupational levels have a protective effect against dementia, three mechanisms may mediate this, one is the establishment of a congitive reserve, the second is that increased intellectual activity may enhance brain repair and recovery mechanism, finally other brain regions may take over the functions of those affected early in the disease, but **Bowler et al. (1998)** stated that the effect of increased education had was to cause the earlier presentation of disease and there is no evidence for the histopathological correlates that would be expected if the brain reserve hypothesis was true. and also depression in elderly people is more common in those with lower educational and occupational attainment and depression is a powerful mimic of early dementia. This will act to cause over representation of apparent dementia among the less educated.

Mortality from all cases is lower in those with higher levels of education. This selective mortality will cause those of lower educational attainment to die early so depriving them of the opportunity to dement in late old age. This may also cause the artefactual early onset of dementia in the less well educated **(Bowler et al., 1998).**

* **We** tried to find a relation between platelet mono-amine oxidase activity and severity of depression, but no significant difference was found neither in degenerative dementia nor in vascular dementia, a finding that is going with that of **Alexopoulos et al. (1984)** and **Fischer et al. (1994).**

*In another trial to find a relationship between vitamin B_{12} level and severity of depression in degenerative dementia or vascular dementia, no significant difference was found, a finding that agrees with the finding of **Fischer et al. (1994).**

This finding provides that depression was not a causal or a determining factor of any importance **in** the dementia of the whole patients group.

*No correlation between platelet mono amine oxidase activity and the presence or absence of psychotic symptoms was found in our study, a finding that is going with the finding of Alexopoulos **et al. (1984).**

A finding provides that the psychotic symptoms was not a causal or a determining factor in dementia.

*In an attempt to find a relationship between platelet mono-amino oxidase activity and clinical characteristic of our patients including

(Diabetes mellitus and hypertension) no significant difference was found either in degenerative or vascular dementia, a finding that disagrees with the finding of **Lakhman and Kour (1997), Stewart and Liolitsa (1999)** and **Kumari et al. (2000).**

Our explenation for this finding is not known but may be attributed to that the patients which involved in our study only with controlled diabetes and hypertention.

*direct analysis of the results there is significant difference as regards the vitamin B_{12} level in relation to diabetes, a finding that is going with the findings of **Takahashi et al. (1994), Nilsson (1998), Smulders et al. (1999)** and **Tamai (1999).**

Cobalamin (vitamin B_{12}) deficiency is more common in the elderly than in younger patients this is because of the increased prevalence of cobalamin malabsorbtion in this age group which is mainly caused by autoimmune disorders like atrophic body gastritis and diabetes mellitus **(Nilsson, 1998).** In addition diabetes mellitus leading to cobalamin deficiency and increased the plasma concentration of homocysteine through affection of glomerular filtration rate and nephropathy **(Wollesen et al., 1999).**

*By direct analysis of results there is a significant difference as regards the vit. B_{12} level in relation to smoking with lower vit. B_{12} level in dementia a finding that is going with the report of **Piythilake et al. (1994), Benton et al. (1997)** and **Weqqemans et al. (1997).**

Vitamin B12 deficiency is common in elderly than in younger patients. This is because of the increased prevalence of cobalamin malabsorbtion in this age group which is mainly caused by autoimmune disorders **(Nilsson, 1998)** in addition **Piyathilake et al. (1994)** concluded that current smokers have vitamin B_{12} concentration, that are lower than those of non-current smoker as a result of direct exposure of tissues and circulation to cigarette smoke.

summary and Conclusion

SUMMARY AND CONCLUSIONS

Our study was a trial to find some kind of biological correlation between platelet mono amine oxidase activity and vitamin B_{12} levels or any of several variables related to the dementia disorder.

40 demented patients were studied, 20 vascular dementia patients and 20 degenerative dementia patients, 10 depressed control subjects and 10 normal control subjects, were also added to the study for comparison reasons.

All patients were subjected to a semistructured interview to collect data and diagnose them according to DSM-IV.Hachinski scale was carried out for differentiation between degenerative and vascular dementia, all patients answered the Zagazig depression scale and hamilton depression scale, platelet mono amine oxidase activity and plasma vitamin B_{12} level were determined chemically to all patients and control subjects.

The main findings in our study were:

Demented patients differed significantly from controls as regards platelet mono amine oxidase activity and vitamin B_{12} level.

Both degenerative dementia patients and vascular dementia patients differed significantly from controls as regards platelet mono amine oxidase activity and differed highly significantly from control, as regards vitamin Bp level.

- A highly statistically significant difference between degenerative dementia and vascular dementia as regards vitamin B_{12} level was found.
- No significant difference was found between degenerative dementia and vascular dementia as regards platelet mono amine oxidase activity.
- No correlation between platelet mono amine oxidase activity and vitamin B_{12} level was found in different patient groups.
- A highly significant difference was found as regard the correlation between severity of dementia and platelet mono amine oxidase activity and vitamin B_{1}, level.
- Platelet monoamine oxidase activity showed no significant correlation with any of the studied parameters. But vitamin B_{12} level showed a significant difference as regards age at onset, smoking and diabetes when compared between degenerative and vascular dementia.

Thus in this study we were able to confirm the finding of Fischer et al. (1994) that demented patients have platelet MAO activity that is significantly higher than in normal subjects and vitamin B_{12} level that is significantly lower than in normal subjects with no significant correlation was found between platelet MAO activity and vitamin B_{12} level.

Recommendation

Researchers interested in our topic "platelet MAO and vitamin B_{12} in dementia" might have better serendipity if they are going to:

- To conduct a longitudinal study that might permit them to observe platelet mono amine oxidase activity and vitamin B_{12} level changes over time in individual patients either with changes in their symptomatology or their medication and nutrition status.
- Take into account that other essential nutrients, such as amino acid, trace elements and minerals have a simultaneous deleterious effect along with the vitamin B_{12} deficiency.

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Appendixes

APPENDIX (I)

PSYCHIATRIC EXAMINATION

- Name
- Age
- Sex
- Education
- Occupation
- Smoking
- Residence
- Age at onset
- Duration of illness
- History of present il Ines
- Family history
- Past history of psychiatric disorder
- Diagnosis according to DSM IV
- Mental state examination

  - General appearance
  - Mood and affect
    Perception
    Thought content
  - Sensorium
  - Orientation
    Memory
  - Concentration and attention
  - General information and intelligence
  - Judj ment
  - Insight

APPENDIX (II)

MEDICAL AND NEUROLOGICAL EXAMINATION

* General examination

  * Temperature * Pulse * Blood pressure

  * Height * Weight * Physique

* Cardio — vascular system

* respiratory system

* Alimentary system

* Genitourinary system

* Endocrine system

* Neurological examination

  - Cranial nerves examination
  - Motor system
  - Reflexes
  - Sensory system
  - Examination of spine and skull
  - Gait

APPENDIX (HI)

FOLSTEIN MMSE

Orientation

1. What is the?	Year?	1
	Season?	1
	Date?	1
	Day?	1
	Month?	1
2. Where are we?	State?	1
	Country?	1
	Town or city?	1
	Hospital?	1
	Floor?	1

Registration

3. Name 3 objects, then ask all three after that. One point for each 3

Attention, calculation

3. Serial sevens. One pcint for each. Stop after 5. 5

Pecall

5. ask the name of 3 objects in question 3. 3

Language

6. point to a pencil and a watch. The patient says the name 2

7. Pepeat (No IFS, ANDS or Buts) 2

8. 3 stages command:
   - Take the paper in your right hand
   - Fold the paper in half
   - Put it on the floor 3

9. Read and obey "Close your eyes"

10. Write A sentence

11. enlarge the design

Total 30

APPENDIX (IV)

HINSKI CEREBRAL ISCHAEMIA SCALE

		SCORE TOTAL
SUDDEN ONSET OF INTELLECTUAL DISTURBANCE	2	———
GRADUAL DETERIORATION	1	———
FLUCTUATING COURSE	2	———
NOCTURNAL CONFUSION	1	———
EMOTIONAL LABLLITY	1	———
HYPERTENSION	1	———
HISTORY OF STROKE	2	———
SICNS OF ATHEROSCLEROSIS	1	———
FOCAL NEUROLOGICAL SYMPTOMS	2	———
FOCAL NEUROLOGICAL SIGNS	2	———
DEPRESSION	1	———
SOMATIC COMPLAINTS	1	———
RELATIVE PRESERVATION OF PERSONALITY	1	———

A TOTAL SCORE OF 4 OR LESS SPEAKS AGAINST A VASCULAR FORM OF DEMENTIA AND IN FAVOUR OF A PRIMARY DEGENERATIVE DEMENTIA. TOTAL SCORES OF 8 OR MORE SUGGEST A VASCULAR DEMENTIA (MULTIPLE INFARCT) OR ONE OF THE COMMON FORMS OF MIXED VASCULAR AND DEGENERATIVE DEMENTIA.

APPENDIX (0

HAMILTON DEPRESSION RATING SCALE

INVESTIGATOR	PATIENT N.	Initials
COUNTRY: Egypt	DAT OF VIST (DD/MM/YY)	□□ □□ □□

I. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

0 0 Absent

1 0 These feeling states indicated only on questioning

2 0 These feeling states spontaneously reported verbally

3 0 Patient communicates feeling states non-verablly (i.e. through facial expression, posture voice, and tendency weep).

4. 0 Patient reports virtually only these feeling states in his spontaneous verbal and non-verbal communication

2. FEELING OF GULLT

0 0 Absent

1 0 Self- reproach, feels he has let people down

2 0 Ideas of gulit or rumintion over past errors or sinful deeds

3 0 Present illness is a punishment. Delusions of gulit

expression, posture voice, and tendency weep).

4. 0 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

o 0 Absent

1 0 Feels life is not worth livingself- reproach, feels he has let people down

2 0 Wishes he were dead or any thoughts of possible death to self

3 0 Suicide ideas or gesture

4.0 Attemps at suicide (any serious attempt rates 4).

4. INSOMNIA EARLY

0 □ No difficulty falling asleep

1 □ Complains of occasional difficulty falling asleep (i.e. more than V2 hour)

2 □ Complains of hightly difficulty falling asleep

INVESTIGATOR'S SIGNATURE: _____

INVESTIGATOR	PATIENT N.	Initials
COUNTRY: Egypt	DAT OF VIST (DD/MM/YY)	□□ □□ □□

HAMLLTON DEPRESSION RATING SCALE (continued)

5. INSOMNIA MIDDLE

0 0 No difficulty falling asleep

1 0 Complains of being restless and disturbed during the hight

2 0 Waking during the hight; any getting out of bed rates 2 (voiding excepted)

6. INGOMNIA LATE

0 □ No difficulty

1 0 Waking in early hours of the morning but goes back to sleep

2 0 Unable to fall asleep again if get out of bed

7. WORK AND ACTIVITIES

0 0 No difficulty

1 0 Thought and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies.

2 0 Loss of interest in activity, hobbies, or work-either directly reported by patient, or indirectly in listlessness, indecision, and vacillation (feels he has to push self to work and activities)

3 0 Decrease in actual time spent in activities or decrease in productivity. In hospital, patient does not spend at least three hours a day in activity (hospital job or hobbies), exclusive of ward chores.

4.0 Stopped working because of present illness. In hospital, patient engages in no activity except ward chores, or if patient fails to per form ward chores unassisted

8. RETARDATION (slowness of thought and speech, impaired ability to concentrate, decrease motor activity)

0 0 Normal speech and thought

1 0 Slight retardation at interview

2 0 Obvious retardation at interview

3 0 Interview difficult

4 0 Complete stupor

INVESTIGATOR'S SIGNATURE: _____

INVESTIGATOR	**PATIENT N.**	**Initials**
COUNTRY: Egypt	**DAT OF VIST (DD/MM/YY)**	□□ □□ □□

HAMLLTON DEPRESSION RATING SCALE (continued)

9. AGITATION

0 9 None
1 0 Fidgetiness
2 9 "Playing with" hand, hair, etc.
3 9 Moving about, cant't sit still
4 9 Hand-wringing, nail-biting, hair-pulling, biting of lips

10. ANXIETY PSYCHIC

0 □ No difficulty
1 9 Subjective tension and irritability
2 9 Worrying about minor matters
3 9 Apprehensive attitude apparent in face or speech
4 9 Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants symptoms of anxiety, such as: gastro-intestinal (dry mouth, wind, indigestion, diarrhoea, cramps, belching, sighing); urinary frequency, sweating.

0 □ Absent
1 9 Mild
2 9 Moderate
3 9 Severe
4.0 Incapacitating

12. SOMATIC SYMPTOMS — GASTRO-INTESTINAL

0 0 None Normal speech and thought
1 9 Loss of appetite but eating without staff encouragement. Heavy feeling in abdomen
2 9 Difficulty eating withoug staff urging. Requests or requries laxatives or medication for bowels or medication for GI symptoms

13. SOMATIC SYMPTOMS- GENERAL

0 □ None
1 9 Heaviness in limbs, back, or head. Backache, headache, muscle aches. Loss of energy and fatigability
2 9 Any clear-ctu symptoms Moderate

INVESTIGATOR'S SIGNATURE: ———————————

INVESTIGATOR	PATIENT N.	Initials
COUNTRY: Egypt	DAT OF VIST (DD/MM/YY)	□□ In □□

HAMLLTON DEPRESSION RATING SCALE (continued)

14. GENITAL SYMPTOMS (e.g., loss of libido, menstrual disturbances)

0 0 Absent
1 0 Mild
2 0 Severe

15. HYPOCHONDRIASIS

0 0 Not present
1 0 Self-absorption (bodily)
2 0 Preoccupation with health
3 0 Frequent complaints, request for help.....
4 0 Hypochondrial delusions

16. LOSS OF WEIGHT (rate either A or B)

A. When rating by history

0 0 No weight loss
1 0 Probable weight loss associated with present illness
2 0 Definite (according to patient) weight loss

B. On weekly rating by ward psychiatrist when actual weight changes are measured:

0 0 No weight loss
1 0 Greater than 0.5 kg weight loss in week
2 0 Greater than 1 kg weight loss in week

17. INSIGHT

0 □ Acknowledges being depressed and ill
1 □ Acknowledges illness but attributes cause to bad food, climate, over-work, virus, need for rest, etc.
2 0 Denies being ill a all

INVESTIGATOR'S SIGNATURE: _____

INVESTIGATOR	PATIENT N.	Initials
COUNTRY: Egypt	DAT OF VIST (DD/MM/YY)	00 00 □□

18. DIURNAL VARIATION

	A.M.	P.M.		
0.	□	□	Absent	If symptoms are worse in the morning
1	□	0	Mild	or evening note which it is and rate severity of variation
2.	0	□	Severe	

19. DEPERSONALIZATION AND DERELIZATION

0 0 Absent
1 □ Mild Such as: Feelings of unreality Nihilistic ideas
2 0 Moderate
3 □ Severe
4 0 Incapacitating

20. PARANOID SYMPTOMS

0 □ None No weight loss
1 0 Suspicious
20
3 0 Ideas of reference
1 0 Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

0 0 Non
1 □ Mild
2 0 Severe

22. HELPLESSNESS

0 0 Not present Absent
1 0 Subjective feelings which are elicited only by inquiry
2 0 Patient volunteers his helpless feelings
3 0 Requires urging, guidance and reassurance to accomplish ward chores or personal hygiene
4 0 Requires physical assistance for dress, grooming, eating, bedside tasks or personal hygiene

INVESTIGATOR'S SIGNATURE: _____

INVESTIGATOR ——————— PATIENT N. ——————— Initials

COUNTRY: Egypt DAT OF VIST (DD/MM/YY) □□

23. HOPELESSNESS

0 □ Not present

1 Q Intermitently doubts that "things will improve" but can be reassured

2 □ Consistently feels "hopeless" but accepts reassurances

3 □ Expresses feelings of discouragement, despair, bessimism about future, which cannot be dispelled

4 Sponthaneously and inappropriately perseverates, "I" 11 never get well" or its equivalent.

24. WORTHLESSNESS: Ranges from mild loss of esteem, feelings of inferiority, self-depreciation to delusional notions of worthlessness.

0 □ Not present

1 $_0$ Indicates feelings of worthlessness (loss of self-esteem) only on questioning

2 spotaneously indicates feelings of worthlessness (loss of self esteem)

3 $_0$ Different from 2 degree: Patient volunteers that he is "no good" "inferior", ... etc.

4 □ Delusional notions of worthlessness — i.e., "I am a heap of garbage" or its equivalent

INVESTIGATOR'S SIGNATURE: ———————

APPENDIX (VI)

مقياس الزقازيق للإكتئاب

نير حسين فوزى
جامعة

رقم السن: ....

زيارة التاريخ: ....

أخرى: ....

....

....

....

كل عباره من العبارات إللى ة ع ـــــ

كام " إنت يوم 1 فاتوا.

التقويم خاص (بالمصحح)

	١V	1';	١o	٤	١١'	١١'	١١				V				r		

العبار

فى النوم

فيها

منظرى يدل على

صح/غلط

٦ كل غللى هو وانا ابقى كويس

V بأصحى بدرى عن المبعاد اللى فروض أصحى فيه

A بأبقى تعبان قوى

أكيد على أنى مضطرب ومن على ض

J.1١٠ ألاقى .... ومـــا ....

أقدر

11 من يوم LA عييت U مبقا عندى إهتمام الجنسية

r الاكل زى

وزنى U

١٤ أنى 44: زى

٥ تلاحظها بسهولة

١ عندى كل الأمراض فى الدنيا

١V أنا خايف قوى

١A مى من الإضطراب

19 وكنى تقريباً

مزاج ل اجات من

٢١ كثير أنى دايخ L519 ميكون حيغ ى .... صح/غلط

٢٢ بأقلق L بدرى باقدر 14 4 تانى .... صح/غلط

r .... صح/غلط

٢٤ ت لى .... صح/غلط

٢o معدتى تعبانة .... صح/غلط

٢ يز عند اجة سهلة و ش ش .... صح/غلط

٢V مزاجى ومبسوط .... صح/غلط

٢A أحس قلبى U .... صح/غلط

٢٩ أخاف قوى لما يكون فيه أى تعب .... صح/غلط

r. الدنيا زى ما تكون اصيق من .... صح/غلط

Arabic Summary

٣ الواحد بقى بطئ لدرجة أنه............إللى يســـاعده صح/غلط
لقل واللبن

بأصحى -ثير ى عز 'لليل
٣ إهتمامى الجنسية تغيرش عن الأول
٣ بأتمنى إنى وأخذ ن من العيشة
٣٥ أنا بأخذ مدة أطول من اللاز ن أدخل الن /
٣ كده قلقان j مش ليه صح غلط
٣٧ افتكر إن -بيئوس منها صـ لط
٣٨ دلوقتى إستحقه على
٣ مخى واقدر أتصرف ة زى ما كنت قبل ه
٠ الن تانى
الصبح
٤ الدنيا
صوتى بالعافية 144 منى هد صح/غلط

٤٣ لو من ربنا كان الوا د
علشان الجو اليومي a.O كان
٤٥ حاجة سغير عليـــها ....
وى
حياتى كار نفسى
٤٧ على جدا أنى أعمل حاجة ة دى
٤٨ لاز نفسه
منى عة يمكن أغلط أى

إنسان -ويس S J أى اسى
لو عن أى مرض بيتهيا أنه is...................... صح/غلط
٢ بأعمله بأ - و أ

الملخص العربى

كانت الدراسة لايجاد نوع من بين ILL الأنزيـ

ا اد الأمينى فى مين فى س مرضى العته.

لدور ين الناتج الم

ت و عش

بيعيين يعانون أى أمراض .

مقابلة اكلينيكية

الأمر الحالـة العقلية

للتعر على العته وتحديد لديهم. التفرقة بين مرضى العته إلـى

مجمو سب كل ن مقياس Ls وطبقن الاكتئاب

هاميلتـ كل و مستوى

ا ينى فى الد 1 L الد

كانت الدر هى زيادة نشاط الأنزيـ

الدموية ونق مستوى فيتامين L5 مرضى 4 كمجمو

ذلك 93 دلالة إحصائية. ولو ذو

دلالة عته الدورة الدموية المخيه ومرضى 11

"ناتـ عن الانحلال وأهمها "نقص " حو" فى CSS C ٢

الـ الناتج عن أيضاً ESC و د

أخذ لاف 93_3 لمستوى مينى المؤكسد بين

" ر .

و أيضا ارتباط

فى الدموية ومعدل a.11 ن فى مستو فيتا ب 1

المر كان j تبـــاط ذو

بين ى فيتا ٢

وأنه أى ار ا ائى أى

"عوا ل الاخرى التى كان

العوامل ر السكر الدم و xll

أن الزيادة فى مستوى الأمينى

إلى

اكبر

وفيتامين بعوامل

مثل ومستوى الا ماض الأمينية

اسة تأثير هد العوامل.

4.11011 الأميني المؤ عسد في

"موية و تاميز مرضى "عنه

من

الطبيب هاشم

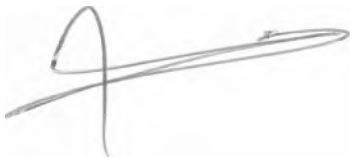
الط،

كلية الط، –

على الدكتور

: ى

الأمراض



منير حسين وزى

أستاذ ا'أ

كلية الط الزقاز،

I. **رفيق lay عبد اللطيف** **./ إيمان حسن رشدى الصافى**

aid J/ J,'

كلية الطب *كلية*

يسرى السيد أبو *40[11].*

أستاذ

كلية Ls – *جامعة*

كلية الطب

جامعة الزقازيق