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Editorial

From Environmental to Mental Well-being

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AWARENESS

'WHO launches mental health 2001 campaign' is the main title of WHO Press (10th Jan 2001)[1]. Disturbance in the ozone attracted people world wide in the last decade but little has been done to realize that mental well-being is equally threatened in this decade. Longevity achieved by excellent and advanced Medicare is proving burdensome to the society. Adolescence to senescence is no longer a happy journey. "An estimated 400 million people today suffer from mental or neurological disorders or from psychosocial problems such as those related to alcohol or drug abuse. One out of four people who turn to the health service for medical care suffer from such disorders, yet, few are diagnosed correctly and few receive treatment. Most of their lives are characterized by undue suffering, disability and at times, premature death". This statement amply testifies the state of affairs on the horizon of mental health.

Awareness is no doubt present amongst professionals but neither is it complete nor action oriented. Morbidity associated with many somatic diseases has an underlying mental element. Dr Gro Harlem Brundtland, Director General of WHO says 'By accident or design, we are all responsible for this situation today'. Society cruelly discriminates those suffering from mental disorders forgetting that the line between mental ill-health and well-being is very thin. Epilepsy in the young and depression in the adults are not only curable but also compatible with normal social and professional life. The social environment around the people afflicted with these disorders is sinful. The scientific discoveries have contributed significantly towards amelioration of symptoms. Participation of the community in the management is vital and crucial. Both Governmental and non-Governmental organizational involvement brings back these unfortunate people back into the normal national fabric.

NETWORKS AND TRANSMITTERS

It is important for all the medical and neuroscientists to realize that the human brain refuses to be totally under mathematical, neuroanatomical or neurophysiological interpretations of both normal and abnormal patterns. From inflammation to neoplasia, the language of life sciences today is biochemical and molecular[2]. To seek answers to

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several issues in neurosciences from a molecular biology perspective may be ridiculous but to a great extent reverential, understandably.

Cajal is credited with the neuron concept and the cellular basis of Brain and its function. He also pronounced the unidirectional axoplasmic flow and dynamic polarization. The complex neural networks are the communication channels with critical functional areas namely 'Synapse'. The scientific sign of the creation lies in the recognition of the 'Synaptic cleft' that provides the neurotransmitter chemical influx from pre-synaptic neurons to the receptors in the post synaptic cells. The electro-chemical mechanisms begin with action potentials opening the calcium channels in the presynaptic neurons allowing the neurotransmitter containing vesicles to release the chemicals into the synaptic cleft. The molecules anchor on the postsynaptic receptors with the simultaneous opening up of channels for sodium entry into the neuronal cytoplasm. This delicate well-orchestrated process underlines the importance of neuronal cells, ionic channel systems and the electrophysiological events. Investigators are reaching beyond mathematical comprehension or molecular predictions.

It is undoubtedly a discovery of tremendous clinical importance, the identification of stem cells in both embryonic and adult life, which offer replacement therapy in Parkinson's disease and demyelinating disorders. Similarly, recognition of axon guidance molecules may rescue patients from serious spinal cord injuries. Survivins may inhibit molecules of suicide enabling neurons to survive. Cognitive processes, though not totally, to a great extent are explained, based on single neuron recordings in monkeys. But monkeys to man developmentally may be a short travel, but intellectually, cognitively and behaviorally, complex man is far away from monkey (but may retain monkey mind!). Neuroscience today is unfolding the sensory and motor responses to retinal stimuli drawn from objective world. Functional neuroimaging, Positron Emission Tomography (PET), MRI enables one to deduce the neurovascular traffic signals in a given environment in human setting. The greatly benefited area is memory. Brend Milner's remarkable studies on an anesthetic patient gave us insights into understanding the memory zone as a distinct cortical function (medial temporal lobe)[3]. But what is elusive is the seat of childhood memories, which were retained in this patient who was devoid of medial temporal lobe. We are now reasonably clear that memory is of two kinds namely declarative and non-declarative. The latter includes learned abilities, motor learning, emotional learning, habit learning. While declarative are possibly located in the medial temporal lobe, the non-declarative is divergent in its locations namely, cerebellum, amygdala, basal ganglia, frontal lobe etc. Certainly many components of non-declarative memory stay unconscious or subconscious in humans.

SENESCENCE IS NO SIN

The two principal neurodegenerative disorders threatening the population beyond 50 years are Parkinson's Disease (PD) and Alzheimer's disease (AD). About 1 million Americans suffer from Parkinson's disease and 50,000 new cases are diagnosed each year as many as 5-10% of individuals over sixty years of age may have the illness (Olson

2000)[4]. The discovery of dopamine as a neurotransmitter by Arvid Carlsson (for which he received the Nobel prize), has been the missing link in Parkinson's disease. The precursor L-dopa replenishes the depleting stocks of dopamine and continues to be the mainstay in the management of PD. Replenishing the chemical might not be right strategy however arresting the loss of dopamine neurons would be the right direction. 'The quest for improved PD treatments progresses in incremental steps. Replacing dopamine neurotransmitter that is lost as the dopamine neurons degenerate (step1) is the mainstay treatment for PD patients. The next steps- transplanting fetal nerve tissue to replace dopamine neurons that have been lost (step 2) and halting the neuronal loss altogether with trophic factors (step 3)'(Olson 2000). Gene therapy with glial cell line derived neutrophic factor (GDNF) results in the rescue of dopamine neurons and reversal of motor deficits in primate model of PD. Their elegant experiments in aged monkeys treated with MPTP heterotoxic injections in basal ganglia and substantia nigra followed by injections of GDNF gene carried in lentiviral vector resulted in remarkable recovery. Despite predictable limitations for early clinical trials, such as dose of the gene, possible complications of toxicity (psychotic illness), the hopes on the effective management of PD by gene therapy are very high in the years to come.

Referring to Alzheimer's disease (AD), Geoffrey Cowley made an appalling statement "the longer we live, the more likely we are to contract this devastating disease 'but quickly adds an optimistic note' but recent discoveries are bringing scientists closer than ever to cure. 'Though sad, the narration of AD profile by Carl Sandburg is worth recalling,' the fog comes on little cat feet. First you notice that you are always misplacing things, or that common noun evading you as stubbornly as the names of new acquaintances. Pretty soon you are forgetting appointments and getting flustered when you drive in traffic. On bad days you find you can't hold numbers in your mind long enough to dial the phone. You try valiantly to conceal your lapses, but they become more glaring. You crash your car. You spend whole mornings struggling to dress yourself properly. And even as you lose the ability to read or play a piano, you're painfully aware of what is happening to you. Then the fog thickens your own children come to look like strangers, and terrifying delusions migrate forcedly from your dreams into waking conciousness. Eventually your limbs, bowels and bladder escape control. You drift into a silent stupor. Death when it comes, is a formality". At the time Alois Alzheimer described the disease, it was fortunately rare. Thanks to modern medicine and nutritional knowledge, man has achieved longevity. A developed country like USA has recorded life expectancy of about 77 years, similar figures are cited from other countries in Europe and Asia. With 1 in 5 of elderly between 75 and 85, the AD is known to affect over 6 million by the end of decade and over 14 million by mid century in USA alone. The world leading laboratories working on Age related disorders, are optimistic as pathology has been reasonably well established and possible pathomechanisms including biochemical events are better understood. The trinity of plaques (amyloid), neurofibrillary tangles (tau protein deficiency) and neuronal loss (secondary to inflammation?) characterizes AD. Apolipoprotein beta, Alpha 2 macroglobulin as distinct genetic risk factors directly or indirectly related to amyloid beta protein, presenilins with associated loss of glue protein 'tau' resulting in tangles and inflammatory response and neuronal loss could now direct the scientists towards more specific therapy. The silver lining in the black clouds of AD

are slowly and steadily appearing in the horizon. The enzymes responsible for one of the two cleavages that generate amyloid beta from APP (amyloid precursor protein) have recently been identified, making it a matter of time before effective inhibitors of the process become available.

Takaomi Saido[5] of Riken Brain Science Institute Japan (Science 2001) showed direct evidence that a amyloid AB degrading enzyme 'Neprilysin' is important in preventing their accumulation, characteristic of Alzheimer's disease. Saido says 'that even partial reduction of neprilysin activity, which could be caused by aging, will elevate AB and thus cause Alzheimer's'. The observation has both pathogenic and pharmacologic significance.

Another novel approach has been to use immunization with the amyloid peptide. This dramatically reduces subsequent plaque formation in mouse models of the disease. And amyloid vaccine has now entered the phase II clinical trials'. Drugs that prevent amyloid aggregation are on the way to join the clinical armamentarium. Dementia, we hope, shall be a word to be forgotten in the years to come.

"***We must strive for parity in the way of mental and physical disorders are regarded. We know what is wrong, we know where solutions lie. We have responsibility to push for changes in both policy and attitude and we are determined to do just that"***

- Dr ***Benedetto Saraceno,***
Director of WHO's Mental Programme.

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