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The Emergence of Neurotherapeutics

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Introduction

Medicine has had a neurological theme throughout its five-thousand year history. The first known practitioner of this art was Imhotep ("the one who comes in peace") who lived in the time of Pharaoh Djoser in Egypt in the third millennium BCE. According to the Edwin Smith Papyrus, Imhotep could "provide remedies for all diseases", but we do not have surviving examples of his techniques, including rituals and the summoning of magic. He was considered "a god of medicine", but there is no evidence that he actually had medical training. None-the-less, he is considered history's first "scientist". Two millennia later, in Greece, Pythagoras theorized that the brain was the organ of thought [1-3]. His religious teachings preceded Christianity by five-hundred years, but were important for the tenet that the soul is eternal (metempsychosis) and is "recycled" until it frees itself through purity of essence. Hippocrates, traditionally thought to be "The Father of Medicine", advocated healthy diet and exercise, but knew that some patients needed intervention in the form of medicines and physical "handling". Most of all, Hippocrates was an "observer of sick people, not diseases". In The Islamic Golden Age of the start of the second millennium CE, Ibn Sina (Avicenna) [4], was a polymath of renown, rendering opinions on the soul and the "Active Intellect", which approached The Pure Intellect of God. The Active Intellect allowed for illumination which permits the essence of things to become clear, the way that the sun allows us to appreciate color [5].

Shakespeare, whose son-in-law was a physician, was a keen observer of human afflictions and probably described Lewy body disease in "King Lear". He also characterized the limbic disorder of romantic love in "Romeo and Juliet" [6].

The 17th century was notable for Willis's contributions to neuroanatomy, leading to his being known as "The Father of Neuroscience". He coined the term, "neurologie". He also described myasthenia gravis, although his paper on this disease was not "discovered" until after the turn of the 20th century [7].

In 1817, Parkinson published "An Essay on The Shaking Palsy", which later bore his name [8]. Around the same time, Justinus Kerner described "sausage poisoning" (botulism) and studied the toxin, concluding that its mechanism of action involved interruption of signals in the somatic and autonomic motor systems, with lethal effects, even in minute quantities [9]. He even suggested that this "botulinum toxin" might have some therapeutic application, using even more minuscule doses. Nineteenth-century medicine was most notable, however, for the French influence of Jean-Martin Charcot, whose triad of multiple sclerosis (nystagmus, scanning speech and tremor) is still relevant today. Charcot also observed that this disorder was notable for "symptoms on one side and signs on both sides". He also described "hysterical" illnesses, including early consideration of what has become known as "post-traumatic stress disorder" even though some of those patients, most assuredly, had organic diseases. Joseph Babinski, Charcot's favorite student, observed that an extensor plantar reflex was indicative of an upper motor neuron lesion and is considered to be the most robust of neurological signs. Babinski also defined the neurobehavioral concepts of anosognosia (denial of illness) and anosodiaphoria (apathy toward illness). Many neurological patients don't/can't know and care about their diagnoses, because the organ of insight is the organ affected by the disease process [10-12].

At the turn of the 20th century, Alois Alzheimer elegantly described the classic neuropathologic features of dementia arising in the presenium, which would later bear his name. These neuropathologic features, amyloid plaques and neurofibrillary tangles, are found in most dementia patients, regardless of age, although "Alzheimer disease" affecting an aged person is more properly called "senile dementia of the Alzheimer type", to differentiate this common condition from the relatively rare "Alzheimer disease".

Whereas the intrinsic nature of neurology is diagnostic, the 20th century was associated with the evolution of the neurologist as "therapist", which has not been a natural transformation, given the above historical review and the cynical, but accurate, description of a neurologist as a physician who was characterized by: "Diagnose…and adios". Early textbooks of neurology were descriptive of progressive, if not fatal, illnesses which had no effective treatments [13].

Freud wrote the definitive treatise on dream analysis and later defined psychoanalysis, which has persisted, although not widely practiced in the current era. Psychoactive drugs seem to have supplanted traditional psychoanalysis which, if properly implemented, continues for years [14,15].

The 20th century also marked the beginning of rational neurotherapeusis, with the development of the barbiturates for epilepsy. Penicillin was adopted for the treatment of neurosyphilis and meningitis, which fostered further exploration of treatments of formerly incurable illnesses. The appearance of the psychotropic medications of the mid-twentieth century ushered in the era of "cosmetic" neurology, which could actually make a person "feel better", whether the affliction involved depression, anxiety or chronic pain. Although these symptoms are still very common, ketamine, a drug which was developed in the 1960s, is finding its way into the mainstream of neuropsychiatry and pain management with astonishing efficacy.

Parkinson was not able to augment dopamine to treat "the shaking palsy", but of interest, Central American ethnobotanical investigation has shown that a traditional treatment of Parkinson disease is the bean from an indigenous legume of that region, Frijol terciopelo (Mucuna pruriens), which contains levodopa, the precursor of dopamine. Dopaminergic augmentation has been the mainstay of the treatment of Parkinson disease for decades. More recent "advances", such as deep

brain stimulation, have been disappointing and may be associated with significant morbidity. A recent rodent study suggests that the gut microbiome plays a role in the production of alpha-synuclein, which is associated with the neuropathological changes (Lewy bodies) in the substantia nigra. This finding, if replicated in humans suffering from Parkinson disease or diffuse Lewy body disease, may open therapeutic pathways aimed at altering the gut microbiome, perhaps with specific antibiotic or even probiotic therapy.

Similarly, Alzheimer lived long before therapeutic efforts were aimed at helping patients who are afflicted with the disease he described. The discovery that degeneration of the cholinergic system was the hallmark of Alzheimer-type dementia led to efforts to augment this neurotransmitter system which governs attention and memory functioning. Early treatments, such as choline, physostigmine and tacrine were abandoned because of adverse risk-benefit ratio. Later iterations of therapy, such as donepezil, rivastigmine and galantamine have been widely-used and are generally safer than their predecessors, but their efficacy is modest. The NMDA modulator, memantine, has been used for decades, suggesting that there may be a co-existent glutamatergic mechanism accounting for this common dementia. Anti-amyloid and anti-tau therapies are being developed (monoclonal antibodies and secretase inhibitors), but may be years away from clinical use. Even if they are found to be safe and effective, these potentially disease-modifying therapies may be cost-prohibitive in an economically fragile healthcare system [16,17].

Myasthenia gravis represented the first "autoimmune" neurological disease to be recognized as such and was treated in the early 20th century with physostigmine, to augment acetylcholine in the neuromuscular junction. Later refinements in cholinergic therapy, as well as immunosuppression, remain the mainstay of therapy, with plasmapheresis, IVIg and thymectomy also commonly employed. This condition remains true to Willis's nomenclature, but quality of life of myasthenic patients has improved with these advances in neurotherapeutics.

No discussion of neurotherapeutics would be complete without recounting the history of imaging, especially the cross-sectional revolution of computerized tomography and magnetic resonance imaging. The 1970s and 1980s were marked by progressive improvement in image quality and speed of performance of these studies, which have vastly improved diagnostic accuracy and are widely available throughout the world. Legend has it that the funding for Sir Godfrey Hounsfield's computerized tomography imaging division at Electric & Musical Instruments in London came from the fantastical success of another of EMI's contracted entities: The Beatles. The first computerized tomography scans were, indeed, called "EMI scans" [18].

Confirming Kerner's genius, botulinum toxin does indeed induce neuromuscular junction dysfunction, but the site of action is presynaptic vis a vis the postsynaptic antibody impairment of signal transmission in myasthenia gravis. While botulism causes a descending paralysis and is fatal if not treated, doses of less than a nanogram, given intramuscularly in selected symptomatic areas, cause focal therapeutic neuromuscular blockade for three months. Alan Scott injected a few picograms of botulinum toxin into the extra-ocular muscles of primates in the early 1970s and injected the first strabismus patient in 1977. The toxin was initially named Oculinum and later became Botox, becoming available in 1990. Dozens of clinical uses for botulinum toxin have been advanced over the past quarter century, but chronic migraine syndrome is currently one of the most common indications. "Botox" is now a household name because of its cosmetic use in "elective wrinkle management", mostly in the United States of America [19].

Charcot also lived a century before the recognition that multiple sclerosis is also an autoimmune illness. Meaningful treatments of multiple sclerosis were attempted in the mid-20th century. Steroids and ACTH were used to treat patients with MS, but it was still called "the crippler of young adults". With advancements in the burgeoning field of neuroimmunology, the role of lymphocytes and cytokines has been elucidated, leading to true disease-modifying therapies, which are in widespread use. While the ongoing vigorous debate about the risk-benefit ratio is thought-provoking, safe and effective treatments are available, with the considerable expense of these treatments being justified by maintaining quality of life for the many patients who might otherwise progress inexorably along the disability scale.

One of the neuroanatomic structures which was described by Willis is the vascular loop at the base of the brain which fosters collateral circulation (when it is complete), if there is an area of circulatory insufficiency in the brain. This cross-flow potential, with cerebral microvascular autoregulation is a built-in mechanism to make the brain naturally stroke-resistant. While Willis was not the first to recognize this elegant loop, it bears his name: The Circle of Willis. Stroke is now a "treatable" entity, but certainly time is of the essence in the recognition, transport, diagnosis and appropriate intervention with thrombolytic or endovascular therapy delivered as quickly as possible (within three hours or less). Healthcare system viscosity or remote location limits the practicality of these therapies. The best treatment is stroke prevention through risk-factor reduction. Effective treatment of hypertension, heart disease, diabetes mellitus, hyperlipidemia and smoking cessation are advised. Stroke-in-the-young may be due to underlying autoimmune, genetic, toxic or traumatic factors. Dehydration may play a primary, but underappreciated role, as this condition may be profoundly promotive of coagulation. Anticoagulant and antiplatelet therapy seems to help in prevention of recurrent stroke. Atrial fibrillation is highly embologenic if untreated and, with the brain receiving 20% of cardiac output, is a very common cause of ischemic stroke, often of a devastating nature.

The foregoing is really "just the beginning", even though neurological history has its roots in Pharaonic Egypt. The 1990s were declared "The Decade of the Brain", but it is abundantly clear that we are now in "The Millennium of the Active Intellect", with thanks to Ibn Sina. Neuroplasticity, neuroprotection, refinements in neurotransmitter manipulation, neuro-integrated microchip implantation, artificial intelligence and advances in resuscitation of hypoxic neurons are on the horizon. Life-extension initiatives are underway as well, but we must, however, cope more effectively with a relatively silent civilizational dilemma: how shall we maintain humane treatment of demented people in an era of stretched healthcare budgeting, as this degenerative condition remains a "final common pathway" of longevity.

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