CONFERENCE REPORT

The Torsion Dystonias: A summary of the Third Dystonia Workshop Vancouver, B.C. March 1980

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The torsion dystonias, also called Dystonia Musculorum Deformans, comprise a group of neurological illnesses characterized by sustained, involuntary twisting movements affecting muscle groups in the limbs, trunk, neck or face. Three hereditary forms may be distinguished; an autosomal recessive form found mostly among the Ashkenazim, an autosomal dominant form, and a rare sex linked form found only on the Phillipine Islands. There are also secondary dystonic states associated with other diseases, toxins or trauma. Neither the biochemical nor the morphological pathology is known, but the abscence of pathological evidence of neuronal cell death and the successful treatment of some cases with drugs or surgery suggests that, when properly understood, the course of dystonia may be arrested.

This report is a brief summary of the Third Dystonia Workshop held in Vancouver, B. C. on March 10 and 11, 1980 under the sponsorship of the Dystonia Medical Research Foundation. Of the thirteen papers presented at the workshop, four were "state of the art" lectures devoted to recent advances in our understanding of the nervous system. The other nine were progress reports on research on dystonia.

Dr. Edith McGeer lectured on "Kainic Acids and Other Neurotoxins". One way in which the brain has been studied by neurobiologists is through surgical or electrolytical destruction of a selected part of an animal brain and observation of behavioral changes. In recent years a variety of new opportunities has been provided by the discovery of a number of neurotoxins that selectively destroy particular types of neurons. One of the most interesting of these is kainic acid which destroys neurons excited by glutamate and has the desirable feature that it attacks only the body and dendrites of a neuron where the receptors are located and usually spares axons in transit. Kainic acid is thought to be "excitotoxic"; it overly excites the neuron and the damage follows from prolonged depolarization. Injections of kainic acid into the striatum of the rat have been used to produce a possible animal model of Huntington's chorea, a disease not found naturally in species other than man. The neurochemical abnormalities produced in the rat agree well with those found in Huntington's chorea. Perhaps an animal model of dystonia can be produced by the proper use of some neurotoxin. In any case, the knowledge obtained from these studies must increase our understanding of all movement disorders including dystonia.

Dr. Charles Markham reviewed the "Anatomy and Physiology of the Basal Ganglia". It is generally believed that dystonia is a disease of the basal ganglia. It shares some symptoms with other diseases in which the basal ganglia are clearly involved, but the nature of the disorder in dystonia has not been identified. The gross anatomy of the basal ganglia has been known for many years, but recently our understanding at the cellular level has blossomed due to the introduction of novel methods of exploration. For example, the pathways between parts of the basal ganglia have been traced by the transport of the enzyme horseradish peroxidase along the axons. Another technique discussed by Markham was the tracing of nigral-striatal connections by stereotactic innoculation of the substantia nigra with the virus herpes simplex. These new techniques may soon illuminate those aspects of basal ganglia function still shrouded in mystery. Markham expressed the view that dystonia secondary to the use of drugs such as the phenothiazines may be a good model of idiopathic dystonia. There is some evidence that such drugs cause a massive release of dopamine and a blockade of its reuptake.

Dr. John Phillis gave a presentation entitled "Neuropeptides in the Brain: New Horizons for the 1980's". Cells communicate with one another over large distances by means of hormones, and across the short distance of the synaptic cleft using neuro-transmitters. In recent years the number of chemical messengers known to exist in the brain

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has increased dramatically with the discovery of the neuropeptides. Some of these act as hormones, some are probably neurotransmitters and others are neuromodulators. The distinction between these may be made roughly as follows. Neurohormones are released into the bloodstream and interact with any neuron having a receptor for them. Neurotransmitters only transfer information from one neuron to those with which it makes synaptic contacts. Neuromodulators are thought to exert a type of gain control; that is, they control the excitability of a synapse by altering the membrane conductance and transmitter release without directly affecting the post-synaptic membrane. Neuropeptides are found in abundance in the basal ganglia which suggests they may play a role in movement disorders but just what role remains unknown. Relatively high concentrations of enkephalins are found in the striatum and globus pallidus, and substance P has a high concentration in the substantia nigra. Attempts have been made to modify the movement disorders of Parkinsonism and Huntington's disease by administering naloxone, a drug that blocks the receptors for some of the enkephalins, but no significant effects were found. No similar attempts have been made with dystonia patients. In the discussion that followed, the comment was made that the neuropeptide, neurotensin, reverses rigidity in experiments on animals.

Dr. Joseph Waltz reviewed the "Present Surgical Treatment of Dystonia". Although there are many more possibilities for drug therapy now than existed in 1955 when surgery for dystonia was introduced, there is still a place for surgery in the treatment of the illness. Dr. Waltz discussed recent work on electrical stimulation of deep brain structures such as the thalamus, and spinal cord stimulation. 66% of dystonia patients showed some improvement following spinal cord stimulation. In 29% of these the improvement was marked.

We now turn to the progress reports on dystonia research presented at the workshop. Three of these dealt with studies of skin fibroblasts from dystonia patients. The most direct way to search for a biochemical defect in dystonia would be to study brain tissue, however, dystonia is a rare disease and seldom fatal, so such tissue is not readily available. Fortunately, other cells in the body have some properties in common with nerve cells and the hope is that the chemical defect responsible for dystonia will be apparent in skin fibroblasts as well as neurons.

Dr. Ivan Diamond reported on "Regulation of Postsynaptic Membrane Proteins in DMD". He is investigating the possibility that dystonia is produced by an abnormality in a biochemical mechanism which regulates receptor proteins in the brain. He drew the analogy with tardive dyskinesia which is produced by neuroleptic drugs which block dopamine receptors and appear to be associated with changes in the number and sensitivity of dopamine receptors. He has found that the acetylcholine receptor is reversibly phosphorylated and dephosphorylated in the postsynaptic membrane by endogenous enzymatic mechanisms. This has led him to study the enzymes that regulate receptor function in skin fibroblasts. The dephosphorylation of receptors by the enzyme phosphatase is the most easily studied process, but he found no abnormality in this process in fibroblasts from dystonia patients. He is presently developing the tools for the more difficult study of phosphorylation of receptor proteins.

Dr. Axandra Breakefield discussed "Neurotransmitter Metabolism in DMD: Studies with Cultured Skin Fibroblasts". There are a number of enzymes and neurotransmitters that are found in both neurons and skin fibroblasts. These include monoamine oxidase (MAO), catecholamine-o-methyl transferase (COMT), nerve growth factor (NGF), and gamma-aminobutyric acid (GABA). Dr. Breakefield found no difference in concentrations of these substances between dystonics and controls. In the course of this work she did find an abnormality in nerve growth factor in the genetic disease familial dysautonomia but not in dystonia.

Dr. Abel Lajtha reported on "Alteration of Neural Membrane Transport Systems in DMD". Membrane defects resulting in altered transport systems could be one of the factors responsible for nerve cell dysfunction in dystonia. If there is a defect in the membranes of neurons, the same defect may occur in other cells. Dr. Lajtha has been studying the transport of amino acids in skin fibroblasts. He has compared three patients with the recessive form of dystonia with three age matched controls. So far no significant differences in amino acid transport have been found.

Dr. William Tatton reported on "Electrophysiological Investigations of Dystonia in Man". Computer controlled torque motors that had previously been used for the study of the mechanisms of movement control in animals are now being used for the study of patients with movement disorders. In these experiments the EMG responses to precisely controlled mechanical stimuli are recorded. Characteristic differences in these responses are found between controls and patients with motor disorders such as Parkinsonism and dystonia. The same abnormality was found in all thirty-five of the dystonia patients tested. This defect was even detectable in two asymptomatic parents of dystonic children. This suggests that these studies may be capable of detecting asymptomatic carriers and thus be valuable for genetic counseling. They should also be useful in evaluating the usefulness of drugs and surgical procedures for movement disorders.

Dr. Donald Riker reported on "Neurochemical and Pharmacologic Investigations of Mesotelencephalic Neurotransmitter Systems in Hereditary Murine Dystonia and Human DMD". Neurons that employ acetylcholine as a neurotransmitter must synthesize it from its precursor choline that is transported across the cell membrane. Dr. Riker and Dr. Robert H. Roth have compared the high affinity choline uptake system in fibroblasts from dystonic patients and controls. Significant differences of affinity constants and maximal transport

capacities are found, but so far only one family with dystonia has been investigated. This was a family with pseudodominant dystonia in which several family members were affected.

Dr. Walter Lovenberg reported on "Hydroxylase Cofactor Activity in CSF of Patients with DMD". The synthesis of dopamine in neurons is dependent on the activity of tyrosine hydroxylase, and this in turn, is regulated by the concentration of hydroxylase cofactor. The naturally occuring cofactor is thought to be tetrahydrobiopterin (BH_4). The same cofactor is involved in the synthesis of serotonin. An assay procedure that is sufficiently sensitive to measure hydroxylase cofactor activity in cerebrospinal fluid has recently been developed in Dr. Lovenberg's laboratory and has been used to measure this activity in both Parkinson's disease and dystonia. The level of cofactor activity was found to be reduced in Parkinson's disease and in both the dominant and recessive form of dystonia. The number of dystonia patients tested is still rather small. The significance of this finding is still not completely clear, but it could indicate an abnormality in the dopaminergic system in dystonia similar to that which is known to exist in Parkinson's disease.

Dr. Steven M. Stahl reported on a "Clinical-Pharmacological Study of Dopaminergic, Cholinergic and Serotoninergic Neuronal Systems in Idiopathic Torsion Dystonia". Dr. Stahl is testing the hypothesis that a dopamine-acetylcholine imbalance in the brain is responsible for the symptoms of dystonia. He is manipulating this balance by using drugs that stimulate or block the dopamine and acetylcholine receptors. The levels of neurotransmitters and their metabolites in blood, urine, and cerebrospinal fluid are being monitored to detect the changes due to the drugs. He has found that the symptoms of some dystonia patients are made worse when the acetylcholine level is raised by physostigmine and are improved by anticholinergics. He is also carrying out clinical trials with bromocriptine, a dopamine receptor agonist. Other drugs being studied are choline and lecithin which should raise acetylcholine levels.

Dr. Leslie I. Wolfson reported on "Studies of Ventricular Fluid, Neurotransmitters and Metabolites in Dystonia". Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), the respective metabolites of dopamine and serotonin have previously been measured in lumbar cerebrospinal fluid with inconclusive results. There are production and transport mechanisms in the spinal cord that make these measurements imprecise methods of studying the metabolism of neurotransmitters of the basal ganglia. Dr. Wolfson and his colleagues took advantage of the availability of ventricular fluid from dystonia patients undergoing thalmotomies at St. Barnabas Hospital. Levels of HVA and 5-HIAA were measured. The patients were divided into a childhood-onset group and an adult-onset group. In the former, the age of onset (3 to 10 years), the initial involvement of the extremities, the severity of incapacity, and the rapid course were all consistent with the recessive form of dystonia. In the adult-onset group, the age of onset (13 to 47 years), the involvement of axial musculature initially, the moderate incapacity, and the slow progress suggested a different form of dystonia. They found that the mean ventricular fluid concentrations of HVA were lower in patients with adult-onset dystonia than in childhood-onset patients. No significant differences in 5-HIAA concentrations were found. These results suggest that the childhood-onset and adult-onset dystonias are different diseases with the latter being associated with diminished dopaminergic activity. This in turn suggests that adult-onset dystonia might respond favorably to L-dopa or other dopamine agonists.

Dr. Anne Messer reported on "Brain Pathology in the Mouse Mutant *Dystonia Musculorum*". Clearly, research on the cause and cure of dystonia would move at a much more rapid pace if an animal model could be found. For this reason, there has been a continuing interest in a mutant mouse discovered by Duchen in 1963 that shows many of the symptoms of human dystonia. Until a few years ago, it was believed that the anatomical abnormalities were limited to peripheral nerves. Dr. Messer found extensive pathological changes in the striatum and the red nucleus that began after the third week of life. In the chemical studies a loss of almost 50% of GABA biosynthetic capacity was found in whole tissue samples from the striatum and substantia nigra while hypothalamic capacity remained unchanged. In the discussion that followed this report, the question of the relation of the dystonic mouse to human dystonia was raised. The pathological changes of the peripheral nerves, the striatum and red nucleus that are found in the mouse have not been found in human dystonia. The comment was made that these changes are more like those of spinocerebellar ataxia than dystonia.

Editor's Note

Dr. Harris is the father of a child with dystonia. He was invited by the Dystonia Medical Research Foundation to attend the workshop and prepare this summary.