SUBJECT REVIEW

The Dystonias

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1. Introduction

Dystonia is a difficult problem for both the clinician and the scientist. It is sufficiently common to be seen by almost all physicians, yet uncommon enough to prevent any physician from gaining broad experience in its diagnosis and treatment. Each case represents a difficult challenge even to the specialist. The basic scientist is faced with investigating a disorder that is without relevant animal models and which is so rare that obtaining suitable tissue for study is a major obstacle. Dystonia may be idiopathic, or associated with lesions from many sources, including a variety of rare diseases. If idiopathic, it may be genetically transmitted or sporadic. If genetically transmitted, it may be generalized or focal, with symptoms varying in different members of the same family. It may be refractory to treatment, or it may respond to any one of a number of individual drugs that have very different mechanisms of action. For idiopathic dystonias, no clear method of genetic transmission has been established and no consistent pathology identified.

This review is intended for both the practitioner and the scientist. Its purpose is to summarize current knowledge regarding the various forms of dystonia, as well as the pathology known to produce the syndrome in specialized circumstances.

The low incidence of the disorder, its prolonged course, and the difficulty of accurate diagnosis has precluded the type of systematic investigation that is possible with many other disorders. Yet such systematic investigation is essential if the mysteries surrounding dystonia are to be unravelled and methods of treatment improved.

Dystonia has been defined by the Scientific Advisory Board of the Dystonia Medical Research Foundation as a syndrome of sustained muscle contraction, frequently causing twisting and repetitive movements, or abnormal posture. It is a clinical term and not a disease description. It refers to all anatomical forms, whether they involve generalized musculature or only focal groups. Although dystonia appears as part of the syndrome in a number of disease states, it is idiopathic dystonia, where inheritance is a major factor, that has aroused the greatest medical interest. This review emphasizes recent literature and those aspects which may contribute to an understanding of the underlying mechanisms of dystonic movement. Excellent reviews giving much more detail on historical aspects, clinical classification, differential diagnosis and therapy are available.[e.g.1-3]

One problem in the dystonic literature is the frequent existence of alternative names for the same syndrome; to help the reader with this problem we have described some of this nomenclature in Table 1.

Idiopathic Forms

Idiopathic forms may be familial or sporadic. The most important form of idiopathic dystonia is torsion dystonia (TD) which tends to be familial. The name is preferred to the classical term dystonia musculorum deformans (DMD).[39] It usually starts in childhood as a focal disorder which progresses overall but, in common with almost all dystonias, it is subject to exacerbations and remissions. The incidence of generalized dystonia is generally thought to be about 2-3 per million (Table 2) but this incidence can be expected to show considerable regional variation depending upon the genetic make-up of the population

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Table 1: Some Dystonia Subtypes and Alternative Nomenclature.

Adult-onset focal foot dystonia:	Much rarer than adult-onset dystonia of the upper limbs but does occur.[4-6] It may be a presenting feature in Parkinson's disease (see Table 3).
Azorean disease:	see Joseph's disease.
Blepharospasm:	Age of onset usually 5-6th decade, Female:Male ratio, 3:1 in 250 patients studied.[7] For review on etiology, diagnosis and treatment see Elston[8].
Brueghel's syndrome:	see Meige's disease.
Cranial/cervical dystonia:	see Meige's disease.
Dystonic stridor:	Frequently thought hysterical but may be a form of segmental dystonia involving the vocal cords - seen in 2 cases of DOPA-treated Parkinsonism along with other symptoms of dystonia,[9] and in a case of idiopathic generalized dystonia.[10]
Joseph's disease (Machado-Joseph disease, Azorean disease):	A familial, autosomal dominantly inherited disease with dystonia as a prominent symptom which was originally described in Portugese families; may be associated with striatonigral and rubro-dentato degeneration.[11] A number of variants may exist (see text and Table 3).
Grisel's syndrome (nasopharyngeal torticollis):	Nontraumatic atlanto-axial dislocation following inflammation in the naso-oro-pharyngeal region.[12]
Machado-Joseph disease:	see Joseph's disease.
Manto syndrome:	Spasmodic torticollis with thoracic outlet syndrome.[13,14]
Meige's disease (Brueghel's syndrome, adult-onset idiopathic blepharospasm and/or oromandibular dystonia, focal cranial dystonia, cranial/cervical dystonia):	Meige's disease is probably most commonly used but is argued against because others, such as Brueghel, Wood and Black, each described it independently.[15-18] Age of onset generally after 50, more common in women then men, no defined pathology, symptoms disappear during sleep.[19] In 100 cases Jankovic and Ford[20] found average age of onset 51.7, 60% female, and a high correlation with essential tremor,[cf21] other movement disorders and positive family histories.[22] It frequently begins with or involves other dystonic symptoms such as torticollis; the legs are seldom if ever involved. Tolosa[23] reports not only a family history of dystonia or other extrapyramidal disorders but a high incidence of prior depression.
Musician overuse syndrome:	Focal dystonia in hand where pain is not present. It must be distinguished from muscle tendon overuse with pain.[24-29]
Oromandibular dystonia:	See Meige's disease.
Pisa syndrome:	Tonic flexion to one side and slight rotation of the trunk, unaccompanied by other dystonic symptoms, sometimes seen after butyrophenones[30,31] or phenothiazines.[32]
Segawa's disease:	A fluctuating, usually hereditary dystonia with diurnal rhythm, responsive to DOPA and usually accompanied by parkinsonian symptoms (see text).
Spasmodic dysphonia:	Believed to be almost always a laryngeal/paralaryngeal movement disorder, frequently associated with Meige's disease.[33-35]
Writer's cramp:	Again often associated with other features of segmented or generalized dystonia.[29,36-38]

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Table 2: Prevalence and Incidence Figures for Idiopathic Dystonias*.

Region and Reference	Prevalence (Total Cases/million) Torsion Dystonia Ash. Jews	Sep. Jews	Gen. Pop.	All Focal Dystonias	Incidence (New Cases Per Year/million) Torsion Dystonia Ash. Jews	Sep. Jews	Gen. pop.	All Focal Dystonias
U.S.[40]	25.2		2.99					
U.S.[41]	59							
Israel[42]					4.82	1.05		
Israel[43]	22	1.5	10.8		0.98	0.11	0.43	
	52.5							
Israel[44]	43.5	8.6	24.2					
Rochester, Minn[45]			18	248			2	24

* Adapted from unpublished summary prepared by S.G. Diamond and C.H Markham.

in question. In the generalized form, there may be widespread and differing dystonic movements and postures. However, the dystonic appearance in each body area is distinctive. "The eyes may screw shut (blepharospasm); the jaw may be forced open or closed with spasms of the mouth (oromandibular dystonia); the neck may twist (torticollis, retrocollis or antecollis); the trunk may bend (scoliosis, lordosis, or flexion); the arm may adopt a characteristic posture of hyperpronation, with flexed wrist and extended fingers, particularly during the act of writing (dystonic writer's cramp); or the leg may be extended with the plantar flexed and inverted, particularly when walking (the dystonic foot)".[46] Although torsion spasms (prolonged sustained muscle spasms which produce characteristic dystonic postures) or slow, sinuous writhing of distal parts of the limbs (athetosis) are often considered characteristic of dystonia, more rapid, irregular or repetitive movements (myorhythmia) or even brief, rapid, myoclonic jerks may occur.[47-48] Postural or action tremor is also often seen. Although dystonic movements usually cease during sleep, certain postures may persist.

Autosomal dominant, autosomal recessive, X-linked recessive and sporadic forms of torsion dystonia have been described.[49-50] It was initially felt that the Ashkenazim form was autosomal recessive[51] but at present there is no consensus about the inheritance pattern, with many workers interpreting the evidence in both Jewish and non-Jewish families as being consistent with an autosomal dominant with reduced penetrance.[44,45,52,53] Others interpret the evidence as indicating a recessive gene that shows "pseudodominance".[54] It is possible that both types of dystonic gene exist.[55] Bressman et al.[56] recently studied the pedigrees of 79 Ashkenazi patients with onset before age 27 and found the data for this early onset pattern consistent with an autosomal dominant transmission but with a minimum penetrance of only 31%. These hereditary cases typically begin in childhood and are usually progressive although Eldridge et al.[49] described a prolonged spontaneous remission in one identical twin of a 61 year female pair with a probable autosomal recessive form of the disease. Although the maximum prevalence probably occurs in the Ashkenazim (Table 2), familial patterns have been described in American Indians, Japanese, Chinese, Arabs, South African colored[57] and Mexicans.[58]

Considerable searching for an identifiable genetic marker in dystonia has taken place without success to date. Bressman et al.[59], assuming an autosomal recessive mode of inheritance for TD, found no linkage in 5 families, each including two affected siblings, with 18 marker systems, including HLA. Breakfield et al.[60] have used restriction length polymorphisms to work through about one-third of the human genome without finding evidence of linkage in families with TD. This, of course, cannot be taken as evidence against a genetic basis for the disease; it only indicates that possible genes have not yet been identified.

The X-linked form is clearly distinguishable on a genetic basis from the autosomal forms even though the clinical symptoms overlap. This form is relatively rare and has been described only on the Philippine Islands.[61]

In some families where a clear autosomal dominant form of inheritance can be established, affected children may have the generalized disease while some of the adults may present only with a focal dystonia.[46] Such mild, late onset cases are clearly a forme fruste of TD. Occasional cases have also been reported where more than one family member suffers from a form of focal dystonia such as writer's cramp[62] or Meige's syndrome[22,63] (Table 1). Severe dystonia was found in one family accompanied by ataxia telangiectasi.[64] The dystonia in this family, but not the ataxia, responded to bromocriptine. Tremor is frequent in affected families[20,21,65] and may occur along with focal dystonia in individual patients.[66] Rare adult-onset forms are thought to be inherited as an autosomal dominant or to be sporadic.[67] In situations where there is late onset of focal dystonia, the disease tends not to spread to generalized dystonia.

Idiopathic spasmodic torticollis[68-70] is the most common form of primary dystonia. An incidence of 3/10,000 is often quoted.[71] Familial cases occasionally occur and an association with both benign essential tremor and Parkinson's disease has

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been noted. Of 200 patients with essential tremor seen at an Italian Movement Disorder Center, 2 also had dystonia and 10 had buccolinguofascial dyskinesias.[72,73]

In summary, every case of dystonia, including focal and late onset forms, should be investigated for a possible familial pattern. It can be anticipated that restriction fragment length polymorphic markers (RFLPs) will be identified for at least some forms of dystonia in the future and these will help to clarify the inheritance problem. Discovery of additional dystonia pedigrees would greatly assist in this endeavor.

Other Inherited or Idiopathic Movement Disorders with Dystonic Symptoms Idiopathic torsion and focal dystonias must be differentiated from other inherited movement disorders with a dystonic component, as well as from acquired cases. The latter may be a consequence of encephalitis, toxins or drugs (see Section 6); focal or generalized cerebral injury; infarcts; brain tumors; or even spinal malformations (see Section 2).[74,75]

A syndrome of hereditary progressive dystonia with marked diurnal variations and frequent parkinsonian symptoms was first described by Segawa et al.[76] and is sometimes called the Segawa syndrome. It responds dramatically to L-DOPA and shows minimum progression in adult life, suggesting it is distinct from other forms of primary dystonia. Others have now reported similar cases in both juveniles and adults.[77-92] Some of the cases vary somewhat in the rhythm of fluctuation and symptomatology and may represent variant forms of the Segawa syndrome; all show the characteristic marked improvement on DOPA. Segawa originally postulated autosomal dominant inheritance with low penetrance for this disease. One family, which included five generations of members with juvenile dystonia-parkinsonism, appeared to conform to such a pattern.[94] Deonna[95] reported 9 sporadic and 11 familial juvenile cases with pedigrees that neither confirmed nor refuted Segawa's hypothesis.

Familial paroxysmal dystonia choreoathetosis (FPDC), a rare autosomal dominant disorder characterized by episodes of sustained generalized dystonic contractions of muscles without loss of consciousness, has been described in 6 families with over 73 affected members.[96-102] One of the victims in one family also had familial ataxia.[102] Graff-Radford[103] described a possibly related family with recessively inherited ataxia and dystonic episodes. Plant et al.[104] reported still another family in which both mother and daughter showed paroxysmal dystonia induced by exercise though not by sudden movement; EEG recordings were normal during these attacks.

Willemse[105] reported 4 cases of idiopathic dystonia with onset in the first year of life; in contrast to childhood onset TD, the course for these infants was benign. He proposed that an imbalance in neurotransmitter development may be the underlying cause. Other cases of benign paroxysmal torticollis in infancy have also been reported[106-110] but they need to be carefully distinguished from iatrogenic forms which are particularly common in children[111] (see Section 6).

"Nocturnal paroxysmal dystonia" (NPD) is the name given to a syndrome characterized by sleep-related, short or long duration seizures with choreoathetoid, dystonic and ballistic movements.[112,113] It has been identified in 14 patients. Lee et al.[114] described a family with dystonic spasms occurring during non-REM sleep that may be another example of this disorder. There is some debate as to whether this is a form of epilepsy or a new dystonic syndrome.[115] EEG studies in a case reported by Godbout et al.[116] favor the epileptic hypothesis but 5 cases reported by Lugaresi and Cirignotta[117] showed no EEG abnormalities either during sleep or wakefulness.

In addition to these idiopathic dystonia variants, the syndrome may occur in association with other diseases (Table 3), including many which are genetically determined. It is a prominent symptom in Hallervorden-Spatz disease[134] and in Joseph's disease,[11,217] two other hereditary, progressive neurodegenerative disorders. Dystonic symptoms are also frequently seen in various forms of gangliosidosis and in juvenile cases of Leigh's disease (an X-linked disorder of purine metabolism sometimes called infantile bilateral striatal necrosis).[145,218-225] They have also been reported in some cases of homocystinuria[167,168] as well as some other enzyme deficiency conditions (Table 3). As indicated in Table 3, several of these conditions have been linked to chromosomes X, especially the Xq28 region. Whether this has any relevance to the possible genetic linkage of any form of primary idiopathic dystonia remains to be determined. Table 3 also lists a variety of other conditions such as Wilson's disease, Parkinson's disease and progressive supranuclear palsy where associated dystonic symptoms have been reported. In instances where only one or two cases have been reported, coincidental association of rare diseases may be the explanation.

In summary, there are a number of identifiable variants of inherited dystonia to be considered in diagnosis, as well as its appearance as part of some disease with more generalized pathology.

Acquired

Delayed onset dystonia may appear 1 to 14 years after a non-progressive cerebral insult such as perinatal anoxia, trauma or cerebral infarction. Tudehope et al.[226] reported that 18 of 117 babies with birth weight less than 1500 g showed dystonia. Symptoms resolved in 13 of them by 8-12 months, but 5 had major neurologic/intellectual problems at that age. Such delayed-onset dystonia following perinatal anoxia is an important diagnostic alternative to TD in childhood cases.[227,228] Burke et al.[229] suggested that the diagnosis of TD should not be made in the absence of a family history but that MRI scans may reveal striatal pathology in cases of dystonia consequent upon perinatal anoxia. Similarly, dystonia may develop late in cases of cerebral palsy.[230] According to Kyllerman et al.[231-232] dystonia occurred in 70% of a series of 116 cerebral palsy cases, with the rate for the dystonic form being 0.17/thousand births. Both Burke et al.[229] and Treves and Korcyzn[230] suggested that a genetic tendency towards dystonia may also be triggered or worsened by perinatal factors.

Painful torticollis is seen in Grisel's syndrome where the underlying cause appears to be an infection in the nasopharyngeal region; this rare condition was seen somewhat more frequently in the pre-antibiotic period.[12,233-235]

Epidemics of an acute torticollis have occurred in eastern and northern China since 1975, particularly among farmers in rural areas where it may affect up to 3% of the population. The individual episodes of spasmodic torticollis last generally for about 10 minutes but may persist for up to 24 hours; the episodes in most cases were seen over a 5-10 day period. The

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Table 3: Some Other Diseases in Which Dystonic Symptoms Occur.

Joseph's disease (Machado-Joseph disease; Azorean disease)	A dominantly inherited multisystem disorder that occurs primarily in people of Azorean descent but has been described in non-Portugese families.[118,119] Dystonia is seen as a variable symptom.[11,118-121] In single cases pathology is reported in CP,[11] GP,[119] SNC,[11] red n.,[11,119] cerebellar dentate n.[11,119] and subthalamus.[119] Brain glutamate dehydrogenase and malate dehydrogenase activities are not abnormal.[122]
Lesch-Nyhan syndrome (and some other X-linked conditions)	Torsion dystonia seen in 8 patients; 1 on autopsy showed no brain histopathology but no HPRT activity.[123] Testicular atrophy and partial failure of the 11β-hydroxylation of steroids in 7 cases.[124,125] The HPRT gene has been assigned to locus Xq26-27.3.[126] The closely related Xq28 is reportedly the locus for a syndrome of torticollis, cryptorchidism, keloids and renal dysplasia described by Goeminne[127] in a large family and believed an X-linked, incomplete dominant.[128] The Xq position has also been linked to Charcot-Marie-Tooth disease[126] which is a hereditary motor and sensory neuropathies sometimes indexed under dystonia although it is not clear how frequent dystonic symptoms are seen. Others[129,130] have linked it to chromosome 1 and it may be a heterogeneous collection of genetic diseases of peripheral nerves.
Rett syndrome	An X-linked disease occurring in females, 1/8 cases showed progressive dystonia and the "hand-washing" automatisms characteristic of the disease[131]. More than 1000 cases have been recognized.[132] A genetic defect in synapsin I, a neuron-specific protein, has been suggested.[133]
Hallervorden-Spatz (HS)	Dystonia is an important feature. Involves deposition of iron-containing pigment and degeneration in GP and SN[134] as well as red n. and dentate n..[135] GP pathology is believed key.[135-138] Some cases also show putaminal pathology.[138,139] Sethi et al.[136] suggested the syndrome may be more common than currently believed and that MRI may be helpful in making the diagnosis, but the occasional case with dystonic and parkinsonian symptoms may have normal CT and MRI.[140] Cysteine accumulation in GP and cysteine dehydrogenase and GABA low only in GP in 2 cases.[141] One case with dystonia showed marked loss of DA in basal ganglia with no loss in limbic areas.[142]
Leigh's disease[143] Subacute necrotizing encephalopathy	Generalized TD is a frequent and may be the only[144] symptom. Pathology in putamen[145-149]and may also involve whole CP[144,150] GP and SN.[150] Clinical symptoms often divergent but histopathology always found in the caudate and sometimes the lenticular n., the mesencephalic tectum, tegmentum and periaqueductal gray.[143] Plasma pyruvate and lactate elevated;[144] four siblings described with no abnormality of pyruvate metabolism in serum or fibroblasts but marked elevation of CSF pyruvate and lactate, suggesting defect in oxidative metabolism limited to brain.[151] Cytochrome c deficiency appears important factor.[152,153]
Type III (adult) GM^1-gangliosidosis	Foot dystonia is often presenting symptom, progressing to generalized dystonia; improved markedly on trihexyphenidyl. In this condition there is a hereditary lack of lysosomal β-galactosidase.[154] Dystonic symptoms seen in 3 members of a family with adult disease, pathology in autonomic neurons.[155]
Type III (juvenile)	Takamoto et al.[156] report a case of juvenile β-galactosidase deficiency with dystonic movements, pyramidal symptoms and mental deficiency.
GM_2 gangliosidosis (hexoseaminidase deficiency) (Tay-Sachs disease)	A 24 year old man presenting with dystonia, dementia, amyotrophy, choreathetosis and ataxia was found to have a partial hexoseaminidase deficiency. A review of the literature in this paper[157] is used to suggest that dystonia and choreoathetosis may be neglected symptoms of chronic GM_2 gangliosidosis and some cases have been reported with progressive dystonia as the dominant[158] symptom or presenting[159] symptom. Sibling of case of typical Tay-Sachs disease had normal hexoseaminidase but microencephaly vera, progressive motor neuron disease and nigral degeneration associated with dystonia and an action tremor.[160] Elwes & Saunders[161] report occurrence of torsion dystonia, focal dystonia and Sandhoff disease (a hexosaminidase deficiency) in a single family but this may represent chance association of rare diseases.
Ataxia-telangiectasia	Ten yr old male with familial disease and severe, progressive dystonic posturing [162, cf64, 102, 103.
Schwartz-Jampel syndrome	Blepharospasm and other abnormalities. Family reported indicates autosomal recessive.[168]
Metachromatic leucodystrophy	Dystonic symptoms seen in 3 siblings of Iranian ancestry[164] and in a Jewish lady,[165] biopsies proved reduced arylsulfatase A.
Triosephosphate isomerase deficiency	Two siblings had prominent progressive dystonia plus tremor, pyramidal signs and evidence of spinal cord motor neuron involvement as well as hemolytic anemia. Poll-The et al.[166] reviewed 14 other cases in the literature and suggested specific involvement of basal ganglia, brainstem and/or spinal cord structures.
Homocystinuria	Occasional dystonic symptoms have been attributed to multiple multiinfarcts in the basal ganglia.[167, 168]
Glutaric acidemia (glutaryl-CoA-dehydrogenase deficiency)	Dystonia may be seen in this inherited disease characterized by defective metabolism of lysine, hydroxylysine and tryptophan[169] 14/16 cases of this autosomal recessive disorder showed debilitating dystonia; 4 studied by CT (including 2 symptom-free cases) all showed bilateral frontotemporal atrophy.[170] Loss of striatal neurons shown in 1 case on autopsy.[171]

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Progressive familial encephalopathy	Eight cases reported in infants showing bilateral spasticity and dystonia, acquired microencephaly, a rapid course to death, and various combinations of basal ganglia calcification and white matter densities with persistant lymphocytosis in the CSF.[172]
Methylmalonic acidemia	Child with bilateral dystonic posturing associated with lucencies in the GP.[173]
Hartnup disease	One case with dystonic posturing showed Purkinje and cortical neuronal loss.[174] 17 month old reported with focal intermittent dystonia.[175]
Niemann-Pick disease (dystonic lipidosis)	7/8 had low skin fibroblast sphingomyelinase.[176] Variant in 43 yr old male[177] and 2 siblings[178] with dystonic symptoms but normal sphingomyelinase. Siblings showed pathology in many nuclei including cortex, basal ganglia and brainstem.
Familial apoceruloplasmin deficiency	Case of 52 yr old woman with blepharospasm and retinal degeneration, accumulation of Fe but not Cu in brain and liver shown.[179]
Wilson's disease	Of 31 patients, 65% show dystonia. Frequent MRI lesions in CP, midbrain, pons and subcortical white matter - dystonia correlated with putaminal lesions.[180] PET-FDG study indicated less involvement of caudate than in HD but no involvement of putamen or GP.[181] Occurrence of generalized dystonia and whispering dysphonia.[182] Dystonia in single cases improved with trihexyphenidyl[183] and worsened on initial penicillamine therapy.[184] Others[185,186] observed cases of TD where there was cupruria and cases of TD occur in the same family with Wilson's disease and spasmodic stiff neck.[187]
Other disorders of Cu metabolism	10 yr old non-Jewish child with non-familial TD who had normal ceruloplasmin, only slight cupraemia but the brain on autopsy contained 3 times the normal amount of Cu - there was lipofuscin in cortical and CP neurons, chromatolysis and vacuolization of neurons in the basal nuclei, VL thalamus, cerebellar dentate and fronto-parietal cortex.[188] A 15 year old with dystonic posturing and low serum and urine Cu, also low blood glutathione but no Kayser-Fleischer rings.[189]
Tyrosinosis	Infant showing blepharospasm and finger movements had markedly elevated (>4-fold) MHPG and HVA (>2-fold) levels in the CSF.[190]
Progressive supranuclear palsy (PSP, Steele-Richardson-Olszewski disease)	Review emphasizes axial dystonia as one of main symptoms - male predominance (60:40), average age of onset 60 years.[191] 8/30 show progressive limb dystonia[192] which may be an early symptom,[193] as may blepharospasm.[194,195] PSP pathology involves basal ganglia, brainstem and cerebellum.[194,195] Several case reports suggesting that multiinfarcts involving the CP, GP, internal capsule, or midbrain (SN and subthalamus), especially in parkinsonian patients, may produce PSP symptoms.[196,197] Excessive yawning frequently seen is reduced or abolished by dopaminergic drugs;[198] such yawning may indicate brainstem involvement.[199]
	Case having also hyperkalemic periodic paralysis (a dominantly inherited disorder).[200]
Parkinson's disease	A focal foot[201] or other form of dystonia[202] is sometimes seen as presenting feature. In some cases where dystonic symptoms occur first, they have been reported to decrease as the parkinsonism progresses and the two respond differently to DOPA.[203,204] Parkinsonian and dystonic features frequently occur together in Segawa's disease.
Tourette	28/29 Tourette patients had blepharospasm[205] and occasional cases with dystonia (4 out of 1377 reviewed) also show vocalizations similar to those in Tourette's disease.[206]
Shy-Drager	Two cases of laryngeal stridor; histological examination ruled out motoneuron loss as cause — believe CNS defect.[207]
Multiple sclerosis	Paroxysmal dystonia as initial manifestation in 8 patients with other symptoms developing as long as 10 years later.[208] 2 cases with bilateral blepharospasm.[209]
Central pontine myelinolysis	Lesion in basal pons; case developed segmental dystonia several months after initial clinically apparent insult.[210]
Whipple's disease	Dystonic eye and jaw movements seen in two middle aged cases.[211]
Paraneoplastic myeloradiculoneuropathy	Single case with retrocollis.[212]
Albinism	4 cases with torticollis and nystagmus.[213]
Scoliosis, camptodactyly	Occur in case of torticollis[214]
Multisystem mitochondrial cytopathy	1/2 cases had torsion dystonia but characteristic triad is ophthalmoplegia, retinitis pigmentosa and heart conditions.[215,216]

Abbreviations used: CP, caudate/putamen; GP, globus pallidus; SN, substantia nigra; SNC, SN, pars compacta; DA, dopamine; HPRT hypoxanthine-guanine phosphoribosyl transferase; HD, Huntington's disease; MHPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid.

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Table 4: Histopathological changes found by CT, MRI*, Histopathology or Pneumoencephalopathy*** in cases with Dystonic Symptoms (see also Table 3 for pathology in cases of dystonia associated with other diseases).**

Area of Lesion	Type of Case and Apparent Cause.
Calcification through brain, including basal ganglia	Female, aged 53, with idiopathic hypoparathyroidism showed writhing movements and parkinsonism.[259]
Striopallidodentate calcification	1 case aged 5 had dystonia and normoparathyroidism, case aged 51 had hypoparathyroidism but **no** dystonia.[260**]
Basal ganglia calcification	In cases of paroxysmal dystonic choreathetosis;[261**262**] in family showing TD with normal parathyroid function;[263**] in 2 of 12 children showing dystonia after perinatal anoxia;[264] in 70 yr female with bilateral dystonia and ballism;[265] in 23 yr old male with progressive hemidystonia after a head injury;[266] and in 2 sisters with autosomal recessive TD (see Section 6 for chemistry).[267] Rapid development with onset of abnormal movements in 58 yr old following anesthetic anoxia.[268]
Corpus striatum, symmetrical infarcts	Young man with blepharospasm following hypoxic encephalopathy.[269]
Basal ganglia infarcts	Children with hemidystonia after head injuries.[270]
Basal ganglia hematoma	64 yr man with post-traumatic transient Meige which disappeared as hematoma resolved.[271]
Dorsal caudate and putamen	Filipino man, age 50, with 6 yr history of progressive dystonia.[272**]
Bilateral caudate, extending into putamen	Female with compulsive movements of hand.[273]
Right lentiform n. and left basal ganglia infarcts	Left hemidystonia developed 2 yrs postinfarct in case later showing systemic lupus erythematous.[274]
Mild atrophy in frontal cortex, dentate, VL thalamus & CP	Case of torsion dystonia - no family history.[275**]
Caudate calcification	30 yr old man with progressive hemidystonia after a head injury.[276]
Bilateral putaminal cystic lesions	30 yr old man with bradykinetic dystonia following methanol poisoning.[277]
Bilateral putaminal hypodensities	3 cases with generalized dystonia;[278] 31 yr old man. with progressive generalized dystonic paraplegia and mental deficiency; not Wilson's disease.[279]
Putaminal infarct	Progressive hemidystonia in 4 children[280,282] and 8 adults.[147*,281*,283-285]
Putamen, unilateral but extensive	Bilateral tardive dystonic movements in 61 yr M, probably an old infarction.[286]
Astrocytoma in lentiform nucleus	Hemidystonia in 8 yr old.[287]
Lentiform n., thalamus & borders of internal capsule	Young man with torsion dystonia following CO poisoning.[288]
Left putamen & mild left frontal atrophy	2 cases of posthemiplegic hemidystonia.[289]
Subdural hematoma	Hemidystonia.[290]
Arteriovenous malformation (AVM) in contralateral cerebral hemisphere	2 cases of progressive hemidystonia; in only 1 did the AVM obviously involve the basal ganglia.[291]
Cortex & (in 1 case) PL thalamus, not striatum	2 cases of posthemiplegia dystonia.[292]
Mildly atrophic cortex	Spasmodic torticollis.[293***]
Mildly atrophic frontal cortex	3 of 5 cases of Meige.[294***]
Slight cortical atrophy	7/15 cases of spasmodic torticollis.[295]
PL thalamic infarction	22 yr F with delayed onset hemidystonia.[296]
Thalamic atrophy, no basal ganglia pathology	3 adults with posthemiplegic dystonia.[284]
Thalamus, not striatum	Posttraumatic focal hemidystonia.[297**]
Unilateral thalamic infarct	Bilateral blepharospasm + hemidystonia in hand.[298]
Bilateral PL thalamic	9 yr M with delayed onset dystonia.[299]

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Area of Lesion	Type and Apparent Cause.
Medial longitudinal fasciculus with hematoma	Post-traumatic dystonic posture.[300]
Rostral brainstem infarcts	4 cases with bilateral bleopharospasm.[209]
Paraneoplastic brainstem	Acute dystonia.[301]
Brainstem	29 yr old man with TD had numerous neurofibrillary tangles (NFT) and mild neuronal loss in locus coeruleus, as well as some NFT in SNC, pedunculopontine n. and dorsal raphe; a 68 yr old man with Meige's syndrome had moderate to severe neuronal loss in several brainstem nuclei including those four.[255]**

torticollis is almost always preceded by chills, fever, malaise and increases in white blood cell count; thus, although the etiology is unknown, a viral infection is suspected. The EEG in all cases is normal.[236] Fox[237] reported a single case in a 3.5 year old female American which seemed to have a similar clinical course. The dystonia signs in the Chinese victims are usually dramatically relieved by intramuscular diazepam.

Komandenko et al.[238] said that, in a series of 35 cases which included 28 patients with spastic torticollis and 7 with other extrapyramidal hyperkineses, one of the most frequent causes was a chronic encephalitis or other infectious process causing damage to extrapyramidal structures. The best treatment they found was repeated courses of dexamethasone in combination with antibiotics and vitamins. A number of cases of transient post-varicella lingual mandibular dystonia have been described[239] and progressive dystonia is also seen in Sydenham's chorea.[240]

Association of Meige's disease or essential blepharospasm[241] with autoimmune disorders, including Sjogren's syndrome, has been reported. Blepharospasm may also occur or be exacerbated during worsening of underlying autoimmune disorders such as systemic lupus erythrematosus[242] or myasthenia gravis.[243] Some AIDS cases also show dystonia, accompanied by MRI-apparent lesions in the thalamus or frontal lobe.[244]

Stress is often a precipitating factor in blepharospasm,[245,246] spasmodic torticollis,[247] and other forms of dystonia, including neuroleptic-induced iatrogenic dystonia.[248] This precipitating effect of stress may explain why dystonia is often seen shortly after peripheral trauma.[249,250]

Dystonia has often been misdiagnosed as being of psychological origin.[251] Although most cases seem clearly neurological, occasional cases of factitious or hysterical dystonia are still reported.[252-253]

In summary, the possibility must be considered that in any given case the dystonia has been permanently or transiently acquired as a result of perinatal or other vascular, anoxic or traumatic lesion; or as a result of infection, autoimmune disease, stress, or even hysteria.

2. Histopathological and Brain Imaging Studies

No consistent neuropathological abnormalities have yet been reported in the brains of patients who have died with idiopathic dystonias, whether hereditary or sporadic, generalized or focal.[18,50,254,255] For example, Hornykiewicz et al.[256] reported no important histological changes in the basal ganglia, cortex, higher brainstem nuclei, locus coeruleus or raphe in two non-Jewish cases who began to develop dystonia at the ages of 5 and 7.5, one of whom had a family history of dystonia. There were some chemical abnormalities (see Section 4). Jankovic and Svendsen[257] derived data consistent with the findings of Hornykiewicz et al. from a 68 year old woman who developed blepharospasm at age 61 with progressive development of other forms of cranial-cervical dystonia (Meige's syndrome). H & E, Bielschowsky's and Luxol fast blue stains of the cortex, hippocampus, striatum, globus pallidus, hypothalamus, thalamus, midbrain, pons, medulla and cerebellum revealed no abnormality.

While CT scans and postmortem pathological examinations have repeatedly found no abnormalities in most cases of either idiopathic dystonia[258] or spasmodic torticollis,[71] cases have been identified which are clearly associated with putaminal or thalamic lesions. Mild cortical atrophy or a brainstem lesion has been reported in other cases (Table 4).

In a review on dystonia with emphasis on Spanish contributions, Gimenez-Roldan and Barraquer-Bordas[302] said that Lopez-Aydillo and Sanz-Ibanez correlated symptomatic dystonia with contralateral putamen-caudate infarctions in 1956. Marsden et al.[303] described 28 patients with focal (arm or leg) hemidystonia due to tumor, arteriovenous malformation, infarction, hemorrhage or hemiatrophy and reviewed 13 other such cases in the literature. In all cases the lesion responsible, as defined by CT scan or pathological examination, was in the contralateral caudate, lentiform nucleus (particularly the putamen), thalamus, or a combination of these structures.

Jankovic[304] described a parkinsonian case with blepharospasm following thalamotomy and reviewed the literature on 14 cases of blepharospasm associated with basal ganglia, thalamus or brainstem lesions.

Lesions of the basal ganglia and/or thalamus are also prominent in many of the diseases which are associated with dystonic symptoms (cf Table 3). For example, CT and/or MRI scans have shown putaminal lesions in a number of cases of familial and spasmodic generalized dystonia with symptoms of other diseases such as Leigh's disease,[145,147,149] or pigmentary degeneration of the retina (probably Hallervorden-Spatz).[139]

Basal ganglia lesions may be more common than indicated by CT scanning. Quinn et al.[305] reported a case of hemidystonia where the CT scan showed only minor asymmetry of the lateral ventricles, but where an MRI scan clearly revealed a large, well

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defined, unilateral lesion affecting the basal ganglia.

Putaminal or striatal lesions do not always produce dystonia. For example, Larsen et al.[306] described a family with a dominantly inherited condition that produced both dystonia and extensive calcification of the basal ganglia. However, calcification occurred without dystonia in some members, and dystonia without calcification in others. Caraceni et al.[263] reviewed the literature on basal ganglia calcification and pointed out that not all of the cases showed dystonic symptoms.

Although dystonia seems the more usual symptom of putaminal pathology, Mas et al.[307] reported a case of hemiballism with a CT-documented lacunar infarct in the contralateral lenticular nucleus, Gross[308] described a case of hemiparkinsonism showing CT evidence of a giant aneurysm in the left lentiform region, and House and Hodges[309] a male with large infarctions of the putamen and globus pallidus but no dystonic symptoms. In many cases where dystonic symptoms do appear as a result of basal ganglia lesions, there may be a delay of years between the insult and onset of symptoms. This implies the necessity of additional changes to a primary lesion being necessary to produce the decompensation causing dystonia.

Another possible site of involvement, particularly for spasmodic torticollis, is the vestibular complex. The occurrence of vestibular abnormalities in more than 70% of 35 patients with this form of dystonia in the absence of other otological or neurological symptoms has been considered as evidence of a primary involvement of the vestibular system.[310] Diamond et al.[311] reported ocular counterrolling abnormalities in each of 8 patients with spasmodic torticollis; such abnormalities had previously been seen only in persons with brainstem problems. Since some of the patients also showed spontaneous vestibular nystagmus in the dark, Diamond et al. suggested an abnormality in central vestibular connections. Similar findings in Machado-Joseph disease have also been interpreted as indicating vestibular involvement.[312] In animals vestibular lesions cause striking derangement of head position (Section 7).

Jankovic and Patel[209] reported several cases of blepharospasm associated with rostral brainstem lesions and suggested a mechanism similar to that postulated for palatal myoclonus. Reports of further cases in which blepharospasm is associated with palatal myoclonus,[313,314] communicating hydrocephalus,[314-316] or other rostral brainstem disorders[317] reinforce their suggestion. Janati[194] argued that occurrence of both blepharospasm and torticollis in a 76 year old man with progressive supranuclear palsy indicates that these two forms of focal dystonia have a common pathophysiology involving the striatum and brainstem.

Dystonia may also occur as a result of peripheral lesions. In some patients with focal dystonia of the hand, electrophysiologic studies have indicated the existence of a peripheral nervous system lesion.[e.g.318-321] Many cases of torticollis are associated with congenital muscular problems or with spinal abnormalities.[e.g.326-329] In some cases, the dystonia may be the cause rather than the effect. For example, spinal abnormalities may result from dystonic posturing rather than being responsible for producing it.[e.g.330-332] Torticollis is sometimes associated with hiatus hernia and disappears on surgical repair of the hernia.[333] Head tilt is often seen in cases with posterior fossa tumors[334] and torticollis has been described with upper spinal cord tumors, syringomyelia[335,336] or as a posttraumatic sequel to insertion of a ventriculoperitoneal shunt.[337]

Torticollis in children may be caused by hemi-aplasia or hypoplasia of the atlas. It was reported to be corrected by surgery in 17 cases.[338] Bagolini et al.[339,cf340] described four cases of ocular torticollis resulting from plagiocephaly - i.e. premature union of the coronal sutures on one side.

Positron emission tomography (PET) studies with [^{18}F]-fluoro-2-deoxyglucose (FDG) on 8 cases of asymmetric idiopathic dystonia showed no abnormality in 6; 3 of these patients had spasmodic torticollis and 3 had mild dystonia of the distal extremities. Two with severe dystonia involving the upper trunk and neck showed no abnormality in the caudate, putamen or thalamus but did show asymmetries of 18 and 21% in the sensorimotor cortex, with lower metabolism contralateral to the symptomatic side.[341] A further possible indication of involvement of the sensorimotor cortex is the report that regional cerebral blood flow, measured by PET, is consistently increased in that region contralateral to vibrotactile hand stimulation by 25±5% over that seen at rest in normal subjects, but only by 16±3% in dystonic patients.[342]

Another PET study with FDG on 16 cases of idiopathic spasmodic torticollis revealed no consistent significant focal abnormality but there was a bilateral breakdown of the normal relationships between the thalamus and basal ganglia, suggesting possible disruption of the pallidothalamic projections.[343]

A patient with trauma-induced hemidystonia showed decreased oxygen extraction and increased blood flow by PET in the contralateral basal ganglia.[344]

PET scanning of a case of hemidystonia with a well defined left basal ganglia lesion, revealed by MRI,[305] showed enhanced radioactive uptake of ^{11}C-spiperone in that area, suggesting an increased density of dopamine receptors.

In one patient with a stroke-induced right putaminal lesion revealed by MRI, producing contralateral hemidystonia, the ^{18}F-fluorodopa PET scan revealed only background activity in the lesioned putamen but normal activity in the ipsilateral caudate and entire contralateral striatum.[285]

In summary, idiopathic dystonia occurs in the absence of any lesion which can be defined either by standard postmortem pathological investigation or in vivo imaging. Some cases of dystonia show clear evidence of basal ganglia or thalamic lesions, but lesions of these areas do not always produce dystonia and, in circumstances where they do, there can be a prolonged time delay between appearance of the lesion and onset of symptoms. Dystonia can also be produced by peripheral lesions, and possibly by cortical or brainstem lesions.

3. Sleep and Other Physiological Studies

Dystonic movements, like most abnormal movements, generally cease during sleep. This is also true for acute neuroleptic-induced dystonia although such dystonic movements usually persist during lighter daytime sleep.[248]

Polysomographic studies in 9 adults with TD and 9 healthy volunteers indicated that the patients slept poorly compared with controls. They showed pronounced high amplitude spindles that were continuous for all stage 2 and portions of stage 3 sleep, instead of spindles that became less frequent. The spin-

dles also did not show the characteristic diminution in amplitude with age. Other sleep parameters were also disturbed.[345,346] In a case of TD showing similar poor sleep and spindle activity, a clinically successful unilateral thalamic operation led to a normalization of sleep parameters and a reduction of the high amplitude spindles.[347]

In a study of 27 cases of TD, patients were found to be slow in falling asleep and frequently wakened during the night. There was also a significant reduction in eye movements during REM sleep.[348]

Narayan et al.[349] studied multimodality evoked potentials in 10 patients with idiopathic spasmodic torticollis. They found no abnormalities and concluded that the lesion does not discernibly involve the visual, auditory or somatosensory pathways. However, Disertori et al.[13,14] studied auditory evoked potentials (BAEPs) in a case of apparent methylparathion toxicity which produced spasmodic torticollis with thoracic outlet syndrome, and found evidence of severe brainstem involvement. Both the neurophysiological and clinical pictures improved on 5-hydroxytryptophan. Abnormalities were also found in the BAEPs in 13 patients with tardive dystonia, suggesting pathology in the caudal or rostral pons, midbrain and/or thalamus. Patients on long-term neuroleptics without tardive dystonia had no such abnormalities.[350] EEG changes in 32 patients with facial paraspasm were also interpreted to indicate involvement of nonspecific portions of the pontomesencephalic brainstem.[351]

In patients with spasmodic dysphonia, Schaefer[35] reported evidence of impairment of somatic and visceral brainstem pathways; both the clinical signs and the brainstem findings appeared to stabilize after 3-5 years.

One case of paroxysmal dystonic choreoathetosis was shown to have a photically inducible epileptiform discharge, suggesting an epileptogenic basis for the disorder[352] but normal EEGs have been reported in other cases.[104]

Some patients with an autosomal dominant inherited form of myoclonic dystonia had widespread symmetrical cortical events in the EEG which were time-locked to the muscle jerks. Ethanol gave dramatic relief.[353]

Blink rate, a reportedly useful index of central dopamine activity in parkinsonism and supranuclear palsy, is normal in dystonia.[354]

EMG studies have been reported to be normal in many cases of Meige's syndrome, spasmodic torticollis and other forms of dystonia.[e.g.355-358] Thus, for example, normal electrophysiology in the corticomotoneuron path, as well as normal muscle spindles, were found in five cases of TD,[359] indicating that the symptoms in TD result from delivery of abnormal central motor commands.

In summary, a few mild and poorly defined changes in physiological measures have been recorded in TD related to brainstem function but they have not been focussed on any specific lesion or any distinct anatomical region.

4. Chemical Pathology

The literature on chemical pathology in dystonia is very sparse. Routine laboratory studies on blood, urine and CSF have been done in many cases without revealing any abnormality. Only two chemical studies appear to have been done on post-mortem brain tissue and both were largely limited to the catecholamines. A few measurements of choline acetyltransferase (ChAT), glutamate and GABA in the cortex and basal ganglia were made in two cases. Even the literature on CSF and blood studies is almost entirely concerned with the aromatic amine neurotransmitters; hence an enormous amount of exploration remains to be done.

Brain Studies

In two non-Jewish TD cases with onset at ages 5 and 7.5, Hornykiewicz et al.[256] reported ChAT, GABA and glutamic acid to be within the control ranges in the cerebral cortex and basal ganglia. However, noradrenaline (NA) levels in the lateral and posterior hypothalamus, mammillary body, subthalamic nucleus and locus coeruleus showed a marked and consistent decrease while those of the septum, thalamus, colliculi, red nucleus and dorsal raphe were increased. The serotonin (5HT) level was subnormal in the dorsal raphe but high in the globus pallidus, subthalamus and locus coeruleus. The dopamine (DA) level was subnormal in the nucleus accumbens and, in one of the two cases, in the striatum. The level of the 5HT metabolite, 5-hydroxyindoleacetic acid (5HIAA), was high in the globus pallidus, subthalamus and nuclei raphe centralis inferior and obscurus. The level of the DA metabolite, homovanillic acid (HVA), showed little consistent change in the regions examined. Unfortunately the interpretation of these data may be confused by the fact that both cases had been subjected to bilateral thalamotomies which were therapeutically ineffective.

Jankovic and Svendsen[257] reported somewhat similar data from a 68 year old woman who showed blepharospasm at age 61 and progressive development of other forms of cranial-cervical dystonia (Meige's syndrome). Measurements of the monoamines suggested that both DA and NA might be markedly (3- and 2-fold, respectively) elevated in the red nucleus, NA might be elevated 4-fold in the substantia nigra (SN) and both DA and NA might be reduced (to about 40%) in some cortical areas. The levels of 5HT, 5HIAA, and HVA seemed about normal in all areas measured and 3-methoxy-4-hydroxyphenylglycol (MHPG, a NA metabolite) was normal in the putamen, red nucleus, SN and lateral globus pallidus but may have been elevated (2.5-fold) in the medial globus pallidus and in one cortical area (2-fold). In all of these cases, routine histopathology revealed no abnormalities.

It has been suggested that these abnormalities in the NA system may reflect an abnormal initial number of NA neurons. Another possibility is that the normal developmental pruning of some NA projections does not occur.

The report that most cases of idiopathic spasmodic torticollis show rotation of the head to the left[360] has been taken to indicate that abnormal asymmetries in DA systems may be involved;[361] no experimental evidence relevant to this suggestion has yet been obtained.

Abnormal brain chemistry has been reported in some situations where dystonic symptoms occur as part of various inherited or acquired neurological diseases but the changes observed are not generally in specific neurotransmitter systems (see Table 3).

CSF Studies

Again, most studies have concentrated on the aromatic

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amines and their metabolites and the results on lumbar fluid have generally indicated no consistent abnormality. Many peptides have not been measured in CSF and the reports on biopterin and neopterin abnormalities deserve more attention despite some inconsistent findings. The studies on ventricular fluid may be of special interest since some believe ventricular levels reflect primarily brain metabolism while lumbar levels emphasize spinal cord metabolism.

(1) Aromatic Amines and Metabolites: Low levels of DA and NA metabolites (HVA, MHPG) have been reported in ventricular fluid from cases of childhood-onset dystonia, with normal levels in other forms of dystonia (Table 5A).

A number of investigators have studied the levels of these metabolites (and of 5HIAA) in lumbar fluid and, while there is some ambiguity, most appear to find normal levels (Table 5B).

(2) GABA: Based on a radioreceptor assay, CSF GABA levels in 6 cases of sporadic torticollis were found not to be significantly different from the levels in a group of 34 controls.[376] In TD, no significant abnormality in CSF levels has been found for any of the commonly determined amino acids, including GABA,[368,373] except for a modest reduction in ornithine.[377]

(3) Peptides: Thal et al.[378] reported data on the concentration of somatostatin (SOM) in ventricular fluid (Table 6) which indicate significantly low levels in childhood onset dystonia. Cramer et al.[379] found the concentrations of SOM in lateral ventricular fluid to be significantly lower in patients with dystonia or parkinsonism than in those with essential tremor. Since Fahn[372] has data indicating that lumbar CSF SOM levels are not abnormal in childhood onset dementia, Thal et al.[378] suggested these results indicate a SOM abnormality limited to the basal ganglia. They also provided evidence in rats that SOM does not cross the blood/brain barrier. No correlation was found in any group between SOM levels and age. Levels of some other peptides (AVP, TRH, ACTH and CCK) in the CSF in TD appear to be normal.[372]

(4) Other: Cullis et al.[380] reported that a CSF protein pattern differing from controls was seen in 11 out of 12 patients with spasmodic torticollis. In 2 of the cases there appeared to be abnormal staining for IgG bands and in 7 there was abnormal staining for ceruloplasmin.

LeWitt et al.[381,382] found CSF levels of total biopterin substantially lower in 8 untreated patients with dystonia (aged 20-

Table 5: Studies on Aromatic Amine Metabolites in CSF.

A. Ventricular Fluid (nmol/liter; number of cases in parentheses).

Disease	MHPG[362]	HVA	5HIAA
Dystonia:			
Childhood onset	8.7 ± 0.6* (9)	1510 ± 478(14)[363]	429 ± 125(14)[363]
Adult Onset	11, 14	984 ± 368(6)[363]	340 ± 120(6)[363]
Unclassified	11.3 ± 0.3 (3)		
Symptomatic	10.8 ± 1.9 (5)		
TD - mainly hyperkinetic		1031 ± 89[365]	
- other		393 ± 51[365]	
Cerebral palsy	15.7 ± 1.8* (6	1280 ± 77(7)[364]	387 ± 68(7)[364]
Parkinsonism		227 ± 17[365]	
		654 ± 209(5)[364]	408 ± 152(5)[364]
Controls	11.7 ± 1.1 (9)	1275 ± 192(7)[366]	
		1346 ± 504(37)[367]	

B. Lumbar Fluid**

Type of Case	HVA	DOPAC	MHPG	DBH	5HIAA	Ref.
9 cases, all non-familial	N	N	N		N	368
5 cases, idiopathic dystonia-parkinsonism	N				N	87
7 cases, sporadic juvenile distal dystonia	N			N	N	369
8 cases, dystonia			N			370
3 cases, torsion dystonia	N				N	371
many, torsion dystonia	N	N	N		N	372
1 case, childhood onset			L			373
1 infant, benign idiopathic dystonia	H?		N		N	105
1 case, action-induced rhythmic dystonia	H				L	378
5 Joseph disease and 1 family member at risk	L					11
1 Segawa disease	L				L	375

* Significantly different from control.
** Examples of literature, more exists. N = normal, L = low, H = high, H? = possibly high but control values not available for age group.

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Table 6: Concentration of SOM in ventricular and lumbar fluid[378]

Disease	Age	N	SOM pg/ml, mean ± SEM
Dystonia, childhood onset	19 (7-66)	18	20.1 ± 1.6*
adult onset	45 (33-56)	12	30.3 ± 3.5
symptomatic	29 (16-56)	6	37.9 ± 5.8
Multiple sclerosis with tremor	37 (21-66)	18	23.6 ± 4.0
Parkinson's	57 (41-72)	33	25.9 ± 1.8
Epilepsy	24 (22-28)	8	26.0 ± 4.9
Epilepsy (lumbar fluid)	30 (16-71)	12	23.3 ± 3.0
Multiple sclerosis (lumbar)	41 (19-60)	21	27.6 ± 3.3
Alzheimer's disease (lumbar)	65 (49-79)	18	34.2 ± 3.4
Controls (lumbar)	40 (16-78)	9	35.4 ± 3.8

* $p<0.001$ vs symptomatic dystonia and lumbar controls; $p<0.01$ vs adult onset dystonia and $p<0.05$ vs Parkinson's disease.

63 years) than in normal controls (ages 20-77 years (12.6 ± 0.9 vs 20.5 ± 1.5 pmol/ml). However, others[372,383] found normal levels in TD with the exception of one family. Williams et al.[384] had previously described low tetrahydrobiopterin levels in some cases of inherited dystonia but normal levels in torticollis.[385] Generalized dystonia with marked diurnal fluctuations like these in Segawa's syndrome has been associated with a significant biopterin deficiency in five cases; four of these also showed low CSF neopterin levels. The HVA and 5HIAA levels were either normal or reduced.[93] Tanaka et al.[386] found large amounts of neopterin with only a trace of biopterin in a 27 year old man with deficient dihydrobiopterin synthesis who showed dystonia along with mild mental retardation, rigid spasticity, hyperreflexia and myoclonus. CSF levels of HVA and 5HIAA were low.

Mehta et al.[387] reported a family in which association of hyperuricaemia and increased CSF uric acid was noted in two members who had classical TD. Other members of the family with no clinical evidence of TD, however, also showed increased serum and CSF uric acid. It is possible that these were cases of the Lesch-Nyhan syndrome (Table 3). Disturbed purine metabolism is part of that disorder. Coleman[388] described a case with a mixed movement disorder, predominantly of a dystonic type, but also including choreic symptoms, who showed hyperuricaemia.

Trace element concentrations in CSF are reported as normal in TD.[372]

Blood Studies

Early reports[389,390] of elevated blood DBH in dystonics aroused considerable interest but subsequent data suggest this is not a consistent finding and the results may have depended on other factors. It is known that DBH is under close genetic control and unaffected family members, as well as patients with both the non-Jewish ("dominant") and Jewish ("recessive") forms of the syndrome, were reported to have higher DBH activities than age- and sex-matched normal school children.[391] Plasma DBH and melatonin and urinary melatonin were measured in 10 Jewish and 9 non-Jewish patients with idiopathic TD and in 22 nondystonic family members; there was no significant difference between the groups.[392] Other studies have found plasma DBH in dystonics to be high, normal or low. Korczyn et al.[393] found normal levels in 25 Jewish patients suffering from TD, Eldridge et al.[49] reported normal levels of NA and DBH in the plasma of 2 twins with a probable autosomal recessive form of TD, and Busard et al.[369] found normal levels in 7 cases of sporadic juvenile distal dystonia. However, Hirase et al.[267] reported low plasma DBH in two sisters with autosomal recessive TD. Friedman and Mendlewicz[394] studied plasma DBH in the probands with spasmodic torticollis and sibs in 4 families. They found normal values in 3 families having only one affected member, while in one family with two affected siblings, the plasma DBH was higher in the probands than in the non-affected sibs (145.5 and 125.5 vs 65.5 nmol/ml-min). They suggested there might be two forms of spasmodic torticollis: a genetic form probably linked to familial TD with altered DBH, and a non-familial sporadic form with normal DBH.

Platelet 5HT concentration and uptake was studied in 11 Jewish cases of idiopathic TD. Levels and the Vmax for uptake were normal, as was the Ki for inhibition of uptake by imipramine, but the Km for uptake was significantly higher in dystonics as compared with controls (2.59 ± 0.86 vs 1.40 ± 0.39 mM).[395]

Erythrocyte acetylcholinesterase has been reported as normal in dystonia.[396]

Serum calcium levels were normal in 17 psychotic patients exhibiting neuroleptic-induced acute dystonic reactions.[397] Borisova[398] reported that blood Mn levels were high in 23 cases of TD, while Fe and Zn appeared normal.

Gannushkina et al.[399] counted T- and B-cells in blood of 37 patients with various hereditary diseases of the nervous system including TD and 22 healthy controls. They found in all the diseases a drop in the content of thymus-dependent lymphocytes and an increase in the capacity of lymphocytes for complementary rosette formation. They proposed the existence of a secondary immunodeficient state, possibly determined by metabolic abnormalities, in hereditary nervous system diseases. Moore et al.[400] also reported a significant decrease of both helper and suppressor lymphocytes in 11 cases of spasmodic torticollis.

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In a study of 67 cases of idiopathic dystonia, no significant linkage was found with any of the HLA A, B and C subtypes; however, 13 patients with idiopathic TD showed a trend towards the DR3 subtype.[401,cf59]

Urine Studies

According to Aggarwal et al.[88], cases of TD showed no increase in HVA or VMA and little increase in DOPAC after a dose of L-DOPA, while a case of progressive dystonia with marked diurnal fluctuations showed increases in HVA and DOPAC but little or no change in VMA and 5HIAA.

A Russian group[402] reported decreased DOPA excretion in most cases of TD while others[403,404] report decreased excretion of DA metabolites in some but not all types. Iadgarov[405] said there was increased excretion of DA in TD with a possible disruption in the diurnal excretion rhythm.[cf404]

Phenylacetylglutamine (PAG) is a major product of phenylalanine. Melnichuk et al.[406] measured it in urine of various kinds of hyperkinetic children and found:

Controls 200 mg/day Torsion dystonia 274 ± 60 (N=15)
Tourette 47 ± 5; (N = 26) Tic hyperkinesia 232 ± 40 (N=15)
Infantile cerebral palsy with dystonia 250 ± 20 (N=15)

They interpreted these data to indicate excessive utilization of phenylalanine in the metabolic route to tyrosine and catecholamines in Tourette and under-utilization in TD, resulting in the changes seen in the alternative PAG route. Therefore they gave phenylalanine to Tourette cases to act as a feedback inhibitor of both phenylalanine and tyrosine hydroxylases and glutamine to TD cases to try to detoxify excess phenylpyruvic acid. They claimed improvement in both situations. Note, however, that dystonic symptoms are frequently seen in the Tourette syndrome and the link between the results reported and changes in DA synthesis are highly speculative.

A complication of dystonia may be myoglobinuria from excessive muscular use.[65]

Fibroblast Studies

Average activity of catecholamine-0-methyltransferase (COMT), a DA and NA metabolizing enzyme, in cultured skin fibroblasts from 8 patients with inherited TD did not differ significantly from the average in 16 controls and, in the controls, no variation was found with age or sex. Average activity of monoamine oxidase-A (MAO-A), another aromatic amine metabolizing enzyme, in 12 cell lines from patients with TD did not differ significantly from the average found in age- and sex-matched controls.[407] Edelstein et al.[408] had reported that MAO activity in cultured fibroblasts from dystonics tended to be low normal.

Cultured skin fibroblasts from patients with hereditary ("recessive") TD or adult-onset sporadic dystonia and from healthy volunteers were compared with respect to total cellular cholesterol, total phospholipids and phospholipid composition. Differences that could be attributed specifically to dystonia were not detected.[409] And studies on samples from 4 patients with TD indicated no abnormality in the phosphoprotein phosphatase activity in fibroblast membranes.[410]

Preliminary gel electrophoretic studies on 2 patients with Joseph's disease suggest possible abnormalities in the fibroblast proteins.[11]

Miscellaneous

Korein[411,412] said that dystonic disorders were rare among non-Caucasians and hypothesized that susceptibility might be linked to decreased melanin metabolism. In a study of 153 Caucasians with torticollis and other dystonias, he found significantly more light eyed than brown eyed people as compared with various control groups (Parkinsonians, cerebrovascular accidents, normals, tardive dyskinetics). In all the control groups except the last, there were more brown-eyed than blue/green/grey/hazel eyed subjects but in the dystonic group, the light eyes occurred in more than two-thirds of the total population of 153. The difference was the same if subgroups of Jewish or British descent were considered.[413]

Lang et al.[414] studied dystonics and non-dystonics of British descent and found a greater proportion of light eyes in all groups. They felt their results did not support those of Korein although there was a significantly higher percentage of light eyes in the dystonics (82%) than in the controls (64%). But there was no significant difference between the dystonics and a group of Parkinsonians (71% light-eyed).

Nutt et al.[415] found a far greater percentage of thyroid disorders (both hypo- and hyper-) in 25 women with Meige's disease (51%) than in a similar group of age-matched women seen in a medical clinic (15%). No males in either group had thyroid disease. Lang[416] reported a family in which 5 of 7 siblings who survived into the 6th decade had a thyroid disorder and two of them had Meige's disease. Rosenfeld et al.[34] described hypothyroidism in a case of spasmodic dysphonia (often associated with Meige's syndrome). It is suggested that thyroid dysfunction may predispose one to Meige's disease. Possibly relevant findings are the occurrence of hypoplasia in rats showing a permanent movement disorder after a single peripheral dose of dimethylaminohexone reductase (Section 7), the association of basal ganglia calcification with parathyroid dysfunction (Table 4), and the report[417] that latent idiopathic TD may be provoked by thyrotoxicosis.

5. Therapy

Pharmacological treatment of the dystonias is unpredictable and often disappointing. A wide variety of drugs - dopamine agonists and antagonists, acetylcholine agonists and antagonists, GABA agonists and miscellaneous compounds - have been tried in the primary dystonias; in general each type is successful in a small proportion of cases but the results are variable and improvement is often only transient. A few exceptions do, however, exist to this generally disappointing scene. First, dystonias of the paroxysmal type, lasting a matter of minutes and sometimes called "basal ganglia epilepsy," usually respond to phenytoin, carbamazepine or clonazepam.[418]

Secondly, cases of juvenile dystonia parkinsonism or progressive dystonia with marked diurnal fluctuations (sometimes called the Segawa syndrome), show a dramatic response to DOPA and are also amenable to anticholinergic therapy[419] (Tables 1, 7). This, plus the usually minimal progression in adult life, has led to speculations that there is a fundamental difference between this and other primary dystonias[94] and that it may be an aberrant juvenile parkinsonism.[420] Even in adult life, dystonia is frequently a presenting symptom of parkinsonism. A

common form is foot dystonia which may occur as an early symptom in parkinsonism, either idiopathic[201] or MPTP-induced,[421] or (in 20-40% of cases) as an iatrogenic response to prolonged L-DOPA therapy. The pharmacological responses are often similar to those seen in juvenile dystonia-parkinsonism but are far less consistent. For example, Poewe and Lees[419] reported cases where the dystonia is abolished by scopolamine and exacerbated by physostigmine. But, according to Klawans and Paleologos,[422] in 11 patients presenting first with dystonia (4 spasmodic torticollis, 2 hemidystonia, 4 Meige's syndrome and 1 writer's cramp), who later developed parkinsonism, DOPA often exacerbated the underlying dystonia while direct DA agonists were less apt to do so. LeWitt et al.[423] reported similar experience in 10 patients.

Thirdly, high doses of anticholinergics (e.g. trihexyphenidyl) have been found to be well tolerated by dystonic children and to a lesser extent by adults.[424-426] They have become the regimen of choice for the treatment of idiopathic TD. They are not effective in all cases, however. Burke et al.[426] reported a clinically significant response in 71% of 31 patients completing a prospective, double blind crossover study. After a mean follow-up of 2.4 years, 68% of the patients continued to take the drug and 42% continued to show a considerable or dramatic benefit. Marsden et al.[427] concluded high dose trihexyphenidyl is the first treatment of choice in children with severe dystonia (they found improvement in 52% without marked side effects) but is less useful in adults (improvement in 41% but most had side effects). In severe axial dystonia in adults, a regimen of tetrabenazine, plus pimozide and trihexyphenidyl as necessary to control side effects and add benefit, was helpful in 75% of the cases. This regimen also benefited 1 out of 2 children with life threatening generalized dystonia. Pakkenberg and Pedersen[428] said that anticholinergics, while the most effective, are tolerated in, and give benefit to, less than 50% of cases. They recommended a combination of an anticholinergic, a benzodiazepine and a third drug (antidopaminergic, carbamazepine or fluperlapine). One adult case of idiopathic torticollis benefited from high dose trihexyphenidyl plus bethanechol to diminish peripheral anticholinergic side effects.[429]

Lang[430] reported high dose anticholinergics to be more effective in idiopathic than "symptomatic" dystonia and to be more useful in children than in adults. In most adult-onset focal dystonias they seem of little benefit.[431,432]

In dystonics on high dose anticholinergics, the acute anticholinergic side effects paralleled the rise and fall of serum anticholinergic levels but the response to dystonia did not.[433,434]

A brief indication of some of the drugs tried in the treatment of various forms of dystonia is given in Tables 7 and 8. Treatment of iatrogenic dystonia is included in these tables but is discussed in Section 7.

The reported efficacy of baclofen (which often acts by inhibiting glutamate/aspartate release) in several cases of hemifacial spasm or Meige syndrome suggests that some of the NMDA antagonists, such as MK-801, now becoming available might well be tested.[547] This suggestion is reinforced by the recent discovery that trihexyphenidyl, and some other antiparkinsonian agents, resemble MK-801 in that they act as antagonists at the σ type of binding site which modulates the NMDA-type excitatory amino acid receptors.[548]

The effectiveness of therapeutic interventions must be evaluated in light of the spontaneous remissions that are known to occur in spasmodic torticollis. In a review of 116 patients, remissions lasting longer than 1 year were observed in 14 patients (12%). This included 1 out of 11 cases with a familial history of dystonia. Spontaneous remissions seem to be more frequent in cases with early onset and usually occur during the first year.[549] Other reports in the literature, reviewed in this paper, indicate a spontaneous remission rate ranging from 7-50%.[cf439,550] In 26 patients with spasmodic torticollis followed for an average of 12 years, the frequency of sustained remission was 23% with the median duration of remission 8 years.[551]

Local injections of botulinum toxin into affected muscles is now widely used for the temporary (2-3 month) relief of focal dystonias,[552] including blepharospasm,[17,553-556] hemifacial spasm,[554,556] age-related entropion,[554] torticollis,[547] and writer's cramp.[548] A flood of similar reports have appeared. Infiltration of a local anesthetic (pancuronium bromide) gives relief for at least 3 weeks in patients with acute torticollis but only for 2-3 hours in patients with a chronic problem.[559] Little light on the underlying pathology of the conditions is, however, given by such treatments, or by the reported effectiveness of EMG (bio-) feedback in some cases,[e.g.500] or chronic spinal stimulation which has been said to give some relief in 68-78% of cases of spasmodic torticollis[e.g.560,561] but to have little benefit in idiopathic (primary) dystonia.[562] Even acupuncture has been tried.[e.g.563]

Surgical lesions of the brain have also been used for symptomatic relief.[e.g.564] At one time, some dentatectomies were done[565] but the more generally chosen site is the thalamus. Cooper was the most ardent exponent of such surgery and he argued from work on over 400 patients in a 20 year period that dystonia "is a manifestation of abnormal sensory communication involving cerebropetal pathways from basal ganglia, cerebellum and reticular substance. A possible role for the red nucleus must be considered."[566] Kandel[567] said that stereotaxic operations for spasmodic torticollis aimed at the ventrolateral (VL) thalamus, subthalamus or interstitial nucleus of Cajal (INC) gave marked or stable improvement in 50% of the cases and Vasin et al.[568] favored destruction of the INC in the rigid form. Others[e.g.569,570] found thalectomy of benefit in a smaller proportion of cases than reported by Cooper. Namba et al.[571] reported that 21 cases of spasmodic torticollis given VL thalectomy did not do any better than 25 cases treated conservatively. Because of the side effects, especially with the bilateral operations needed in generalized dystonia, such operations are generally regarded as a last resort. But such work does provide possible clues to the anatomical basis of dystonia. Peripheral surgery used in some cases of torticollis[e.g.572,573] contributes little to an understanding of the etiology.

Stahl et al.[454] argued from the pharmacology that various movement disorders are due to imbalances in basal ganglia dopamine/acetylcholine systems as indicated below:

Syndromes of dopamine excess and acetylcholine deficiency

Tardive dyskinesia	Tourette syndrome
Huntington disease	L-DOPA dyskinesia

Syndromes of dopamine deficiency and acetylcholine excess

Parkinson disease	Acute drug-induced dystonia
Drug-induced parkinsonism	Torsion dystonia

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Table 7. Summary of some of the Literature on the Number where Dystonic Symptoms Improved or (Worsened) on Treatment with Some Relatively Commonly Used Drugs[1]

	TYPE OF DYSTONIA											
	Probably idiopathic				Iatogenic		Associated with			Birth		
Type of Drug	TD or General	Torti-collis	Meige	Other focal	Neuro-leptic	Dopa	H-S	L-N	Park	Anoxia Trauma	Overall Percent	References
DA agonists[2]												
Dopa/sinemet	70/158 (24/121)	9/49 (3/9)	3/51 (7/23)	0/2 (3/3)		10/10[3]	(1/1)	0/8 (1/8)	2/7 (2/7)		33% (24%)	123,134,202,256,258,272, 294,375,381,420,428,441-59
Lisuride	4/16	16/23	40/68	4/26	2/3	8/9			0/4	0/4	52%	202,449,460-9
Other	24/135 (13/66)	33/113 (8/67)	24/64	1/15 (5/10)				0/8 (1/8)	1/1	0/1	19% (18%)	123,202,272,428,451,454-6, 463,465-7,470-5
DA antagonists[3]	4/21 (4/4)	18/26	28/135 (2/11)	3/9	1/84	4/13		0/8			20% (40%)	123,202,256-8,272,283,294, 428,444,448-9,454-6,458,472 477-83
Cholinergics												
Anti-AChE	0/4 (3/3)	(1/1)	0/6 (7/7)		0/42	0/9 (7/9)					0% (90%)	202,272,294,427,434,451,458, 474
Choline/deanol			6/19	3/8	few/42						<33%	428,444,449,483-6
Nicotine										1/1		487
Anticholiner-gics[2,4]	12/20	9/19 (2/5)	53/116 (3/3)	7/12	18/45	7/9	2/3	2/6 (1/6)			48% (43%)	134,202,257-8,272,424,428, 433-4,444,449,455,458,472-3, 475,479,481-3,485,488-500
Lithium	1/3	0/2	0/2		0/1	7/7					53%	272,483,501-5
Amine releasers[5]	12/23 (2/19)	0	43/133 (9/57)	20/54 (17/33)	9/58 (1/15)						<31% (23%)	7,257,272,428,449,479,483, 506-11
Benzodiazepines[2,6]	7/14	0	15/47	5/6	0/42			0/8		0/1	23%	100,102,123,201,256-8,272, 282, 428,479,483,492,513-5

1) Abbreviations used: TD, torsion dystonia; DA, dopamine; AChE, acetylcholinesterase; H-S, Halloverden-Spatz; L-N, Lesch-Nyhan; Park, parkinsonism. General reviews on therapy may be found in references 46, 427, 428 and 435. The percentages of cases showing improvement must be taken as rough approximations since much depends upon the criteria used by various investigators and the literature reviewed is by no means complete. The figures are probably over-optimistic since many of the references found are to uncontrolled studies. Double blind, placebo controlled studies in most cases shcw lower rates of improvement, and many negative clinical results are not reported.

2) All cases of fluctuating dystonia are said to respond very well to DOPA,[76,77,79,83,84,87,90-92,94,95,436,437] lisuride or bromocriptine;[87,437] the few cases tried have also shown a response to tetrahydrobiopterin[381] or benzodiazepines, and some show an improvement on anticholinergics.[87,438] See Lang[439] for a general review on therapy with DA agonists. In 1973 Eldridge et al.[440] reviewed the responses of 203 dystonic patients to levodopa: 21% improved, 70% were unchanged and 9% worsened.

3) Tardive complications are seen in about 5% of patients with idiopathic dystonia treated with DA antagonists.[476]

4) Anticholinergics appear more generally useful, especially in young cases, than indicated by these figures (see text). The dramatic improvement in 2 siblings with Hallervorden-Spatz syndrome on benztropine, in contrast to the ineffectiveness of other anticholinergics, is attributed to an augmentation of DA release in the caudate overcoming the presumed hypoactive DA system.[134]

5) See reference 506 for discouraging review.

6) In an attempt to raise brain GABA levels, Korein et al.[512] gave a mixture of L-glutamine, isoniazid, pyridoxine and diazepam to a group of patients who had proven refractory to other therapy and reported marked improvement in some of those with spasmodic torticollis.

Table 8: Other Drugs Reported to Have Some Use or No Benefit in Various Forms of Dystonia (Many Tested in Only a Few Cases).

	References Reporting	
Drug	**Some Cases Benefit**	**No benefit**
5-HTP	Manto's disease (13)	(514)
5-HTP + carbidopa + clomipramine		(123)
Methysergide		(272)
Tizanidine	Stiff man syndrome (515)	(516)
ACTH	(517)	
Baclofen	(479,518,519)	Iatrogenic(483,520)
Valproate	(282,428,521)	(522)
Valproate + baclofen	(523-526)	
Dantrolene	(282)	(272,484)
γ-VinylGABA		(527-529)
Isoniazid		(376)
Progabide		(530); essential tremor (531)
Carbamazepine	(112,428,446)	
Acetazolamide	(102)	
Phenytoin		(483)
Propranolol	(428,479)	(257,272)
Clonidine		(483,532)
Antihistamines*	(483)	(272)
MAO inhibitors	(479)	(483)
Sedatives.		
meprobamate		(256)
phenobarbital		(256,483)
Cannabidiol	(534,535)	
Ethanol	(353,536-538)	
Nitrous Oxide	(430,539,540)	
Ethyl chloride	(541)	
Naloxone		Worsens (542)
Benzhydrol	(487)	
Ca^{+2} channel blockers.		
verapamil	Iatrogenic (543)	Not lasting
diltiazem	Iatrogenic (544)	(545)
Calcitonin	(451)	
Oxiperamide		(483)
Mepiridine		(483)
Chlormezanone	Wry neck (546)	
Piribedil	(282)	

*May be initially fluctuating response to antihistamines.[533]

Syndrome of dopamine excess - acetylcholine excess

Idiopathic orofacial dyskinesia (Meige's syndrome)

In support of this view, Ortiz[574] reported a case of Meige that responded best to a combination of haloperidol and benztropine, but the pharmacologic results in general are too erratic to support such a simple postulate (Tables 7-9) and it seems clear that the many other neurotransmitter systems in the basal ganglia (and rest of brain) must be taken into account in explaining the spectrum of pharmacological responses in dystonia.

6. Iatrogenic Dystonia

Iatrogenic forms of dystonia have been induced by many different types of drugs (Table 9) and can take a variety of forms such as torticollis, blepharospasm and oromandibular dystonia. Dystonic movements of facial or throat muscles seem to be frequently involved.

The dystonic reactions are idiosyncratic, occurring only in susceptible patients, with the susceptibility decreasing with age.

No consistent picture emerges as to what central neurotransmitter systems might be involved. Dystonic reactions occur most frequently in persons treated with DA receptor blockers and are usually promptly relieved by anticholinergics or antihistamines. This has been taken to indicate that the basic mechanism is a relative DA deficiency (analogous to that in parkinsonism). However, such DA blockers are occasionally useful in the treatment of idiopathic dystonia with similar symptomatology.[e.g.586] Dystonic reactions also occur following DOPA treatment and even, occasionally, following treatment with the same antihistamines and anticholinergics useful in the treatment of iatrogenic dystonic reactions. Moreover, some drugs not known to effect any of these systems occasionally produce dystonic symptoms (Table 9).

Rupniak et al.[655] estimated the incidence of acute dystonic reactions in patients treated with neuroleptics to be 2-3%, but some authors give rates closer to 50%[656] (Table 10). The incidence is particularly high (50-63%) in children or young adults[663-665] and some have advocated that such patients be giv-

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en concurrent benztropine during the first week of neuroleptic treatment as a prophylactic measure.[665-668] Others have indicated that dystonic reactions may occur on high dose neuroleptics even with concurrent anticholinergic therapy. They have suggested that lower doses of neuroleptics (200-400 chlorpromazine equivalents daily) should be used.[248, 669]

Acute dystonic reactions occurred in 6 out of 7 young cocaine addicts after 1-2 doses of haloperidol suggesting the effects of cocaine addiction rendered the subjects particularly sensitive to dystonia induced by dopaminergic blockers[670] (cocaine is a DA uptake inhibitor and chronic use may produce subsensitivity of DA receptors). Prior abuse[397] or current use[671] of alcohol may also be a precipitating factor. However, incidences of acute dystonic reactions following antipsychotic administration as high as those seen in the cocaine users have also been reported in some other groups of young adults[666] and alcohol is said to relieve some dystonic symptoms (Table 8). Stress is also said to be a factor in precipitating these reactions[672,673] and patients with a history of birth trauma or childhood convulsions may be particularly at risk.[592] Gosper and

Table 9: Some Drugs Causing Acute Dystonia and Some Reported Pharmacology.†

Eliciting Agent	Drugs Reported to Alleviate, (Not Affect) Or [Worsen]
Dopamine blockers*,[48]	
Neuroleptics[575-8](e.g. chlorpromazine,[579-582] proclorperazine,[583] haloperidol,[582,584-586] pimozide,[584,587] thiethylperazine,[588-9] promethazine,[590]fluphenazine,[591] flupenthixol.[592])	Withdrawal of neuroleptic[31, 605]diphenhydramine,[576-8] [584,587,594]benztropine,[576-8] diazepam;[584,587,599] baclofen[606]
Antiemetics (e.g. metoclopramide,[593-600] domperidone,[601-603] Tigan[604])	Diphenhydramine, benztropine
Amine depleters	[Diphenhydramine, haloperidol][608]
Tetrabenazine[607]	
Tetrabenazine+α-methyl-p-tyrosine[608]	
DA uptake inhibitor (normifensine[609])	Withdrawal of drug[609]
Tricyclic antidepressants (e.g. amitriptyline,[610] trazodone,[611] amoxapine[612-3] (also a DA. blocker)[614]	
Anticonvulsants	(Anticholinergics)
Carbamazepine,[615-9] Tegretol,[615-7] Phenytoin[619-23] Dilantin[621-23] diphenylhydantoin,[593] diazepam[624-6]	
Antihistamines (e.g. Benadryl,[627-8] oxatomide,[616, 629] diphenhydramine,[627,630-1]azatadine[632])	Neuroleptics;[627,630,631] benztropine[632]
Decongestants (chronic)[633]	Haloperidol
Dimotrop elixir (acute)[634-6]	
Ketamine[637]	
Lithium[638-9] (Reinduces neuroleptic malignant. syndrome in 2 patients[640])	
L-DOPA*[48,641-643]	Diphenylhydantoin*; dopamine agonists[48,202,204,644] Anticholinergics[48,202] Baclofen[634,636]
Antimalarial drugs (e.g. chloroquine),[645]*	Chlorpromazine*
Anticholinergics (benztropine[646]).	
Cholinomimetics (bethanechol)[647]	
Ergot[648]	
Methylparathion[13]	5-Hydroxytryptophan[13]
Carbon monoxide[288]	
Manganese poisoning[649]	Haloperidol + diazepam or L-DOPA + benseramide[649]
Verapamil,[650] nifedipine[651] (Ca^{+2} influx inhibitors).	
Chloroxazone[652]	
Caffeine + aminophylline[643]	Diazepam, benztropine[653]
Anti-cancer drugs.	
Tegafur (furanyl-5-fluorouracil)[654]	

† Often reports of single cases in children.
*See text for additional references. Case report of dystonia precipitated in a child who was on methylphenidate + phenothiazine when the phenothiazine was stopped[576]

Table 10: Some Incidence Figures on Iatrogenic Dystonia.

Neuroleptic malignant syndrome	0.4-0.5% of patients, M: F, 2:1[657] 0.5-1.4% of patients, M:F, 1.4:1; median. age of onset 36[658] <0.2% of hospitalized patients on. neuroleptics[659]
Metochlorpromide-induced	28.6/million prescriptions, F:M, 1.8:1, mostly. in young; in women aged 12-19 incidence is 191/million[660]
Prochlorperazine-induced	2.7/million prescriptions[661]
Haloperidol-induced	14.7/million prescriptions[661]
Neuroleptic-induced dystonia	36% of 135 cases, especially in young males[662] 33% of 120 cases[657]

Jankovic[606] report rapid onset of dystonia during thioridazine therapy in a patient with neuronal ceroid-lipofuscinosis and suggest patients with certain degenerative diseases of the nervous system may be at increased risk; the dystonia was refractory to most drugs but improved on baclofen.

The acute dystonic reaction may take the form of a laryngeal-pharyngeal dystonia. This can lead to death through asphyxiation but, if recognized, is easily controlled with diphenhydramine or benztropine. Such reactions have been seen in isolated cases after haloperidol,[674-676] thiothixene[677] or droperidol.[678]

Acute dystonic reactions can also be induced in non-human primates by neuroleptics[655] (Section 7).

Acute dystonic reactions to neuroleptics usually occur 24-72 hours after initiation of the antipsychotic therapy but they can occur at any time during maintenance therapy. In either case they are generally relieved by diphenhydramine or benztropine.[665,679,680] Occasionally, however, the dystonic symptoms persist despite treatment with benzodiazepines or anticholinergics.[592] Acute reactions must be distinguished from the late-onset and persistent dystonia seen in many cases treated with neuroleptics. The latter is known as tardive dystonia.[681,682] Tardive dystonia has to be distinguished from another, more common movement disorder, classic tardive dyskinesia. This is a choreic disorder that predominantly affects the oral region. Patients with tardive dystonia may or may not benefit either from treatment with anticholinergics or by withdrawal of neuroleptics.[683] By contrast, patients with tardive dyskinesia usually experience an exacerbation of their abnormal movements when withdrawn from neuroleptics or given anticholinergics to counteract their movement disorder.[684] The two conditions also differ in age and sexual prevalence. In contrast to tardive dyskinesia, tardive dystonia decreases with age and shows no female preponderance.[685] The incidence of tardive dystonia in one population of chronic hospitalized patients was 1.5%.[686] Risk factors in this small population appeared to be mental retardation and convulsive therapy. On the other hand, Kwentus et al.[687] reported an improvement in tardive dystonic symptoms in a patient who received ECT for depression.

Burke et al.[483] described 42 patients with tardive dystonia with the age of onset being from 13-60 years and the time of antipsychotic treatment before onset ranging from 3 days to 11 years. Younger patients tended to show more generalized dystonia although some showed Meige-like symptoms.[688] In a few patients, spontaneous remission occurred, but in most the dystonia persisted for years. In adults, some cases diagnosed as Meige's syndrome may be tardive dystonia.[689]

Kang et al.[690] retrospectively reviewed data on 67 patients with tardive dystonia and found no predilection for any particular age group or sex. Tetrabenazine and reserpine were the most effective drugs in controlling the dystonic reaction, having an improvement rate of over 50%; anticholinergics diminished the dystonia in 46%.

Dystonic reactions must also be distinguished, though they may be part of, the neuroleptic malignant syndrome which involves mainly fever, labile blood pressure, tachycardia and muscular rigidity. It is particularly common in young men.[691,692] Bromocriptine and damrolene are helpful while anticholinergics, benzodiazepines and ECT are not. In a fatal case of the neuroleptic malignant syndrome, acute myopathic features with absence of muscle glycogen and neutral lipid were found, suggesting that the primary biochemical abnormality responsible for uncontrolled heat production might be muscular rather than central (hypothalamic).[691]

Metoclopramide and droperidol, which are dopaminergic blockers commonly used as antiemetics in cancer patients undergoing irradiation, can also induce acute dystonic reactions. Selective 5-HT_3 receptor antagonists are being tested for such antiemetic use and it is thought that they will be unlikely to cause dystonic reactions.[694] The dystonic reactions seen after the dopaminergic blockers are usually controlled by diphenhydramine or benztropine. The incidence is relatively rare in adults (4-7%) but is much more common in children.[695-697] According to Bateman et al.[698] the pharmacokinetics of metoclopramide are the same in children showing dystonic reactions as in other children or in healthy adults. The risk of such reactions is increased by concomitant administration of chloroquine.[595] A rapidly fatal outcome was described in a 49 year old female receiving metoclopramide after hexamethylmelamine, a drug known to produce a parkinsonian-like disease and tremor.[699]

Episodes of blepharospasm have been reported in 2 out of 3

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cases of MPTP-induced parkinsonism during drug "holidays" when they were not receiving dopa.[700]

Marsden and Jenner[701] suggested that acute dystonia might be due to DA activation rather than blockade. Korczyn,[702] on the other hand, proposed that the iatrogenic dystonia produced by DA blockers was due to a relative noradrenergic hyperactivity. This hypothesis was based upon reports (later contested, see Section 4c) of high DBH levels in patients with the dominant form of dystonia, coupled with an absence of reports of dystonia in any patients given DA depletors such as reserpine or tetrabenazine. However, Burke et al.[608] reported dystonic symptoms in a Huntington's disease case during treatment with tetrabenazine and α-methyl-p-tyrosine; the dystonic symptoms in this case were worsened by diphenhydramine or haloperidol. Subsequently, the same group[607] reported acute dystonic reactions in four patients being treated with tetrabenazine.

The confusing picture painted by drug-induced dystonias is evident in a review by Rupniak et al.[655] They point out that not only can neuroleptics produce such reactions but that L-DOPA also does in a proportion of parkinsonians[202,703-706] (Table 9). This proportion is particularly high in older patients.[707] Such patients may have painful dystonic spasms before the first dose of DOPA each day, during off-periods, or at the beginning, peak, or end of the effectiveness of a DOPA dose.[708] Off-period dystonia has been said to be by far the most common drug-induced dystonia encountered in Parkinson's disease, with an overall incidence varying from 20-33% of patients receiving DOPA treatment for more than 3 years.[636,709,710] The off-period dystonia, usually involving prolonged abnormal postures and torsion spasms, may be relieved by challenge doses of DOPA or a DA agonist.[202] On the other hand, these drugs may worsen some dystonic movements, usually writhing of the neck and cranial dystonia, which occur at the peak action of DOPA; this again suggests that the different types of movement grouped under the term dystonia may have different neurochemical bases. It may be of significance that DOPA-induced dyskinesias are said to occur more often in parkinsonians (50% of cases) than in TD, Hallervorden-Spatz or Huntington's disease cases being similarly treated (11%).[711]

Although DOPA-induced dystonia has been reported to be relieved with diphenylhydantoin,[712] this and other anticonvulsants may induce dystonia in intoxicated epileptic patients[713] (Table 9); phenytoin has been reported to cause dystonia in some epileptics[623] and also occasionally in parkinsonians. Symptoms disappeared when carbamazine was substituted for phenytoin.[714] Antimalarial agents such as chloroquine and amodiaquine can provoke acute florid oro-bucco-linguo-facial dyskinesias[645,715-717] and this chloroquine-induced dystonia is relieved by chlorpromazine.[645] Even antihistamines such as diphenhydramine, which relieve neuroleptic-induced acute dystonia, can themselves produce dystonias which are relieved by neuroleptics (Table 9).

Although cholinomimetics do not in themselves generally induce acute dystonic reactions in humans (but see Section 7), Shafrir et al.[647] reported such an episode induced in a 10 month old infant with bethanechol. This infant also had acute dystonic reactions following both metoclopramide and a phenothiazine. A brother had a similar reaction to metoclopramide at the age of 2 years.

7. Possible Animal Models of Dystonia

Idiopathic

The most useful model of idiopathic torsion dystonia may be the Sprague-Dawley rat mutant dystonic (dt) which follows an autosomal recessive pattern of inheritance. Clinical signs begin to appear about postnatal day 10 and include twisting of the axial musculature, hyperflexion of the trunk, self-clasping of forelimbs and hindlimbs and poor placement of the limbs during locomotion. No morphological lesions have been observed with routine light microscopy in whole brain or on Golgi-impregnated striatal sections. A very interesting recent finding is that such animals exhibit markedly abnormal σ_h binding in whole brain, with a Bmax more than twice normal and a k_d more than four times normal.[718] The σ_h site is a haloperidol-sensitive receptor site which is non-dopaminergic and non-opiate. It is found in many brain areas involved in motor function, including particularly the cerebellum, red nucleus, locus coeruleus and substantia nigra pars compacta (SNC).[719] Exploration of σ_h binding in the dystonic rat was based upon the discovery that microinjection of a selective σ_h ligand (1,3-di-o-tolylguanidine) into the SNC of normal rats produced circling, and injections into the red nucleus produced dystonic movements.[720,721] Dystonic (dt) rats show normal DA levels and turnover, normal dopaminergic and muscarinic binding parameters, and the normal response of increased locomotion after apomorphine or amphetamine. However, the development of a cataleptic response to haloperidol was decreased, although it was normal after morphine.[721,722] These results suggest that defective σ_h receptors may underlie this and perhaps other forms of dystonia.

Earlier work on these dystonic rats had revealed some cerebellar abnormalities. Cerebellar NA levels were significantly elevated, although cerebellar levels of MHPG and of β-adrenergic binding sites, as well as the levels of NA in other terminal fields of the locus coeruleus were similar to those in normal littermates.[723,724] The mutants showed not only high cerebellar NA levels but a reduction in sensitivity to the NA-depleting effects of reserpine, a change also confined to the cerebellum. GAD activity was found to be abnormally high in the deep cerebellar nuclei but normal in other regions examined (vermis, cerebellar hemisphere, caudate and globus pallidus). The abnormality in GAD was confined to the nucleus interpositus at 16 days of age but was present in all 3 cerebellar nuclei (fastigal, interpositus and dentate) at 20 days of age.[725] Treatment with diazepam significantly reduced the frequency of dystonic movements.[726] There were also lower levels of cerebellar 3',5'-cGMP, a biochemical marker of Purkinje cells, under both basal and harmaline-stimulated conditions and a failure to show tremor after administration of harmaline. The dystonic rats, like normal rats, did show tremor after oxotremorine.[727]

No differences in the pattern or density of NA innervation of the cerebellum were apparent using histofluorescent techniques and cerebellar morphology appeared normal except for a reduction in Purkinje cell size. On the basis of this morphological finding, and the biochemical abnormalities in GAD and 3',5'-cGMP, it was suggested that the alteration in cerebellar NA may be secondary to a functional change in the target Purkinje neurons.[723] Nevertheless, some amelioration of the abnormal movements was reported on clonidine administration.[728]

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Dystonic mouse mutants have also been described. One was due to a mutant autosomal recessive gene occurring spontaneously in a random bred strain.[729] Homozygous animals began to show incoordination and mild posturing during the second week of life. There was a rapidly progressive course leading to severe ataxia and overall writhing motions. Pathology was seen mainly in the sensory pathways leading from the spinal cord encephalad to the thalamus. Histochemical studies of selected lysosomal hydroxylases in animals 5-28 days old suggested an early defect of axonal transport in primary sensory neurons. Segmental demyelination, axon swelling and degeneration was also seen in peripheral nerves, including motor fibers.[730,731] Schwann cell counts in peripheral nerves,[732] as well as transplant studies of peripheral nerves between affected and normal littermates suggested that an underlying Schwann cell defect existed.[733] Such defects do not occur in idiopathic human dystonia which suggests that these mice may not be good models of the disorder.

A number of alleles of this mutant have appeared in other stocks of mice. Dramatic pathological changes are seen not only in sensory afferents, including prominent degeneration of large neurons in the dorsal root ganglion, but also in the large neurons of the caudal red nucleus. Reported neurochemical changes in the CNS include a reduced capacity for GABA synthesis in the striatum and substantia nigra but not in the hypothalamus,[734] an increased turnover of NA (high MHPG and tyrosine hydroxylase but normal NA) in the cerebellum with normal DA, HVA, DOPAC and tyrosine hydroxylase in the striatum,[735] and decreases in glutamate, aspartate, glycine and GABA in the cerebellar vermis with increases in the taurine/glutamate ratio in the cerebellar hemispheres. These changes in amino acids have been said to be more comparable to those occurring in Friedreich's ataxia than dystonia.[736] There is no evidence of Purkinje cell pathology and cGMP-dependent protein kinase, a Purkinje cell-specific marker, is normal.[735] A reduction of NGF in salivary glands and sciatic nerve has been reported.[737]

The pathology in the red nucleus may be of importance.[738] Stanley et al.[739] report that allelic differences exist in the age of onset and severity of this pathology. The magnocellular neurons of the Jackson allele (dt^1) almost completely disappear prior to 4 weeks of age, while some of these cells are retained in the adult of the Albany strain (dt^{A1b}). In the latter strain, however, acetylcholinesterase staining suggests that the remaining rubral neurons are non-functional.

A form of idiopthic torticollis in ducks was reported by Gopalakrishnakone[740,741] but no pathological examination of the CNS was made; the neck muscles showed myodegeneration with an inflammatory reaction that consisted of an infiltration of lymphocytes, monocytes and macrophages. Neuromuscular junctions had degenerated mitochondria and large accumulations of glycogen granules.

Dystonia Acquired Following Peripheral Drugs or Infections

Dystonia has been reported in two out of 6 monkeys receiving L-DOPA as a successful therapy for severe MPTP-induced parkinsonian symptoms.[742]

Administration of neuroleptics to primates results in acute dystonic reactions very similar to those seen in a proportion of psychiatric patients. The time course and pharmacology has been reviewed by Rupniak et al.[655] The acute neuroleptic-induced dystonias in man or non-human primate are easily reversed by neuroleptic withdrawal or treatment with an anticholinergic. Identical dystonic reactions can be induced in haloperidol-primed monkeys with either selective D1 or D2 antagonists.[743] Anticholinergics are effective in either case. In accord with the apparent role of cholinergic systems, physostigmine worsens neuroleptic-induced dystonia in primates.[744,745] Cholinergic agonists can induce dystonia in monkeys primed with haloperidol[746] or by direct injection of the agonist into the neostriatum.[747,748] Four out of five monkeys given sulpiride to reduce persistant neuroleptic-induced dyskinesia developed acute dystonia which had to be reversed by anticholinergic medication.[749]

The effect of drugs acting upon monoamine or GABA systems is more controversial. Haloperidol-induced dystonia in cebus monkeys, which was readily relieved by an anticholinergic, was only slightly reduced by the 5HT antagonist methysergide. Other 5HT blockers (minanserin, ketanserin, ritanserin) and a specific 5HT uptake inhibitor (citalopram) had no significant effect.[750] The tyrosine hydroxylase inhibitor, α-methyl-p-tyrosine (AMPT), was found not to alter neuroleptic-induced dystonia in baboons when given alone,[744,751] but pretreatment with reserpine plus AMPT reduced the intensity and duration of neuroleptic-induced dystonia.[744] In monkeys, however, AMPT was found to worsen neuroleptic-induced dystonia[745] and even to induce acute dystonia by itself.[746] As in man, DA agonists, such as apomorphine,[745] or L-DOPA[746] may alleviate neuroleptic-induced dystonia even though L-DOPA is itself capable of producing an acute dystonic reaction in monkeys.[752-754] Benzodiazepines[746] are also beneficial. Pargyline has been reported to reduce or prevent the neuroleptic-induced acute dystonia in monkeys.[755] In one study, both picrotoxin and muscimol increased the severity of neuroleptic-induced dystonia.[745] However, treatment with the $GABA_B$ agonist, baclofen, is reported to have either no or an opposite, beneficial effect.[746, 756]

Liebman and Neale[756-758] found that an acute dystonic reaction could also be induced in squirrel monkeys by treatment with tetrabenazine, but the syndrome differed from the neuroleptic-induced symptoms in being reversible by D-amphetamine.

Biochemical studies on the brains of such neuroleptic-treated dystonic monkeys are few but Haggstrom et al.[759] reported a reduction in nigral GAD in the brains of cebus monkeys treated chronically with haloperidol. The monkeys showed acute dystonic behavior lasting several hours after the last neuroleptic dose, followed by tardive dyskinesia as the acute dystonia subsided.[760] The reduction in nigral GAD seemed more related to the emergence of tardive dyskinesia than to the acute dystonia.

Rupniak et al.[655] reviewed the chewing movements in rats evoked by neuroleptics. These may constitute a rodent model of acute dystonia but the relationship is not completely clear.

The head shakes, vertical neck dyskinesia and random circling behavior induced in rats by chronic administration of iminodipropionitrile have been said to resemble closely spasmodic torticollis. The behavioral syndrome is inhibited by ketanserin, suggesting that serotonin ($5HT_2$) receptors are involved.[761]

Prenatal exposure to the fungicide dinocap causes behavioral

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torticollis as well as ballooning and cleft palate in mice but not in rats or hamsters.[762]

The only other report noted of a possibly related movement disorder following peripheral administration of a drug is the permanent circling with head tossing syndrome produced in mice or rats by single oral or parenteral doses of dimethylaminohexose reductone. Symptoms are ameliorated by chlorpromazine or thiouracil. Thyroid hypoplasia has been reported in affected rats. Central pathology has not been described.[763,764]

Rabbits often show torticollis after diseases which lead to central infection - e.g. with Psoroptes cuniculi, Pasteureka multocida and Encephalitozoon cuniculi. No common pathology is reported.[765]

CNS Lesions and Chemical Injections

The barrel rotation in rats, first described after intraventricular injection of SOM, and also observed following intraventricular injection of substance P, arginine-vasopressin or chlorpromazine methiodide (CPZMI) has been called a form of "experimental dystonia". It is not associated with activation of cortical EEG and is therefore not a convulsive phenomenon.[766] Using stereotaxic injections of CPZMI into various nuclei bordering the 4th ventricle, Burke and Fahn[767] found that only injections into the vestibular nuclear complex produced the effect; injections into the locus coeruleus, for example, did not. A specific neuroanatomical basis involving vestibular mechanisms is suggested for this barrel rotation and it may involve cholinergic systems since it is enhanced by atropine and inhibited by carbachol. Moreover, CPZMI is a potent inhibitor of QNB binding[767] and is, therefore, presumably a muscarinic agonist or antagonist. Others, however, say that the reaction produced by CPZMI is not antagonized by pretreatment with anticholinergics, diazepam, diphenhydramine, haloperidol, atropine, propranolol, apomorphine or amphetamine. Treatment with CPZMI (unlike treatment with CPZ) does not alter striatal DA or serum prolactin levels and CPZMI has no effect on ^{3}H-spiroperidol binding to striatal membranes suggesting that its action is not through a DA system.[768]

Unilateral electrolytic destruction of the ventral tegmental area of Tsai (VTA) in cats led to the appearance of torticollic rotatory head postures associated with a marked drop of 5HT in the ipsilateral caudate. Excitotoxic lesions of the VTA did not produce such abnormal postures, suggesting they might depend upon lesions of axons of passage in the VTA. The authors suggested descending tracts from the interstitial nucleus of Cajal (INC) may be important[769,770] and electrolytic or kainic acid lesions of that nucleus cause frontal torticollis (head tilt) in monkeys and cats.[771,772] Fukushima-Kudo et al.[773] said that the dorsiflexion of the neck and impairment of vertical eye movement seen in cats with INC lesions is very similar to that seen in progressive supranuclear palsy. Moreover, they claimed that a retrospective analysis of previous clinical-pathological data indicates that the dorsiflexion of the neck in progressive supranulear palsy correlates better with ICN than with basal ganglia lesions.

Jacquet and Abrams[774] said that postural asymmetry and a movement disorder are produced in rats after unilateral microinjection of $ACTH_{1\text{-}24}$ or ACTH N-terminal fragments, but not $ACTH_{,1\text{-}39}$ into rat brainstem. Jacquet[775] suggested a role for an abnormal (mutated) ACTH peptide in dystonia. Sandyk and Consroe[776] proposed that enhanced release of such a peptide may be important in trauma-induced dystonia.

Marked postural asymmetries of a transient or permanent nature have been induced, respectively, by GABA infusions into, or kainic acid lesions of, the nucleus fastigii but not adjacent sites.[777]

Whether or not such postural asymmetries in animals have any resemblance to dystonia in humans remains open to question. However, the involvement of brainstem nuclei in many such reports suggests the importance of pathological examination of brainstem systems in dystonia. Particularly important ones may be those involving acetylcholine, glycine or various peptides.

However, horizontal head asymmetry has also been reported following electrolytic or 6-hydroxydopamine-induced lesions of the nigrostriatal tract in cats[772] or marmosets[778] and an extreme torsion dystonia plus barrel rotation are seen in rats following injections of tetanus toxin into the basal ganglia.[779] It may be of some interest in relation to the last report that the dystonic reaction sometimes seen early during treatment with neuroleptics has been called "pseudotetanus".[780,781] Injection of GABA antagonists in or near the zona incerta of monkeys is reported to induce torticollis and circling behavior in contrast to the types of movement disorders produced by similar infusions into the subthalamus (chorea or hemiballismus), lateral segment of the globus pallidus (choreoathetoid) or putamen (myoclonic).[782]

8. Summary

Both the pharmacological and pathological data suggest that the dystonias may be a group of disorders with multiple etiologies. Knowledge in this field would be immeasurably advanced if a genetic linkage or a consistent regional or chemical brain pathology could be identified for any single subtype. Both kinds of advance are required before the specific etiology can be identified. The problem in trying to identify disturbances in a disease where no obvious neuronal degeneration can be found is rendered extremely complex by the large numbers of chemically distinct, but functionally interrelated, neurotransmitter systems in the brain. The problem is well exemplified by the relatively little progress that has been made in understanding the etiologies of the psychoses despite the many years of intense research effort. An additional difficulty in the dystonia field is the relative scarcity of postmortem tissue available for examination. It thus seems incumbent upon researchers in the field to garner whatever clues they may from the available literature. Each reader of the literature will probably form his own opinion as to the most fruitful brain regions and chemical avenues for research. This review seems to suggest, however, that the following brain regions may deserve the closest scrutiny for possible detection of a lesion:

basal ganglia - including the zona incerta - with particular emphasis on the putamen (see sections 2, 4, 7, Table 3)
red nucleus and surround (see sections 2, 4, 5, 7) vestibular nuclei (see sections 2, 3, 7)
nucleus of Cajal (see sections 2, 3, 7)
nucleus fastigii (see sections 2, 3, 7)
parabrachial area (see sections 2, 3, 7)

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sensorimotor cortex (see section 2)

Other regions worth attention are the spinal cord, premotor area, motor cortex and thalamus.

It is even more difficult to decide on the types of chemical or histochemical assays that should receive priority. Recent work indicating that immunohistochemical staining for the immune complex glycoprotein HLA-DR can readily reveal areas of active neuronal degeneration, not detected by the usual histological methods, in a number of progressive neurological diseases[783] suggests that such staining should be tried in dystonic brains. The hints in the literature that dystonic symptoms may be provoked or exacerbated by autoimmune processes (Sections 1b, 1Bb, 4c) would be further reason to undertake such staining. It is this literature which has already led Sandyk et al.[784] to suggest that hypothalamic dysregulation of immune responses might be of fundamental importance in focal dystonia.

Immunohistochemical staining for the astrocyte marker, glial fibrillary acidic protein (GFAP), can easily be done at the same time as staining for HLA-DR and, while the latter reveals regions of active degeneration at the time of death, the former can reveal areas of past neuronal loss.

Much of the progress in the biochemical pathology of various diseases has been achieved by focusing on particular neurotransmitter systems. While the interesting observations on possible abnormalities in noradrenaline (see Section 4a) deserve attempted confirmation, the paucity of data on any other system suggests that the focus should be also on these rather than just the aromatic monoamines. Certainly the pharmacological activity of anticholinergics indicates that the cholinergic system, both presynaptic and postsynaptic, should be explored as thoroughly as possible with particular emphasis upon brainstem cholinergic systems. Brainstem cholinergic systems in the human are difficult to assess quantitatively but both biochemical techniques for ChAT and the modified histochemical method for acetylcholinesterase[785] could be used as presynaptic indices, while radioautographic binding methods for cholinergic receptors should be attempted. Nicotinic sites are probably more important to assess than muscarinic sites because of the relatively heavy concentration of the former in regions such as the substantia nigra.

Glutamate/aspartate and GABA systems deserve attention because of their enormous importance in motor control; in these amino acid systems the techniques available for studying the postsynaptic binding sites are far more applicable to human postmortem tissue than are indices for the presynaptic systems.

The peptide neurotransmitters offer a vast and almost untouched field for exploration with reference to dystonia. The problem is in choosing the peptides worth particular attention. One possible group might be the tachykinins, including substance P. Substance P probably has an important role in the basal ganglia, as well as a cotransmitter role in brainstem cholinergic projections.[786] There is a probability also that it innervates the red nucleus (unpublished observations). Another choice might be neurotensin because of the abundant evidence that this peptide strongly modulates the activity of both basal ganglia and limbic dopaminergic systems. Thyrotropin-releasing factor (TRH) might be of interest because of the frequent interrelation between thyroid disorders and dystonic symptoms (Section 4f). TRH also appears in the basal ganglia. The rat "models" of dystonia indicate that the σ_h binding sites should be examined, particularly those in the region of the red nucleus. The reports of abnormal levels of SOM in ventricular CSF from dystonic patients would also promote this peptide into the ranks deserving priority. Fortunately, the availability of immunohistochemical procedures for these peptides means that several can be examined in a single brain but a major difficulty in such work is studying sufficient human postmortem controls and dystonic cases to ensure that differences are not just reflections of variations in tissue stainability.

In the meantime, new drugs are being developed, particularly ones which interact with peptide and the glutamate/aspartate systems. It is important that these be tested in dystonics not helped by presently available drugs. Such clinical trials may not only bring better immediate relief to present sufferers but provide the clues which basic researchers need to focus their investigations. Because of the probability that dystonia is not a homogeneous disease, care should be taken in both the clinical trials and basic research to define as clearly as possible the type(s) of dystonia involved.

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