This review will encompass work performed in the last 20 years funded by the National Institute of Child Health and Human Development, National Institute of Mental Health, both divisions of the United States National Institutes of Health, as well as work at the Institute for Developmental Behavioral Neurology where I have been director since 1987 following my post as associate professor of neurology at Mayo Medical School in Rochester, Minnesota.

As recently as perhaps 25 years ago, the majority view would have held that developmental disorders that adversely affect learning for the most part are the result of perinatal stress. Further, that the manifestations would primarily be in the perceptual motor domain, as well as the probability that symptoms would be manifest only during childhood and adolescence with either spontaneous remission or at least compensation on the part of the learner. Finally, that from an educational standpoint, only the training of perceptual motor skills might be appropriate and these provided only in early childhood because of the presumption of spontaneous favorable outcome. If there was a medical component to treatment, it involved only the use of psychostimulants such as methylphenidate or dextroamphetamine and that these agents primarily were of assistance to hyperkinetic behavior.

It is not that each of these preceding notions are inaccurate, it is just that they now appear to apply to a minority of the students now perceived as one of several developmental disorders called “learning disabilities.” As we shall see, increasingly there is evidence of a genetic component in the etiology of these disorders which may be exacerbated by perinatal factors, that instruction even preschool directed at language, in early school directed at reading and motor skills in penmanship are appropriate, that symptoms tend to persist throughout the life-span, although altered, and a wider spectrum of pharmaceutical agents is now available, some of which may have a specific effect on selected aspects of cognition which favorably influence learning, memory, and attention.

With the passage of the Aid to all Handicapped Children’s Act in the late 1960’s in the United States, a nomenclature has evolved compatible for those in medicine and allied services, as well as education (See Table 1). Thus, specific learning disabilities may impact reading, written expression, arithmetic, or combinations of these, as well as fine or gross motor skills, communication skills, social and emotional components of learning, and a variety of disorders which may adversely affect attention, some of which are associated with motor hyperactivity in which about one-third have a concomitant disorder of reading and almost 40% a concomitant disorder of arithmetic skills, but some have no manifest academic underachievement. Thus, those in medicine (neurology, developmental pediatrics, psychiatry), speech and language, occupational and physical therapy, as well as school or clinical psychology are appropriate collaborating colleagues in the assessment and provision of services in which educational intervention will be primarily in the hands of the school and its educational staff.

Following are the highlights of current research in the educationally pertinent domains of reading and oral language, attention, and nonverbal learning.

Reading Disorders

Whether using the terms dyslexia, specific reading retardation, or developmental disorder of reading, it is clear, beginning with the early descriptions in 1896 by Pringle-Morgan, that there are individuals who from early in school years have difficulty in the acquisition of learning to decode words in whom the salient deficit is in world recognition in the language in which the student is reared.

It is perhaps worth calling attention to the fact that throughout the world our species speaks; but in many
societies, humans never learn to read or to write either because of lack of education or, in some instances, there being no written language. Thus, reading and writing are not “natural” human acts but require a system of neural functions, exposure and instruction in script relating to the spoken language in which the individual is raised for reading and writing to develop.

That there was a link between spoken and written language was suggested by the very title of the late Samuel T. Orton’s book *Reading, Writing, and Speech Problems in Children* published in 1937 by Norton.\(^3\)

Among the human universals in spoken language is the sequence of developmental speech production and speech perception which occur in all languages worldwide. Additionally, humans can distinguish the difference between natural human spoken voice versus speech sounds generated artificially which, to many, would have a “normal” voice quality as may be generated computers. This capacity is present in humans as early as six months following full-term gestation.\(^4\) That this biological capacity is influenced by one’s society is demonstrated by work of Patricia Kuhl at the University of Washington, in the United States, which has demonstrated that children exposed to English by 18 months of age no longer will have a capacity to respond to those speech sounds that are not indigenous to English as in, for instance, Swedish, and the same for the reverse.\(^5\)

Of all the predictors of reading under-performance, those associated with speaking and understanding speech show the strongest correlation. In English, the capacity to rhymen can be taken as a sign of capacity in phonological awareness, which is essential to decoding written words. Additionally, the capacity for letter recognition when there has been exposure to the letters of the alphabet for a year or more also correlates with reading acquisition.\(^6\) Failure of these skills to develop is a strong negative prognostic indicator. Thus, children who demonstrate disorders of spoken language, either expressive or receptive, should be construed as “at risk” for reading failure.

A potential correlated of these observations regarding spoken language are those pertaining to the acquisition of a second language by persons in whom reading or writing have poorly developed. One study at Harvard University documented failure to acquire proficiency in a second language in which those demonstrating this inability did no suffer intellectually but rather had childhood histories of difficulty in the acquisition of reading skills and, as young adults, still demonstrated problems in reading rate, as well as in spelling accuracy. Of all of these students’ pre-university coursework, that of difficulty in a foreign language was documented.\(^7\) The university officials, recognizing this was not a problem in motivation, waived the foreign language requirement for such students to achieve the baccalaureate degree. The implications may be that for those cultures such as those in Asia where commerce especially directs the need bi- or polylingualism may require modification of instruction in acquisition of a second language for those in whom spoken or written language deficits are present in childhood.

Among the physical signs that may occur in the quantitative neurological examination of students with reading, writing, or speaking problems is that of permutation of hand posture while holding a writing instrument referred to as a distal or “brush stroke” posture.\(^8\) Although not diagnostic, it is statistically more prevalent among those with oral language difficulties.\(^8\)

Educationally, training in phonological awareness, sound-symbol relationships, in a graduated, structured manner such as those described by Patricia Lindamood known as

### Table 1  Medical vs. Educational Classification of Learning Disabilities

<table>
<thead>
<tr>
<th>DSM-IV</th>
<th>ICD-9-CM code</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>315.0</td>
<td>Learning disability</td>
</tr>
<tr>
<td>Mathematics</td>
<td>315.1</td>
<td>Reading</td>
</tr>
<tr>
<td>Written expression</td>
<td>315.2</td>
<td>Mathematics</td>
</tr>
<tr>
<td>Other</td>
<td>315.9</td>
<td>Spelling, expressive writing</td>
</tr>
<tr>
<td>Motor skills disorders</td>
<td></td>
<td>Reasoning</td>
</tr>
<tr>
<td>Developmental incoordination</td>
<td>315.4</td>
<td>Writing</td>
</tr>
<tr>
<td>Communication disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expressive language</td>
<td>315.31</td>
<td>Speaking</td>
</tr>
<tr>
<td>Mixed receptive expressive language</td>
<td>315.31</td>
<td>Listening</td>
</tr>
</tbody>
</table>

**Co-Morbid/Overlapping**

<table>
<thead>
<tr>
<th>Pervasive</th>
<th></th>
<th>Social-emotional, mathematics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asperger disorder</td>
<td>299.80</td>
<td></td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>314.01</td>
<td>Any or none</td>
</tr>
<tr>
<td>Inattentive</td>
<td>314.00</td>
<td></td>
</tr>
<tr>
<td>Hyperactive-impulsive</td>
<td>314.01</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>314.9</td>
<td></td>
</tr>
<tr>
<td>Tic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourette disorder</td>
<td>307.23</td>
<td>Any or none</td>
</tr>
</tbody>
</table>

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Duane
the “Auditory Discrimination in Depth program” or the computer-assisted program known as “Read, Write, and Type!” developed by Dr. Jeanine Herron have recently been documented to have a favorable impact on reading success among those seen at risk for reading failure in the primary grades.\(^9,10\) Since the 1940’s in the United States, the Orton-Gillingham system and its various permutations which direct one’s awareness toward word recognition appear to improve prognosis.

The last two decades have been associated with remarkable scientific understanding of the biological source of reading disorders. Beginning with the report in 1979 by Kemper and Galaburda, evidence from autopsy specimens of five males and three females that symmetry of the temporal plane, a pattern that occurs in less than 10% of the general population, as well as developmental anomalies of the cortex microscopically, referred to as focal cortical dysgenesis, represents the hallmark characteristic of this disorder at post mortem. The cortical anomalies are reminiscent of those observed in some forms of epilepsy which may explain why one of the subjects at least had experienced a nocturnal seizure at the age of 16 years and furthermore why in a series of those with seizure disorder coming to an epilepsy clinic in late childhood or early adolescence demonstrated an increased rate of occurrence of antecedent learning disorders.\(^11,12\)

A variety of in vivo anatomic studies have been carried out of adults with reading disorders. These magnetic resonance imaging investigations suggest, in dyslexics, a variation in the length of the Sylvian fissure and multiple Heschl’s gyri.\(^13\) These magnetic resonance imaging abnormalities may occur in clinically unaffected relatives of those with reading disorder. Thus, they appear to be under genetic influence with some unknown factor which may minimize the clinical expression of the disorder.

Regional cerebral blood flow studies of adults with partially compensated reading disorder diagnosed during childhood by the late June Orton, widow of S. T. Orton, demonstrate an alteration from the usual pattern during reading in which activation is more posterior toward the angular gyrus rather than in the superior temporal region.\(^14\) Thus, there is a metabolic component which persists, as does the post mortem anatomic findings through the life-span of those with dyslexia.

Position emission tomography studies of normal decoding acquisition suggest network activation involving the left superior temporal, left cingulate, and right cerebellar region. This network inactivates once the word has been mastered, only to be reactivated when new words are to be learned.

Clinical electroencephalograms sometimes reveal in those with reading disorder and other developmental disorders focal or multifocal epileptiform discharges which may be the consequence of the developmental cortical anomaly described by Kemper and Galaburda.\(^15\) Occasionally, the treatment of the electroencephalographic abnormality with an antiepileptic agent may have a favorable impact on the cognitive deficit underlying the developmental disorder of reading or of attention, even though there has never been a clinical seizure recorded. As will be discussed further, mid-latency auditory evoked potentials in this, as well as other developmental disorders, demonstrate long latencies which distinguish control subjects from those with developmental disorders.

Functional MRI studies performed by colleagues at Yale University have suggested that the pattern in adult females during tasks activating phonological awareness, tend to induce bilateral frontal activation in females, whereas in males, the activation tends to be left frontal.\(^16\) This may explain why localized disease of the left hemisphere in adults may more frequently be associated with clinical aphasia in males than in females. This same pattern has been described by the same investigators in children and may play a role in why severity for reading disorder may be greater among males than females.

Among the most productive lines of research has been that the genetics of reading disorders. Led by colleagues at the University of Colorado and University of Denver, studies of monozygotic versus dizygotic twins have revealed three chromosomal sites associated with reading disorders. These are: The short arm of chromosome six in which phonological awareness deficit is most prominent and in whom two out of three mothers of children with reading disorder demonstrated elevated titers of the autoimmune antinuclear antibody (ANA); chromosome 15, the site originally suggested in the mid-1980’s in which now it appears the clinical deficit is in orthography; and, finally, a site on chromosome one in which orthography or spelling may be the salient clinical manifestation.\(^17\) Whether genetic engineering would result in an improvement in reading acquisition without sacrificing that set of traits sometimes associated with reading disorder that favor skills as might be useful in engineering, sport, or surgery, remains to be seen.

All developmental disorders in which lack of success in school marks the individual’s early academic development carry a risk for emotional maladjustment. Among those with reading disorder, it would appear depression is the most prevalent affective manifestation.

Although there are no medicinal “cures” for reading disorder, some students who have combined attention deficit disorder with reading disorder may improve in their response to the educational intervention with appropriate use of a psychostimulant. A recent study by our group suggested pemoline offered greater benefit to those with reading disorder than did methylphenidate, but the study is from a tertiary referral population and is small in size.\(^18\)
Consequently, its generalizability is unclear. Certainly, agents such as piracetam, originally developed for senior citizens with memory disorder, has been shown to have a favorable impact on verbal processing. We have observed the same in our own facility, as well as similar effects from ergoloid. Where memory deficiency is the greatest concern, facilitation of acetylcholine metabolism with oral phosphatidylcholine may be of assistance as verified by test-retest paradigms involving short and long-term verbal or visual memory. Whether stronger agents which impact acetylcholine metabolism offer benefit in any developmental disorder as they do for Alzheimer’s disease, i.e., Cognex and Aricept, awaits careful clinical assessment in controlled settings.

The co-occurrence of attention disorder with reading disorder may have an underlying shared genetic mechanism. It appears that a genetic risk for depression, based on observations of family members, may be a factor in why depression occurs in greater frequency in those with reading disorder. Most recently, PET studies by Frank Wood at Wake Forest University Medical Center suggests in adults with reading disorder nine patterns of hypometabolism, some of which correlate with concomitant mood or behavioral disturbance and that which affects decoding skill characterized by right mid-temporal hypometabolism during tasks of single-word recognition.

**Attention Deficit Disorders**

Criteria need to be met to assure accurate clinical diagnosis of this group of disorders in which perhaps 40% in preadolescence demonstrate motor hyperactivity. Behavioral rating scales are used to define the presence of unusual levels for a given culture of inattentiveness, hyperactivity, and/or impulsivity. Symptoms should be present for more than six months, commence prior to the age of seven years, and be observed in multiple settings. Ratings by teachers and family members assure multiple setting criteria are met. In our institute, cognitive measures are included as crucial characteristics of the disorder in which inattentiveness may be confirmed using a variety of neuropsychological instruments, including those that measure attentiveness specifically such as the Letter Cancellation Task, Test of Visual Attention, and Conners’ Continuous Performance Test, the latter two computer generated.

Seventy percent of probable idiopathic cases demonstrate two biologic traits. First, a much higher occurrence in males (a ratio of 4-6 to 1) and second, strong familial occurrence. In adult males with a history of attention deficit disorder who have at least on male offspring similarly affected, Zametkin et al have demonstrated by PET scan reduced cortical glucose metabolism. Attempts to replicate the observations in adolescents was less definitive. Indeed, the strongest similarity to the adult findings was observed in adolescent females with attention deficit disorder.

No studies of post mortem neuroanatomy, either gross or microscopic, have yet been produced in this group of conditions, but MRI studies suggest reversed asymmetry of the caudate nucleus in two studies, one in the United States and the other in Europe, as well as thickening of the corpus callosum as have been described in Tourette syndrome, including those with Tourette syndrome without evidence of attention deficit disorder.

Physiologically, almost all of these students evaluated in our setting demonstrate prolonged latencies as contrasted with controls in auditory mid-latency potentials, especially the P-300. When pharmacologic therapy is successful, not only may cognitive improvement occur, but latency shortening closer to those of the general population can be observed, verifying the biologic effect of these psychostimulants.

On clinical quantitative neurological examination of left body motoric signs, including dystonic postures, unilateral impaired balance, reflex asymmetry and slowed timed alternate motion rate of hand and/or foot is observed. These left lateralized signs correlate best with the inattentive type of attention deficit disordered subjects who may also, by pupillometry, demonstrate nonwakefulness. Pupillometry first developed in an effort to quantify, demonstrate nonwakefulness. Pupillometry first developed in an effort to quantify pupillary responses in ophthalmology subsequently became useful in the diagnosing and measurement of clinical effectiveness of psychostimulants in adult narcolepsy. Approximately one out of three of those with attention deficit disorder and especially those with inattentiveness without hyperactivity, demonstrate non-alertness in which pupil size descends relatively promptly in the course of a 10-minute recording conducted in a darkened room in the mid-afternoon. What is not clear is the number of such observations which must be positive to assure accuracy in designation of non-wakefulness in the child and adolescent population.

Psychiatrically, the risk for multiple psychiatric disorders in the individuals themselves as well as in their families, has been observed both in studies led by Joseph Biederman et al and confirmed in our own patient population. Risk is highest within affected individuals for anxiety, depression, and obsessive-compulsive disorder. This last psychiatric state may be exacerbated by psychostimulants and thus must be assessed as to its presence or absence and monitored during any treatment protocol involving psychostimulant medication. The effectiveness of psychostimulants may be assessed on the
basis of pupillometry or on mid-latency auditory processing time but is most conveniently assessed with repeat cognitive measures in altered form in which effectiveness of psychostimulants such as methylphenidate and amphetamine may be assessed within one hour of a test dose. In assessing pemoline effectiveness, three mornings of use are required. Agents with broader cognitive effects, and especially on verbal functioning, such as piracetam and ergoloid, require 10 to 15 days at least before their benefit or lack thereof can be ascertained.

Despite the strong evidence for a genetic mechanism underlying at least some forms of attention deficit disorder estimated at perhaps 70% the remaining third are likely secondary to acquired factors such as perinatal stress, head injury or central nervous system infection, the specific genetic site is unclear but may relate in some instances to the same site where a reading disorder has been identified. Our investigation of those with non-alertness and attention deficit disorder suggest that HLA types that are observed in narcolepsy, DR-2 and DQW-1, are more prevalent in attention deficit disordered individuals in which concomitant psychiatric symptomatology is observed, as well as non-alertness.

**Nonverbal Learning Disorders**

This curious group of developmental disorders was first described by Doris Johnson, a special educator in the United States, who wisely observed students who might be motorically awkward but more so socially awkward in whom awareness of social propriety seemed innately difficult, including the appreciation of vocal intonation and facial/body gesture. These might be impaired both expressively and receptively.

This group of disorders is reminiscent of some form of childhood pervasive disorder but for whom reality testing is not at issue. Characteristics include much lower performance than verbal IQ and, where factor analysis is carried out, lowered perceptual organization factor versus verbal comprehension factor in which freedom from distractibility factor, as is common in attention deficit disorder, may also be reduced. Processing speed may or may not be reduced as a factor subanalytic characteristic from the IQ measures. These children tend to speak well in the sense of having a large vocabulary, but the prosody or melody of their speech is often flat and their manner of speaking pedantic. Both males and females are affected; and in our own patient pool, non-right-handedness is uncommon. Here motor signs are clearly lateralized to the left hemibody leading to the designation by Martha Denckla in the past of these as a “right hemisyndrome.”

Good verbal fact memory is a characteristic, but weak visuospatial memory is likewise a characteristic, impairing performance in coursework such as geometry.

The exact combination of symptoms and signs is variable requiring, hopefully soon, classification of subtypes of this condition, some of which demonstrate clear-cut motoric awkwardness marked by slow timed alternate motion rate and incoordination, others with more prominent features of math calculation disorder, but most showing difficulties in visuospatial memory and all at least some degree of social inappropriateness, expressively or receptively. Although reading at the decoding level is strong, reading comprehension may be significantly impaired, especially the comprehensive of affective information in script.

To date, there are no post mortem examinations to clarify what may be the neuroanatomic substrate. PET scans have suggested in one poster presentation by Dilucca hypoperfusion of the right hemisphere. Although in some instances mid-auditory latency evoked potential prolongation may occur, it is not the rule in those with adult manifestations. In the study our center reported at the Cruickshank Memorial Lectureship and in another at the American Academy of Neurology, we observed in adults with chronic symptoms of this condition a high rate of success in areas such as the law, psychiatric social work, education, but chronically adversely affected by recurring symptoms of anxiety and depression, as if these psychiatric symptoms were a concomitant and not a reaction to the deficits in this condition. Mapped visual evoked potential studies are apt to be associated with hyperreactivity to light in the right frontal region.

It is likely that this disorder, like attention deficit disorder, not uncommonly is of genetic origin but may also follow on the heels of acquired brain insult. Treatment here is most frustrating in that pharmacotherapy is not clearly associated with improved social awareness. Social skills training has been advocated but not objectively confirmed to favorably impact social intercourse or emotional stability. Psychotropics are commonly required, whether they be atypical neuroleptics to address issues of anxiety and obsessiveness, SSRI’s to assist in the control of depression or in obsessive-compulsive disorder.

**Summary**

The foregoing three conditions represent biologic variation in human neuroanatomy, neurophysiology, and neurochemistry which in some instances today can be readily appreciated and even optimized. Work in this field cross culturally confirms the university of the human condition in which individuals, whether genetically or through acquired insult, may be placed at disadvantage.
in their oral or written communication, attentiveness, or social awareness. This group of disorders stimulates interdisciplinary collaboration in the assessment and treatment of these students and their longitudinal evaluation into adulthood.

You are wise in Hong Kong to be addressing these issues so directly.

References