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Autism in search of a home in the brain

Isabelle Rapin, MD

Investigators have attempted to define the neural pathophysiology of autism ever since the hypothesis of "refrigerator parents" as its cause was replaced by the view that it is a developmental disorder of the immature brain. As the article by Minshew et al.¹ and the Views & Reviews by DeLong² in this issue of *Neurology* show, consensus has yet to be reached. Minshew et al. examine whether abnormal control of eye movements is best explained by impaired vermal or frontal lobe dysfunction; DeLong's focus is on the temporal lobes and on abnormal maturation of serotonergic pathways. These are by no means the only brain regions implicated; earlier studies have invoked maldevelopment or, rarely, damage of the cerebellum and some brainstem and diencephalic nuclei, involvement of the basal ganglia and thalamus, frontal neuronal migration deficits, thinness of parietal gyri and posterior corpus callosum, and dysfunction of dopamine and opiate neurotransmitter pathways.

Similar to dementia in the elderly, autism (pervasive developmental disorder [PDD] in Diagnostic and Statistical Manual of Mental Disorders, 4th ed. [DSM-IV] and International Classification of Diseases [ICD]-10 parlance) is not a medical diagnosis but a behaviorally defined syndrome of early childhood with a variety of biologic causes. Its severity varies so widely that DSM-IV divides it into five behavioral subtypes. All have in common impaired sociability, language, nonverbal communicative skills, and imagination, together with stereotypic behaviors and preoccupations. Other features are lack of cognitive flexibility, poor organizational skills and insight into what others may be thinking, rigidity, perseveration, and often heightened anxiety. Intelligence is affected in many but not all individuals, although intelligence quotient (IQ) is not a defining feature of autism. DSM-IV specifies that the behavioral deficits must be out of proportion to the individual's cognitive level, without defining this discrepancy in quantitative terms.

The five DSM-IV subtypes are based on the presence, number, and distribution of 12 behavioral descriptors and on age at onset. The subtypes are 1)

autistic disorder (classic autism), which requires at least six deficits, with no fewer than two in sociability and one each in language and range of interests and activities, and a clinical onset before age 3 years; 2) Asperger's disorder (see Book Review section, p. 1112), which is a less severe subtype with at least three deficits, two in sociability and one in range of interests and activities severe enough to cause significant functional impairment, without delay in language development or important cognitive deficit; 3) disintegrative disorder, which applies to children with normal early development, including speaking in sentences, who between ages 2 and 10 years undergo a severe language, behavioral, and cognitive regression resulting in autism, provided they do not have a degenerative disease of the brain; 4) PDD not otherwise specified (PDD-NOS), the subtype to be used for children with severe impairments in sociability, language, and range of activities who do not meet criteria for the first three disorders; and 5) Rett's disorder, a biologically specific genetic neurologic syndrome in girls with postnatal failure of brain growth.

It is estimated that in ~20% of individuals with autism, the condition has a currently definable biologic cause, none of them invariably associated with autism. Some defined causes, like intrauterine exposure to rubella, thalidomide, or valproate, and herpes encephalitis, are acquired, whereas others are single gene defects or deletions such as those that cause tuberous sclerosis, phenylketonuria, and fragile-X, Angelman, and Cornelia de Lange syndromes. In his article, DeLong² refers to cases with a defined cause as secondary autism, which he postulates involves both hemispheres and therefore has a poor prognosis. In the other 80% of individuals on the autistic spectrum, those whom DeLong labels as having primary autism attributed to unilateral hemispheric dysfunction, the cause is unknown, and clinical brain imaging rarely reveals a relevant pathologic state. Studies in monozygotic and dizygotic twins and in families with several affected members suggest that genetics plays an important, but not exclusive, causal role when other signs of

See also pages 911, 917, and 1057

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brain disorders are lacking, because <100% (70% to 90%) of monozygotic twins are concordant for diagnosis although not necessarily for severity. Polygenic inheritance is likely, because concordance in dizygotic twins and the recurrence rate in multiplex families are both <10% and because there is an excess of other developmental disorders, including, according to DeLong and others, major depression and bipolar disease in the families of individuals with so-called primary autism. The rarely occurring disintegrative disorder and the report of early regression of language and sociability in ~30% of children with autism suggest that in some cases what is inherited may be inordinate susceptibility to some deleterious environmental influence. The utility of dividing autism into primary and secondary types and into the DSM-IV behaviorally defined subtypes awaits further progress toward identifying its causes and unraveling its pathophysiology.

A major obstacle to identifying the neuroanatomic basis (or bases) of autism is that <30 detailed post-mortem examinations of the brain have been published. An early report of cerebellar abnormality passed unnoticed until the studies of Kemper and Bauman, starting in 1985 and recently summarized,³ confirmed developmental cellular abnormalities in the posterior inferior cerebellar hemispheres (less so in the vermis) in all nine cases they examined. Bailey et al.⁴ found similar abnormalities in six additional brains. There was a paucity of Purkinje and, to a lesser extent, granular cells, without evidence of inflammation, ischemia, or major structural anomaly. Kemper and Bauman interpreted these findings and those in the inferior olive and cerebellar roof nuclei as evidence for the persistence of a fetal olivary-dentate circuit, which typically regresses by 30 weeks of gestation—an interpretation that would provide an outside date for the cerebellar pathologic state. The influential MRI study in 1988 by Courchesne et al.⁵ described selective smallness of lobules VI and VII of the vermis in 14 of 18 men with autism. A series of MRI studies by the Courchesne group and others have both confirmed and refuted these vermal MRI findings (see the correspondence on this topic in this issue, page 1106). The seemingly frequent—perhaps characteristic—cerebellar cellular pathologic findings in autism was unexpected because individuals with autism do not have the motor symptoms typical of acquired cerebellar damage. These findings have contributed to a renaissance of interest in the contribution of the cerebellum to language, attention, and other higher cerebral functions.

The cerebellum and prefrontal cortex are extensively connected via the fronto-ponto-cerebello-thalamo-cortical loop. Functional imaging, autopsy findings in four of six British cases,⁴ and neuropsychological evidence strongly implicate frontal dysfunction in the pathophysiology of autism. Minschew et al.¹ champion the involvement of multimodal, notably lateral prefrontal, neocortical pathology in au-

tism. They describe in this issue of *Neurology* a systematic study of the control of eye movements in autism designed to ascertain whether abnormalities originate in the vermis or the frontal eye fields. They detected no alteration in the velocity or latency of saccades in a visually guided task, or in automatic disengaging, shifting, or reengaging of visual attention—findings that would have been expected from the pathologic state in vermal lobules VI and VII, to which Courchesne et al. attribute slowed orienting of attention in autism. What was abnormal in the study by Minschew et al. was the ability to voluntarily suppress or delay oculomotor responses to visual targets, which the investigators ascribe to prefrontal dysfunction because these latter tasks are dependent on working spatial memory and executive control. Whether a fetal cerebellar pathologic state can masquerade as (or even induce) frontal dysfunction because of the massive cerebello-frontal connections is uncertain, although the reverse is illustrated by the classic gait ataxia of some patients with acquired frontal pathologic conditions.

The results of the study by Minschew et al. may transcend the pathophysiology of autism, because there are similar deficits in the control of antisaccades in schizophrenia, where they are correlated with deficits in ostensibly prefrontal planning tasks like the Wisconsin Card Sort Test.⁶ Schizophrenic patients regularly have impaired smooth visual pursuit, which has not been reported in autism. Autism and schizophrenia are clearly different disorders, but with enough overlapping symptoms and neuroimaging abnormalities to point to commonalities in brain involvement. It may be no coincidence that Kanner⁷ and Asperger⁸ independently borrowed the term *autism* from Bleuler,⁹ who coined it to describe the profoundly impaired sociability of schizophrenia.

MRI has failed to detect structural abnormalities in the vast majority of the many hundreds of individuals with autism who have undergone clinical imaging, except for an occasional unsuspected brain tumor, arachnoidal cyst, mild ventricular enlargement, or other abnormality whose relevance to the behavioral syndrome is conjectural. Kemper and Bauman³ found the neocortex, as well as the basal ganglia and thalamus, of their nine subjects to be normal, to their surprise in view of the frequent cognitive impairment and epilepsy in autism. This lack of neocortical pathology may have been a sampling artifact, because there was aberrant cortical lamination, neuronal orientation, and density in four of the six cases of Bailey et al.⁴ with evidence of ectopic neurons in the white matter in the other two, findings supporting fetal brain maldevelopment. Kemper and Bauman observed stunted closely packed neurons in the hippocampus, anterior cingulate gyrus, amygdala, diagonal band of Broca, and other diencephalic nuclei. The Bailey group did not corroborate hippocampal neuronal pathology in their six cases, but they had yet to examine the diencephalic nuclei. Both groups highlighted increased brain weights in

some of their patients, in accordance with reports of large head circumferences, and increased brain volumes by morphometry in subsets of individuals with autism. Courchesne et al.¹⁰ point out in this issue of *Neurology* that increased brain weight was found in 19% of a total of 21 postmortem brains. This high percentage and the relative rarity of micrencephaly is further evidence for a dysgenetic rather than a destructive process in most individuals with autism. Clearly, it is premature to decide what findings are constant and specific to autism until a much larger number of brains becomes available for detailed study.

Mesial temporal involvement in autism is an attractive theory, because limbic and diencephalic circuits have long been known to control drive and affect, which are conspicuously abnormal in autism. Bilateral ablation of the hippocampus and amygdala in neonatal monkeys produces behavioral deficits reminiscent of autism.¹¹ Chugani et al.¹² reported that on follow-up, 14 of 18 infants with infantile spasms in whom PET scanning had disclosed bitemporal hypometabolism were severely retarded, non-verbal, and autistic. The language disorders of minimally verbal children with autism and severe comprehension deficits implicate lateral temporal neocortical involvement. An unknown proportion of children with autism have subclinical centrotemporal epileptic discharges similar to those of children with acquired epileptic aphasia or Landau-Kleffner syndrome, most of whom have verbal auditory agnosia or word deafness. The potential role of subclinical temporal epilepsy as a cause of autistic regression and disintegrative disorder remains controversial because a systematic study carried out close in time to the regression has yet to be reported.

The serotonin theory of autism advanced by DeLong² attempts to integrate the classic views of hemispheric functional asymmetry derived from adults with unilateral brain lesions with genetic evidence of major affective disorders in the families of individuals with autism. He speculates that classic autism without a discernible cause may be the consequence of an early disorder of serotonin metabolism that affects the left hemisphere selectively, whereas it affects the right hemisphere in socially inept children of the Asperger type who are verbally fluent but interpret language literally, do not understand jokes, and have difficulty interpreting prosody and facial expression. This theory implies that there is also impaired interhemispheric communication, because children with an early lateralized brain lesion are not aphasic, whether it affects the left or the right hemisphere. He offers as supporting evidence the recent report¹³ that describes asymmetric serotonin metabolism by PET study in seven sleeping boys with autism, but not in one girl, using a marker for serotonin synthesis. In five of the boys there was decreased frontal and thalamic synthesis on the left;

and in two, on the right. In all seven there was increased serotonin synthesis in the contralateral dentate nucleus. The trajectory of serotonin synthesis in the brain is atypical in autism, and about a third of individuals with autism have elevated levels of serotonin in their platelets. Serotonin uptake inhibitors like fluoxetine have gained popularity because they lessen obsessive behaviors and, according to DeLong, may promote a spurt in language development in preschoolers with autism.

This list does not exhaust the critical nodes in the complex interconnected networks likely to be responsible for the behavioral deficits of autism. Research on the neurobiology of autism is young; at this juncture, myopic investigators are still patting the elephant. Even if they are well designed, narrow studies on a few subjects rushed to publication are intriguing and potentially heuristic but may contribute to the current confusion. The need for tissue donation from well-studied subjects and normal control subjects of all ages is emphasized, because state-of-the-art neuropathologic examination provides a foundation for interpreting the findings from electrophysiologic, functional imaging, genetic, and pharmacologic studies. Research on dementia leaped forward when neuroscientists and families of affected individuals joined forces to mount a concerted effort. A similar effort is currently in place for autism, and it augurs well for the future.

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Sympathetically maintained pain

Has the emperor no clothes?

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Leriche's report¹ during World War I that periarterial sympathectomy relieves pain in soldiers with nerve injury popularized the hypothesis that sympathetic efferent activity in some way augments chronic pain, and launched a series of sympathoablative treatments that remain in common use today. United States physicians carry out approximately 43,000 sympathetic nerve blocks per year for the treatment of pain.² Blocks that result in pain relief prompt more permanent interruption of the sympathetic chain by surgery, by injection of neurolytic agents, or by thermocoagulation. The diagnosis in most of these patients is reflex sympathetic dystrophy (RSD), more recently termed complex regional pain syndrome (CRPS) type I, consisting of pain, allodynia, or hyperalgesia disproportionate to the inciting injury and edema, changes in skin blood flow, or abnormal sudomotor activity in the painful region; or causalgia caused by a peripheral nerve injury, now termed CRPS type II.³

The rationale for sympathoablative treatments was strengthened in the 1980s by animal studies showing that sympathetic efferent activity may augment pain in models of both nerve injury and inflammation, and that anatomic changes, such as increased densities of axonal adrenergic receptors or sympathetic fiber sprouting into dorsal root ganglia, may underlie sympathetically maintained pain after nerve injury.⁴

As the field of pain research has matured, there have been critiques of the "sympathetic hypothesis." Raja et al.⁵ pointed out that only some patients with nerve injury or RSD respond to sympathetic nerve blockade, and they proposed that patients' pain be defined as "sympathetically maintained" or "sympathetically independent" according to their response to temporary sympathetic nerve block. They also criticized local anesthetic blocks of the sympathetic ganglion as being invasive, difficult to blind, and confounded by a large placebo response and by the systemic effects of lidocaine, which inhibits ectopic sodium currents at nerve injury sites. They proposed

an alternative procedure: systemic infusion of the alpha-adrenergic antagonist phentolamine,⁵ which can be more readily blinded and whose results appeared to correlate well with results of lidocaine ganglion blocks.

These modest revisions were not enough for more radical skeptics such as Geoffrey Schott⁶ and Jose Ochoa (see Verdugo et al.⁷), who have argued that the apparently beneficial effects of any type of sympathetic ablation result either from a placebo effect or from interrupting visceral primary afferent fibers that run with some sympathetic nerves.⁶ A controlled study⁷ compared IV phentolamine with IV phenylephrine (an alpha-1 adrenergic agonist that should increase sympathetically maintained pain) in 29 patients with causalgia, polyneuropathy, or RSD and found no difference in pain resulting from the two oppositely directed sympathetic interventions. A comparison of IV phentolamine with placebo and with epidural lidocaine-fentanyl in 37 patients with failed back surgery found only one phentolamine responder.⁸ A study of lidocaine versus saline sympathetic ganglion blocks in patients with CRPS type I showed that a saline block produced an average of 20 hours of nearly complete relief,⁹ which should give pause to clinicians who proceed to permanent sympathetic ablation after several successful temporary local anesthetic blocks. Recent meta-analyses of studies of sympathetic ablation found little evidence of efficacy.¹⁰ There are additional problems with long-term sympathoablative treatments; systemic drugs such as doxazosin or phenoxybenzamine are poorly tolerated because of postural hypotension, whereas neurolytic sympathectomy may cause neuralgias, and the mean duration of effect is only 6 months.¹¹

The attempted demolition of the sympathetic hypothesis has generated thoughtful responses. Raja et al. have refined the phentolamine method by showing that it takes higher doses than they (and Verdugo et al.) originally used.¹² Raja et al. have also developed easily blinded pain-provocative proce-

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dures. Injection of adrenergic agonists near an amputation stump neuroma¹³ or into hyperalgesic skin in CRPS type I increased pain.¹⁴ A double-blind study showed that infiltration of phenylephrine or epinephrine into skin affected by postherpetic neuralgia exacerbated pain compared with saline.

Positive data from recent clinical experiments, as well as most of the animal data on sympathetically maintained pain, are limited to cases with peripheral nerve lesions, which represent a minority of the cases in which sympathetic blocks are used in the clinic. For this reason, great interest was recently aroused by three independent reports (including one from our group) that the pain and mechanical hyperalgesia caused by the application of strong capsaicin preparations to the skin of normal volunteers was increased by adrenergic agonists¹⁶ and decreased by systemic¹⁷ or local administration of phentolamine.¹⁸ Capsaicin, the pungent ingredient in chili peppers, is a favorite experimental stimulus among pain researchers because its initial application causes massive discharge of peripheral pain nociceptors that carry vanilloid receptors and temporarily sensitize both peripheral and central sensory neurons. These three reports suggested that this ability of capsaicin to produce sympathetically modulated pain in most human subjects supports the plausibility of a sympathetic component to chronic pain and provides a model in which the specific mechanisms of this interaction might be worked out. In the face of the claim by Ochoa's group and by Schott that the emperor had no clothes, this finding provided a vestige of modesty.

Alas, Baron et al.¹⁹ strip that fig leaf away with their elegant study reported in this issue of *Neurology*. As in the previous studies, they produced pain and allodynia by applying capsaicin to the forearm skin of normal volunteers. Instead of pharmacologic modulators of sympathetic neurotransmission, they used natural stimulation of the subjects' sympathetic system by heating or cooling with a thermal suit. Marked increases and decreases in sympathetic efferent activity were confirmed by measurements of skin blood flow and temperature in the index finger of the capsaicin-treated arm, but no changes in spontaneous pain or hyperalgesia occurred in the capsaicin-treated area. These results, based on maximum natural stimulation of the subjects' own sympathetic system, refute those based on pharmacologic manipulations. The contradiction between the current results and the three positive capsaicin studies raises concerns about the validity of the pharmacologic tests in the capsaicin model and in patients. At the concentrations reached, adrenergic agonists may have pain-promoting actions, and phentolamine may have pain-relieving actions that go beyond excitation or blockade of adrenergic receptors.

It would be a mistake to abandon the sympathetic pain hypothesis on the basis of a few negative trials just when less toxic ablative interventions, such as biological regulation of adrenergic receptors or su-

perspecific adrenergic antagonists, may be within reach. Investigators not as invested in the current polemic should examine whether there is a specific response to sympathetic block in patients with nerve lesions or CRPS type I, reported to be rare or nonexistent by Verdugo et al.⁷ Randomized, double-blind controls with multiple provocative and inhibitory tests should be used, including natural perturbations of the sympathetic system as illustrated by Baron et al.,¹⁹ and correlated with the long-term outcomes of treatments that modify sympathetic activity.

If neurologists are unable to enter patients into controlled clinical trials, should they still use sympathoablative treatments on patients with nerve injury or CRPS type I? In fairness to the advocates of sympathetic blockade, a large proportion of accepted surgical and regional anesthetic procedures have not been validated by randomized trials. No one questions the observation that stellate ganglion or lumbar sympathetic blocks often have powerful pain-relieving effects that far outlast the expected 6- to 12-hour effect of the local anesthetic. Such relief often makes possible vigorous physical therapy, a key component in rehabilitation of the pain patient. Whether pain relief is due to sympathetic blockade, placebo, or spillover of anesthetic onto somatic nerves does not matter unless one tries to infer whether a permanent ablation of the sympathetic chain is indicated. The current critique (reviewed above) raises concerns about the benefit-risk ratio of permanent sympathetic ablation, and about how one might identify patients likely to get pain relief from the more invasive procedures. Response to several high-dose phentolamine infusions compared with placebo under double-blind conditions appears to be the best available criterion until additional diagnostic tests, including sympathetic augmentations, have been better validated, although the caveats of Baron et al. about the possible nonspecific effects of phentolamine remain worrisome.¹⁹

Sympathetically maintained pain was once a reigning hypothesis in pain research, but does the emperor now have no clothes? On his recent visits to the clinic, we think he looked pretty close to naked, but that is because sartorial standards have been rising. More human studies with the rigor exemplified by Baron et al. may give him what he lacks—perhaps even a hot and cold running water suit.

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Editorial

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Restless legs syndrome

A disease in search of identity

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Restless legs syndrome (RLS) is not rare but is rarely diagnosed by clinicians. Articles published in this and recent issues of *Neurology* reflect the growing interest in this area, fueled by new findings from pharmacologic, electrophysiologic, and neuroimaging studies. Despite a lucid description over 50 years ago by Ekbom,¹ there is considerable misconception about RLS. Persons with RLS, even when their symptoms are quite troublesome or disabling, often do not seek medical attention, or the symptoms are wrongly attributed by physicians to nervousness, insomnia, stress, muscle cramps, arthritis, or a simple consequence of aging. Although no medical specialty has claimed rights of ownership to RLS, the correct diagnosis is usually made by neurologists, movement disorder experts, and sleep specialists.

The poor recognition and frequent misdiagnosis have hampered epidemiologic studies in RLS. Esti-

mated prevalence rates vary widely, from 1% to 15%, but the true prevalence is probably close to 5% in the general population and considerably higher in the elderly. One study of 133 patients with typical RLS found the mean age at onset to be 27.2 years and the presence of RLS in at least one first-degree relative in 63% of cases.² Future epidemiologic studies will be aided by the diagnostic criteria formulated by the International Restless Legs Syndrome Study Group (IRLSSG).³ The minimal criteria include the following: 1) an intense, irresistible urge to move the legs, usually associated with sensory complaints (paresthesia or dysesthesia); 2) motor restlessness; 3) worsening of symptoms at rest and relief with motor activation; and 4) increased severity in the evening or at night. Periodic limb movements in sleep (PLMS), detected by an overnight sleep study and present in at least 80% of patients with RLS, is the

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only laboratory abnormality typically associated with RLS. There is, however, night-to-night variability, which makes it problematic to use PLMS as a confirmatory finding. Therefore, other laboratory diagnostic criteria are needed. Neurophysiologic changes, such as blink reflex and H-reflex abnormalities, startle reflex and spinal flexor reflex hyperactivity, and magnetic brain stimulation finding of motor cortex disinhibition, have been noted in some patients with RLS, but their sensitivity and specificity have yet to be determined. As there are no physiologic markers for RLS, the severity is best measured by the unified rating scale recently developed, but not yet validated, by the IRLSSG.

Validated diagnostic criteria will allow rigorous genetic studies in RLS. Up to one-third to one-half of RLS cases are transmitted as an autosomal dominant trait. There are no twin studies and linkage has not been established in RLS. In this issue of *Neurology*, the observation by Gemignani et al.⁴ of RLS in 10 of 27 (37%) patients with Charcot-Marie-Tooth neuronal type (CMT2) and in 0 of 17 with CMT1 support the conclusion that a disorder of the sensory input may play a role in the pathogenesis of RLS. The findings also suggest that CMT2 associated with RLS represents a discreet genetic subgroup. Autosomal dominant cerebellar ataxia may be another genetic disorder associated with RLS. Schols et al.,⁵ for example, observed RLS in 45% of 89 patients with familial ataxia, of whom 59 had the SCA3 type. These studies suggest genetic as well as phenotypic heterogeneity in RLS.

Primary (sporadic or genetic) RLS may be difficult to differentiate from RLS associated with neuropathy, uremia, iron deficiency, or other disorders (secondary RLS). One study⁶ found that 15 of 41 patients with RLS had electrophysiologic evidence of polyneuropathy or radiculopathy, although only 7 of the 15 showed clinical signs of neuropathy. Positive family history of RLS was more common in the primary than in the secondary forms.⁶ Another study⁷ involving a consecutive series of patients with polyneuropathy, however, documented only a 5% frequency of RLS. Sural nerve biopsy findings in 7 of 8 patients with primary RLS were consistent with an axonal neuropathy,⁸ although there may be other explanations. It is not clear why some patients with peripheral neuropathy develop symptoms of RLS whereas others do not.

There have been scattered reports of deficiencies—such as vitamin B₁₂, folate, magnesium, and iron—causing secondary RLS. O’Keefe et al.⁹ first reported low iron, measured by ferritin levels, in RLS patients. Iron is needed as a cofactor for tyrosine hydroxylase, the rate limiting enzyme in the synthesis of dopamine; therefore, iron deficiency may impair the normal production of dopamine. Furthermore, D2 receptor is an iron containing protein and, hence, iron deficiency may impair the normal function of D2 receptors. Whether iron deficiency is primarily responsible for causing RLS or whether it

simply aggravates or triggers RLS symptoms in patients who are already predisposed to develop RLS, however, remains to be determined.¹⁰

Pharmacologic studies have provided indirect evidence of dopaminergic abnormality in RLS. Levodopa,¹¹ for example, nearly always relieves, and dopamine antagonists often worsen, RLS symptoms. Exacerbation of RLS in the evening when dopamine activity is at its lowest level, and exacerbation with iron deficiency, which may interfere with the production of dopamine, are further evidence in support of impaired dopamine transmission in RLS. In this issue of *Neurology*, Montplaisir et al.,¹² using pramipexole, and Wetter et al.,¹³ using pergolide, confirmed the findings of other recent controlled studies^{14,15} that dopamine agonists are effective in the treatment of RLS. Montplaisir et al.¹² found that, compared with placebo, pramipexole, a D2 and D3 receptor agonist, was associated with a robust reduction in the PLMS index at doses of 0.375 to 0.75 mg/day. Furthermore, pramipexole markedly alleviated leg discomfort at bedtime and during the night as measured by home questionnaires. The study by Wetter et al.¹³ showed that 0.5 mg of pergolide 2 hours before bedtime significantly reduced PLMS and prolonged total sleep time by 2 hours compared with placebo. In addition to the sleep benefits, pergolide produced a meaningful improvement in quality of life. It is not clear which of the available dopamine agonists is most potent against the symptoms of RLS. Furthermore, longitudinal studies are needed to determine whether the benefits from dopamine agonists are more sustained than those derived from levodopa alone. Opiates, which are beneficial in RLS, may also act through the dopaminergic system, as evidenced by the observation that the beneficial effects of opiates may be blocked by pimizide,¹⁶ a dopamine antagonist. The role of opiates in RLS is further supported by the finding that naloxone, an opiate antagonist, reverses the benefits of opiates.¹⁷

Recent imaging studies using functional MRI (fMRI) and PET scanning have drawn attention to the possible role of upper brainstem and diencephalon in the pathogenesis of RLS. Turjanski et al.¹⁸ provide evidence of striatal dopamine receptor dysfunction in RLS. In this issue of *Neurology*, they report that patients with RLS have normal ¹⁸F-dopa striatal (putamen) uptake, but D2 binding, determined by ¹¹C raclopride PET scan, is mildly (10%), but significantly, reduced in the putamen. These findings agree with those of Staedt et al.,¹⁹ who found reduced striatal D2 binding using ¹²³I-IBZM (Iodobenzamide) SPECT in patients with PLMS. Turjanski et al.¹⁸ suggested that reduced putamen D2 binding indicated an increase in endogenous dopamine in RLS. In a study by Montplaisir et al.,²⁰ levodopa-responsive RLS patients showed increased CSF levels of dopamine and its metabolite homovanillic acid, supporting the hypothesis of increased dopamine release or turnover. Turjanski et al.¹⁸ further suggested that reduced putamen D2 binding in RLS could be due to decreased central

dopaminergic transmission secondary to prefrontal overactivity, which inversely correlates with striatal dopamine transmission. However, absence of prefrontal overactivity by fMRI in RLS argues against this hypothesis. A recent fMRI study²¹ showed that RLS patients with only sensory symptoms had activation of bilateral cerebellum and contralateral thalamus, whereas those with the additional features of periodic limb movements in wakefulness also showed increased activation of the red nuclei and of brainstem sites in the region of the reticular formation.

The role of impaired central dopaminergic transmission in RLS is further suggested by the overlap between some symptoms of PD and RLS. For example, akathisia—an inner feeling of restlessness frequently associated with complex stereotypic movements—may be seen in patients with PD as well as during chronic treatment with dopamine receptor blockers. In contrast to RLS, akathisia usually does not have diurnal variations and is not typically associated with paresthesias or dysesthesias. It is possible, however, that separate dopaminergic systems are involved in PD and RLS. Whereas the nigrostriatal dopaminergic system is primarily involved in PD, other dopaminergic systems, such as the diencephalic-spinal dopaminergic system, may be involved in RLS.²² In support of this hypothesis is the observation that diencephalic A11 dopaminergic cells project to the spinal cord and that lesions of this midbrain region with 6-hydroxydopamine in a rat produce behavioral features similar to RLS.²³

Several electrophysiologic studies have suggested that brainstem or the spinal cord may be the site of generation for PLMS in RLS. Absence of cortical prepotentials on back-averaging,²⁴ normal EEG, and absence of high amplitude cortical potentials in the somatosensory evoked response argue against these movements being of cortical origin. Several studies of patients with RLS or PLMS, however, have found some support for the presence of hyperexcitable brainstem reflexes. Briellmann et al.²⁵ and Wechsler et al.,²⁶ for example, found enhanced excitability of the late component of the blink reflex. In contrast, Bucher et al.²⁷ found no abnormalities of the blink reflex in such patients. These studies, however, need to be repeated during both the symptomatic and asymptomatic periods. In this issue of *Neurology*, Tergau et al.²⁸ studied intracortical inhibition in 18 RLS patients and 17 age-matched controls by using paired transcranial magnetic stimulation technique. They found a significant reduction of intracortical inhibition in RLS, suggesting motor cortex disinhibition, possibly as a result of subcortical mechanisms.

The possibility remains that some involuntary movements, including PLMS, may be of spinal or propriospinal origin. The presence of PLMS in patients with spinal cord lesions, including complete thoracic transection,^{29,30} provides support for the location of a generator for PLMS in the spinal cord. It is well recognized that generators for cyclical motor behaviors (e.g., locomotion) exist in the isolated spi-

nal cord.³¹ Thus, suprasegmental spinal cord lesions may disinhibit the lumbosacral spinal cord generator to produce PLMS. A recent study using flexor reflex response³² in seven patients with RLS–PLMS and in 10 normal controls provided evidence of enhanced excitability of the spinal cord mechanisms, facilitated by the loss of supraspinal inhibition. In another study,³³ the pattern of muscle activation in 18 patients with RLS–PLMS suggested a propriospinal mechanism. Finally, some preliminary studies support the presence of individual limb oscillators that may be capable of producing PLMS.³⁴

Although the studies reviewed here do not put RLS to rest, they signal an exciting era of clinical and basic research that promises to provide new insights into the pathophysiology of RLS–PLMS. Future clinical, epidemiologic, and genetic studies should build on the existing knowledge by designing controlled studies of well-defined populations of patients using modern neurophysiologic, functional, metabolic, biochemical, and neuroimaging techniques. Because RLS patients are peculiarly susceptible to placebo effects and natural remission of RLS symptoms occurs for prolonged periods in some patients, double-blind, placebo-controlled, multicenter, clinical trials are needed to find the best treatments for these patients. Finally, because of the lack of pathologic material and, consequently, of any pathologic–clinical correlates, a mechanism needs to be developed that would facilitate the harvesting, storing, and processing of neural tissues, including brain, spinal cord, and peripheral nerves, from patients with RLS. A detailed morphologic and biochemical examination of such tissue would undoubtedly further our knowledge about this common and mysterious disorder.

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