TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

MEDICAL GRAND ROUNDS

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Updates in the medical management of Parkinson disease

ABSTRACT

Most, if not all, currently available drugs for Parkinson disease address dopaminergic loss and relieve symptoms. However, their adverse effects can be limiting and they do not address disease progression. Moreover, nonmotor features of Parkinson disease such as depression, dementia, and psychosis are now recognized as important and disabling. A cure remains elusive. However, promising interventions and agents are emerging. As an example, people who exercise regularly are less likely to develop Parkinson disease, and if they develop it, they tend to have slower progression.

KEY POINTS

Parkinson disease can usually be diagnosed on the basis of clinical features: slow movement, resting tremor, rigidity, and asymmetrical presentation, as well as alleviation of symptoms with dopaminergic therapy.

Early disease can be treated with levodopa, dopamine agonists, anticholinergics, and monoamine oxidase-B inhibitors.

Advanced Parkinson disease may require a catechol-*O*-methyltransferase (COMT) inhibitor, apomorphine, and amantadine (Symmetrel). Side effects include motor fluctuations, dyskinesias, and cognitive problems.

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More than a dozen drugs have been approved by the US Food and Drug Administration (FDA) for treating Parkinson disease, and more are expected in the near future. Many are currently in clinical trials, with the goals of finding ways to better control the disease with fewer adverse effects and, ultimately, to provide neuroprotection.

This article will review the features of Parkinson disease, the treatment options, and the complications in moderate to advanced disease.

PARKINSON DISEASE IS MULTIFACTORIAL

Although the cure for Parkinson disease is still elusive, much has been learned over the nearly 200 years since it was first described by James Parkinson in 1817. It is now understood to be a progressive neurodegenerative disease of multifactorial etiology: although a small proportion of patients have a direct inherited mutation that causes it, multiple genetic predisposition factors and environmental factors are more commonly involved.

The central pathology is dopaminergic loss in the basal ganglia, but other neurotransmitters are also involved and the disease extends to other areas of the brain.

CARDINAL MOTOR SYMPTOMS

In general, Parkinson disease is easy to identify. The classic patient has[1]:

- **Tremor at rest,** which can be subtle—such as only involving a thumb or a few fingers—and is absent in 20% of patients at presentation.
- **Rigidity,** which is felt by the examiner rather than seen by an observer.

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- **Bradykinesia** (slow movements), which is characteristic of all Parkinson patients.
- **Gait and balance problems,** which usually arise after a few years, although occasionally patients present with them. Patients typically walk with small steps with occasional freezing, as if their foot were stuck. Balance problems are the most difficult to treat among the motor problems.

Asymmetry of motor problems is apparent in 75% of patients at presentation, although problems become bilateral later in the course of the disease.

NONMOTOR FEATURES CAN BE MORE DISABLING

Although the archetypical patient is an elderly man with shaking, masked facies, and slow gait, these features are only the tip of the iceberg of the syndrome, and nonmotor features are often more disabling (TABLE 1).

Pain is common, but years ago it was not recognized as a specific feature of Parkinson disease. The pain from other conditions may also worsen.

Fatigue is very common and, if present, is usually one of the most disabling features.

Neuropsychiatric disturbances are among the most difficult problems, and they become increasingly common as motor symptoms are better controlled with treatment and patients live longer.

TABLE 1

Nonmotor features of Parkinson disease

Craniofacial features
Masked facies (reduced facial expression)
Sialorrhea (drooling; may appear decades before the onset of tremor)
Anosmia (loss of sense of smell)
Hypophonia (soft speech)
Dysarthria (difficulty pronouncing words)
Dysphagia (trouble swallowing)

Sensory features
Paresthesia (sensations of tingling, prickling, or numbness)
Pain

Autonomic features
Urinary disturbance—urgency, nocturia
Constipation
Sexual dysfunction

Neuropsychiatric features
Depression
Anxiety
Apathy
Dementia
Psychosis

Other
Fatigue
Sleep disturbance
Seborrheic dermatitis
Eye abnormalities

INCREASINGLY PREVALENT AS THE POPULATION AGES

Parkinson disease can present from the teenage years up to age 90, but it is most often diagnosed in patients from 60 to 70 years old (mean onset, 62.5 years). A different nomenclature is used depending on the age of onset:

- 10 to 20 years: juvenile-onset
- 21 to 40 years: young-onset.

Parkinson disease is now an epidemic, with an estimated 1 million people having it in the United States, representing 0.3% of the population and 1% of those older than 60 years.[2] More people can be expected to develop it as our population ages in the next decades. It is estimated that in 2040 more people will die from Parkinson disease, Alzheimer disease, and amyotrophic lateral sclerosis (all of which are neurodegenerative diseases) than from kidney cancer, malignant melanoma, colon cancer, and lung cancer combined.

Classic parkinsonian motor symptoms are often just the tip of the iceberg

DIAGNOSIS IS STILL MAINLY CLINICAL

The diagnosis of Parkinson disease remains clinical. In addition to the motor features, the best test is a clear response to dopaminergic treatment with levodopa. If all these features are present, the diagnosis of Parkinson disease is usually correct.[3]

Imaging useful in select patients

The FDA recently approved a radiopharmaceutical contrast agent, DaTscan, to use with single-photon emission computed tomography (SPECT) to help diagnose Parkinson disease.

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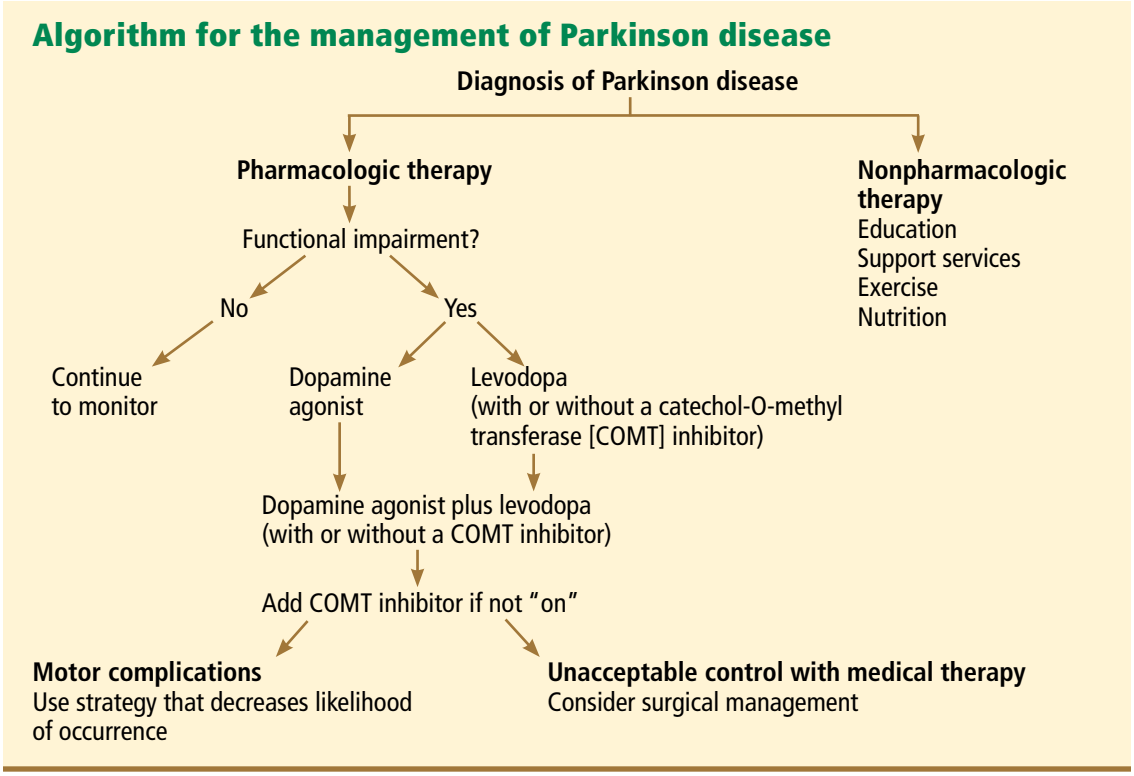

FIGURE 1

SPECT imaging with DaTscan is approved to diagnose Parkinson disease

DaTscan is a dopamine transporter ligand that tags presynaptic dopaminergic neurons in the basal ganglia; a patient with Parkinson disease has less signal.

The test can be used to distinguish parkinsonian syndromes from disorders that can mimic them, such as essential tremor or a psychogenic disorder. However, it cannot differentiate various Parkinson-plus syndromes (see below) such as multiple system atrophy or progressive nuclear palsy. It also cannot be used to detect drug-induced or vascular parkinsonism.

Check for Wilson disease or brain tumors in young or atypical cases

For most patients, no imaging or blood tests are needed to make the diagnosis. However, in patients younger than 50, Wilson disease, a rare inherited disorder characterized by excess copper accumulation, must be considered. Testing for Wilson disease includes serum ceruloplasmin, 24-hour urinary copper excretion, and an ophthalmologic slit-lamp examination for Kaiser-Fleischer rings.

For patients who do not quite fit the picture of Parkinson disease, such as those who have spasticity with little tremor, or who have a minimal response to levodopa, magnetic resonance imaging should be done to see if a structural lesion is present.

Consider secondary parkinsonism

Although idiopathic Parkinson disease is by far the most common form of parkinsonism in the United States and in most developing countries, secondary causes must also be considered in a patient presenting with symptoms of parkinsonism. They include:

- Dopamine-receptor blocking agents: metoclopramide (Reglan), prochlorperazine (Compazine), haloperidol (Haldol), thioridazine (Mellaril), risperidone (Risperdal), olanzapine (Zyprexa)
- Strokes in the basal ganglia
- Normal pressure hydrocephalus.

Parkinson-plus syndromes

Parkinson-plus syndromes have other features in addition to the classic features of idiopathic Parkinson disease. They occur commonly and can be difficult to distinguish from Parkinson disease and from each other.

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Parkinson-plus syndromes include:

- Progressive supranuclear palsy
- Multiple system atrophy
- Corticobasal degeneration
- Lewy body dementia.

Clinical features that suggest a diagnosis other than Parkinson disease include poor response to adequate dosages of levodopa, early onset of postural instability, axial more than appendicular rigidity, early dementia, and inability to look up or down without needing to move the head (supranuclear palsy).[4]

MANAGING PARKINSON DISEASE

Most general neurologists follow an algorithm for treating Parkinson disease (FIGURE 1).

Nonpharmacologic therapy is very important. Because patients tend to live longer because of better treatment, education is particularly important. The benefits of exercise go beyond general conditioning and cardiovascular health. People who exercise vigorously at least three times a week for 30 to 45 minutes are less likely to develop Parkinson disease and, if they develop it, they tend to have slower progression.

Prevention with neuroprotective drugs is not yet an option but hopefully will be in the near future.

Drug treatment generally starts when the patient is functionally impaired. If so, either levodopa or a dopamine agonist is started, depending on the patient's age and the severity of symptoms. With increasing severity, other drugs can be added, and when those fail to control symptoms, surgery should be considered.

Deep brain stimulation surgery can make a tremendous difference in a patient's quality of life. Other than levodopa, it is probably the best therapy available; however, it is very expensive and is not without risks.

Levodopa: The most effective drug, until it wears off

All current drugs for Parkinson disease activate dopamine neurotransmission in the brain. The most effective—and the cheapest—is still carbidopa/levodopa (Sinemet, Parcopa, Atamet). Levodopa converts to dopamine both peripherally and after it crosses the blood-brain barrier. Carbidopa prevents the peripheral conversion of levodopa to dopamine, reducing the peripheral adverse effects of levodopa, such as nausea and vomiting. The combination drug is usually given three times a day, with different doses available (10 mg carbidopa/100 mg levodopa, 25/100, 50/200, and 25/250) and as immediate-release and controlled-release formulations as well as an orally dissolving form (Parcopa) for patients with difficulty swallowing.

The major problem with levodopa is that after 4 to 6 years of treatment, about 40% of patients develop motor fluctuations and dyskinesias.[5] If treatment is started too soon or at too high a dose, these problems tend to develop even earlier, especially among younger patients.

Motor fluctuations can take many forms: slow wearing-off, abrupt loss of effectiveness, and random on-and-off effectiveness ("yo-yo-ing").

Dyskinesias typically involve constant chorea (dance-like) movements and occur at peak dose. Although chorea is easily treated by lowering the dosage, patients generally prefer having these movements rather than the Parkinson symptoms that recur from underdosing.

Deep brain stimulation can make a tremendous difference in quality of life, but it is expensive and not without risks

Dopamine agonists may be best for younger patients in early stages

The next most effective class of drugs are the dopamine agonists: pramipexole (Mirapex), ropinirole (Requip), and bromocriptine (Parlodel). A fourth drug, pergolide, is no longer available because of associated valvular heart complications. Each can be used as monotherapy in mild, early Parkinson disease or as an additional drug for moderate to severe disease. They are longer-acting than levodopa and can be taken once daily. Although they are less likely than levodopa to cause wearing-off or dyskinesias, they are associated with more nonmotor side effects: nausea and vomiting, hallucinations, confusion, somnolence or sleep attacks, low blood pressure, edema, and impulse control disorders.

Multiple clinical trials have been conducted to test the efficacy of dopamine agonists vs levodopa for treating Parkinson disease.[6–9] Almost always, levodopa is more effective but in-

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volves more wearing-off and dyskinesias. For this reason, for patients with milder parkinsonism who may not need the strongest drug available, trying one of the dopamine agonists first may be worthwhile.

In addition, patients younger than age 60 are more prone to develop motor fluctuations and dyskinesias, so a dopamine agonist should be tried first in patients in that age group. For patients over age 65 for whom cost may be of concern, levodopa is the preferred starting drug.

Anticholinergic drugs for tremor

Before 1969, only anticholinergic drugs were available to treat Parkinson disease. Examples include trihexyphenidyl (Artane, Trihexane) and benztropine (Cogentin). These drugs are effective for treating tremor and drooling but are much less useful against rigidity, bradykinesia, and balance problems. Side effects include confusion, dry mouth, constipation, blurred vision, urinary retention, and cognitive impairment.

Anticholinergics should only be considered for young patients in whom tremor is a large problem and who have not responded well to the traditional Parkinson drugs. Because tremor is mostly a cosmetic problem, anticholinergics can also be useful for treating actors, musicians, and other patients with a public role.

For a younger patient or one with milder symptoms, trying a dopamine agonist first may be worthwhile

Monoamine oxidase B inhibitors are well tolerated but less effective

In the brain, dopamine is broken down by monoamine oxidase B (MAO-B); therefore, inhibiting this enzyme increases dopamine's availability. The MAO-B inhibitors selegiline (Eldepryl, Zelapar) and rasagiline (Azilect) are effective for monotherapy for Parkinson disease but are not as effective as levodopa. Most physicians feel MAO-B inhibitors are also less effective than dopamine agonists, although double-blind, randomized clinical trials have not proven this.[6,10,11]

MAO-B inhibitors have a long half-life, allowing once-daily dosing, and they are very well tolerated, with a side-effect profile similar to that of placebo. As with all MAO inhibitors, caution is needed regarding drug and food interactions.

EFFECTIVE NEUROPROTECTIVE AGENTS REMAIN ELUSIVE

Although numerous drugs are now available to treat the symptoms of Parkinson disease, the ability to slow the progression of the disease remains elusive. The only factor consistently shown by epidemiologic evidence to be protective is cigarette smoking, but we don't recommend it.

A number of agents have been tested for neuroprotective efficacy:

Coenzyme Q10 has been tested at low and high dosages but was not found to be effective.

Pramipexole, a dopamine agonist, has also been studied without success.

Creatine is currently being studied and shows promise, possibly because of its effects on complex-I, part of the electron transport chain in mitochondria, which may be disrupted in Parkinson disease.

Inosine, which elevates uric acid, is also promising. The link between high uric acid and Parkinson disease was serendipitously discovered: when evaluating numerous blood panels taken from patients with Parkinson disease who were in clinical trials (using what turned out to be ineffective agents), it was noted that patients with the slowest progression of disease tended to have the highest uric acid levels. This has led to trials evaluating the effect of elevating uric acid to a pre-gout threshold.

Calcium channel blockers may be protective, according to epidemiologic evidence. Experiments involving injecting isradipine (DynaCirc) in rat models of Parkinson disease have indicated that the drug is promising.

Rasagiline: Protective effects still unknown

A large study of the neuroprotective effects of the MAO-B inhibitor rasagiline has just been completed, but the results are uncertain.[12] A unique "delayed-start" clinical trial design was used to try to evaluate whether this agent that is known to reduce symptoms may also be neuroprotective. More than 1,000 people with untreated Parkinson disease from 14 countries were randomly assigned to receive rasagiline (the early-start group) or placebo (the delayed-start group) for 36 weeks. Afterward, both groups were given rasagiline for another 36 weeks. Rasagiline was given in a daily dose of either 1 mg or 2 mg.

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The investigators anticipated that if the benefits of rasagiline were purely symptomatic, the early- and delayed-start groups would have equivalent disease severity at the end of the study. If rasagiline were protective, the early-start group would be better off at the end of the study. Unfortunately, the results were ambiguous: the early- and delayed-start groups were equivalent at the end of the study if they received the 2-mg daily dose, apparently indicating no protective effect. But at the 1-mg daily dose, the delayed-start group developed more severe disease at 36 weeks and did not catch up to the early-start group after treatment with rasagiline, apparently indicating a protective benefit. As a result, no definitive conclusion can be drawn.

EXTENDING TREATMENT EFFECTS IN ADVANCED PARKINSON DISEASE

For most patients, the first 5 years after being diagnosed with Parkinson disease is the "honeymoon phase," when almost any treatment is effective. During this time, patients tend to have enough surviving dopaminergic neurons to store levodopa, despite its very short half-life of only 60 minutes.

As the disease progresses, fewer dopaminergic neurons survive, the therapeutic window narrows, and dosing becomes a balancing act: too much dopamine causes dyskinesias, hallucinations, delusions, and impulsive behavior, and too little dopamine causes worsening of Parkinson symptoms, freezing, and wearing-off, with ensuing falls and fractures. At this stage, some patients are prescribed levodopa every 1.5 or 2 hours.

Drugs are now available that extend the half-life of levodopa by slowing the breakdown of dopamine.

Catechol-*O*-methyltransferase (COMT) inhibitors—including tolcapone (Tasmar) and entacapone (Comtan) (also available as combined cardidopa, entacapone, and levodopa [Stalevo])—reduce off periods by about 1 hour per day.[13] Given that the price is about $2,500 per year, the cost and benefits to the patient must be considered.[14–17]

Rasagiline, an MAO-B inhibitor, can also be added to levodopa to extend the "on" time for about 1 hour a day and to reduce freezing of gait. Clinical trials have shown it to be well tolerated, although common side effects include worsening dyskinesias and nausea.[18,19]

Apomorphine (Apokyn) is a dopamine agonist given by subcutaneous injection, allowing it to avoid first-pass metabolism by the liver. The benefits start just 10 minutes after injection, but only last for about 1 hour. It is a good option for rescue therapy for patients who cannot swallow or who have severe, unpredictable, or painful off-periods. It is also useful for situations in which it is especially inconvenient to have an off-period, such as being away from home.

Many agents have been tested for improving the off-period, but most work for about 1 to 2 hours, which is not nearly as effective as deep brain stimulation.

Managing dyskinesias

Dyskinesias can be managed by giving lower doses of levodopa more often. If wearing-off is a problem, a dopamine agonist or MAO-B inhibitor can be added. For patients at this stage, a specialist should be consulted.

Amantadine (Symmetrel), an *N*-methyl-D-aspartate (NMDA) receptor antagonist and dopamine-releasing agent used to treat influenza, is also effective against dyskinesias. Adverse effects include anxiety, insomnia, nightmares, anticholinergic effects, and livedo reticularis.[20,21]

Deep brain stimulation is the best treatment for dyskinesias in a patient for whom the procedure is appropriate and who has medical insurance that covers it.

Epidemiologic studies show that smoking may offer neuroprotection in Parkinson disease, but we don't recommend it

NONMOTOR FEATURES OF PARKINSON DISEASE

Dementia: One of the most limiting nonmotor features

Often the most limiting nonmotor feature of Parkinson disease is dementia, which develops at about four to six times the rate for age-matched controls. At a given time, about 40% of patients with Parkinson disease have dementia, and the risk is 80% over 15 years of the disease.

If dementia is present, many of the drugs effective against Parkinson disease cannot be used because of exacerbating side effects. Treatment is mainly restricted to levodopa.

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The only FDA-approved drug to treat dementia in Parkinson disease is the same drug for Alzheimer disease, rivastigmine (Exelon). Its effects are only modest, and its cholinergic side effects may transiently worsen parkinsonian features.[22]

Psychosis: Also very common

About half of patients with Parkinson disease have an episode of hallucinations or delusions in their lifetime, and about 20% are actively psychotic at any time. Delusions typically have the theme of spousal infidelity. Psychosis is associated with a higher rate of death compared with patients with Parkinson disease who do not develop it. Rebound psychosis may occur on withdrawal of antipsychotic medication.[23–27]

Patients who develop psychosis should have a physical examination and laboratory evaluation to determine if an infection or electrolyte imbalance is the cause. Medications should be discontinued in the following order: anticholinergic drug, amantadine, MAO-B inhibitor, dopamine agonist, and COMT inhibitor. Levodopa and carbidopa should be reduced to the minimum tolerable yet effective dosages.

For a patient who still has psychosis despite a minimum Parkinson drug regimen, an atypical antipsychotic drug should be used. Although clozapine (Clozaril, FazaClo) is very effective without worsening parkinsonism, it requires weekly monitoring with a complete blood count because of the small (< 1%) risk of agranulocytosis. For that reason, the first-line drug is quetiapine (Seroquel). Most double-blind studies have not found it to be effective, yet it is the drug most often used. No other antipsychotic drugs are safe to treat Parkinson psychosis.

Many patients with Parkinson disease who are hospitalized become agitated and confused soon after they are admitted to the hospital. The best treatment is quetiapine if an oral drug can be prescribed. A benzodiazepine—eg, clonazepam (Klonopin), lorazepam (Ativan), diazepam (Valium)—at a low dose may also be effective. Haloperidol, risperidone, and olanzapine should not be given, as they block dopamine receptors and worsen rigidity.

Depression occurs in about half of patients with Parkinson disease

Mood disturbances

Depression occurs in about half of patients with Parkinson disease and is a significant cause of functional impairment. About 25% of patients have anxiety, and 20% are apathetic.

Depression appears to be secondary to underlying neuroanatomic degeneration rather than a reaction to disability.[28] Fortunately, most antidepressants are effective in patients with Parkinson disease.[29,30] Bupropion (Wellbutrin) is a dopamine reuptake inhibitor and so increases the availability of dopamine, and it should also have antiparkinsonian effects, but unfortunately it does not. Conversely, selective serotonin reuptake inhibitors (SSRIs) theoretically can worsen or cause parkinsonism, but evidence shows that they are safe to use in patients with Parkinson disease. Some evidence indicates that tricyclic antidepressants may be superior to SSRIs for treating depression in patients with Parkinson disease, so they might be the better choice in patients who can tolerate them.

Compulsive behaviors such as punding (prolonged performance of repetitive, mechanical tasks, such as disassembling and reassembling household objects) may occur from levodopa.

In addition, impulse control disorders involving pathologic gambling, hypersexuality, compulsive shopping, or binge eating occur in about 8% of patients with Parkinson disease taking dopamine agonists. These behaviors are more likely to arise in young, single patients, who are also more likely to have a family history of impulsive control disorder.[31]

THE FUTURE OF DRUG THERAPY

Clinical trials are now testing new therapies that work the traditional way through dopaminergic mechanisms, as well as those that work in novel ways.

A large international trial is studying patients with newly diagnosed Parkinson disease to try to discover a biomarker. Parkinson disease is unlike many other diseases in that physicians can only use clinical features to measure improvement, which is very crude. Identifying a biomarker will make evaluating and monitoring treatment a more exact science, and will lead to faster development of effective treatments.

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