

ON THE BRAIN



Present and Future Treatment of ADHD

We expect children to have occasional trouble sitting still, paying attention, following instructions, and obeying rules. But for some children, those problems are so pervasive and constant that they interfere with schoolwork, family life, and emotional and intellectual development. These children may be given a diagnosis of attention deficit/hyperactivity disorder, or ADHD for short.

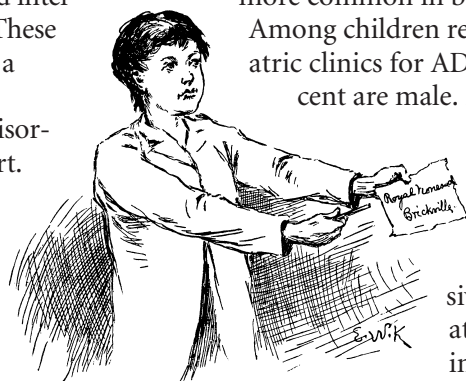
Restlessness or hyperactivity is the easiest symptom to notice. Children with ADHD may be difficult to hold and soothe even as infants. Later, they climb into medicine cabinets and rush into traffic. In a classroom, they fidget and squirm, tap their feet, shake their legs, and repeatedly jump up from their seats.

Impulsiveness is a related problem. Children with ADHD have a low tolerance for frustration and difficulty in suppressing their feelings. They cannot wait their turn and do not think before acting. In conversation, they interrupt, talk too much, too loud, and too fast, and may blurt out whatever comes to mind. They pester parents, teachers, and other children. Often they seem clumsy and accident-prone.

Even when not in motion or acting impulsively, these children are easily distracted — the attention deficit gives the diagnosis its name. It is hard for them to concentrate on one task at a time. They tune out conversations,

procrastinate, abandon unfinished projects, repeatedly make careless mistakes, and switch haphazardly between activities. Sometimes they convey the impression of deliberately ignoring advice, requests, and warnings.

The disorder is at least three times more common in boys than in girls. Among children referred to psychiatric clinics for ADHD, nearly 90 percent are male. Boys are more like-



ly to suffer from the most troubling symptoms — hyperactivity and impulsiveness. Lack of attention, especially in classrooms, is more often the main

problem for girls, who may be ignored because they seem to be simply day-dreaming or shy.

Diagnosis Proves Challenging

ADHD is diagnosed in 5–7% of children in the United States and accounts for half of all visits to child psychiatric clinics. However, it is important to be careful in diagnosing ADHD, because many people show some of the symptoms some of the time. A diagnosis of hyperactivity or

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Larry King Leads Symposium on Stroke for HMNI

Larry King was awarded The David Mahoney Prize at a dinner in his honor on October 23, 2000. The evening was a great success, with over 300 attendees. Prior to the dinner, there was a symposium on stroke, with an expert panel talking about the most up-to-date information regarding stroke. Larry King was the moderator of the panel and conducted it with his usual lively, focused, entertaining and stimulating style.

The three distinguished panelists were Dr. Anne Young, Chief of Neurology at Massachusetts General Hospital; Dr. Louis Kaplan, Director of the Cerebrovascular Unit at Beth Israel/Deaconess Medical Center, and Dr. Emilio Bizzi, Professor of Brain Sciences and Human Behavior at Massachusetts Institute of Technology. On the following pages is an excerpt of the symposium on stroke.

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attention deficit is not appropriate for every adult who seems lazy or disorganized, every child who is messy, runs around too much, defies authority, or receives lower grades than his parents think his abilities merit. Sometimes parents or teachers have unrealistic expectations. Some children who seem fidgety or easily distracted need nothing more than a different environment — smaller classes, better teaching, firmer discipline or more loving attention from their parents. Symptoms that resemble ADHD may also result from other conditions, including stress, anxiety, abuse and neglect, personality disorders and alcoholism (in adults), and mood disorders (in both children and adults).

Behavior may be inconsistent

Another source of confusion is inconsistency in the behavior of people with ADHD. A boy may be disruptive in a classroom but no trouble on the playground, or his homework excellent one week and neglected the next. The symptoms are most likely to appear when a child has to persevere at a task or maintain a routine. Children with ADHD often seem to behave better when they are in small groups or there are few distractions. Often they show no symptoms at all in a novel situation when they are receiving close one-on-one attention — for example, an interview in a doctor's office.

Experts caution that children should not be given the diagnosis of ADHD unless they show signs of hyperactivity, impulsiveness, and distractibility in more than one environment — both classroom and home, for instance. And the diagnosis should not be applied casually. Requirements include a medical and psychiatric history and examination, tests of vision,

hearing, and speech, careful observations of the child's behavior, and, most important, thorough interviews with parents,

teachers, and the children themselves.

Information about the family's medical and psychiatric history and the quality of family life is also useful. For many children

and adults with ADHD, just finding out that there is a name for their problem is a great relief and the beginning of a solution.

Treatments with medication

The most consistent — and still controversial — finding of research on ADHD is that the stimulant drugs methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) often provide immediate relief for its most troublesome symptoms. In controlled experiments, these drugs are helpful for 70–90% of children five and older with ADHD. There are fewer studies of adults, but the results seem to

be similar. These drugs

have few side effects. Loss of appetite, stomachaches, nervousness, insomnia, and muscle twitches may develop, almost always temporarily.

Some children's growth is slightly slowed, but they catch up in a few years. Although stimulants are potentially addictive (and classified under the law as controlled substances), tolerance does not seem to develop with appropriate use, and there has not been much evidence that they are abused. In fact, children and adolescents are often reluctant to take them.

Other drugs are sometimes prescribed, usually when stimulants prove ineffective. The tricyclic antidepressant desipramine (Norpramin) and a relatively new antidepressant, bupropion

(Wellbutrin), have been found effective in controlled studies. Another drug that sometimes helps is clonidine (used chiefly to treat high blood pressure). Two more drugs, guanfacine and tomoxetine, are currently in clinical trials. These drugs are not thought to be addictive, but they all have more side effects than stimulants.

Other psychological disorders and ADHD

Even when effective, drugs may solve only part of the problem. Children with ADHD may have other behavioral difficulties as well. Many have learning disabilities, especially dyslexia (reading problems), or suffer from depression and anxiety. Dr. Joseph Biederman and his colleagues at Harvard Medical School have shown that other psychiatric disorders tend to accompany ADHD. Their studies of families have shown that ADHD and depression occur together within families beyond what one would expect by chance alone. Their research also suggests that ADHD and bipolar disorder (also known as manic

depressive disorder) often occur

together as well. Indeed,

about 20 percent of

children with

ADHD are

eventually

diagnosed

with bipolar

disorder.

And, as many

as a third are

not only hyperac-

tive and impulsive but

also aggressors who break rules

and hurt others — throwing tantrums,

picking fights, bullying, cheating, steal-

ing, and vandalizing property. Some of

this misbehavior may have the same

source as ADHD symptoms — a lack of

impulse control.

Therapy provides additional treatment

Behavior therapy or psychotherapy may also be helpful, particularly by enabling children or adults develop skills they have never learned, undo bad habits, or relieve accumulated frustration and shame. People with ADHD need struc-

Even when not in motion or acting impulsively, these children are easily distracted — the attention deficit gives the diagnosis its name.

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ture and routine in their lives, with many external prompts and cues and clear rules consistently applied. They can be taught to schedule, organize, avoid distractions, and reflect before acting. Cognitive therapy may help them dismiss self-defeating behaviors, and psychotherapy may be useful for anxiety and depression. Group therapy and mutual aid groups help them cope with chronic anger, alcoholism, and low self-esteem. They meet people with the same problems and share experiences. They learn how to listen, and they get a better idea of how their behavior affects others. Families can be involved through family therapy, mutual aid groups, and a program known as parent management training. Children with the disorder need close monitoring, predictable schedules, immediate tangible rewards and reprimands, repeated directions, and constant feedback. Sometimes tutoring or special classes are necessary. Under federal law, schools must accommodate ADHD as a disability.

Biological risk factors are inconclusive

Today most experts believe that ADHD results from subtle brain abnormalities. There is some evidence that ADHD is associated with birth complications — especially oxygen deprivation during pregnancy or delivery, premature birth, long labor, smoking during pregnancy, and brain injuries. ADHD is common in children with fetal alcohol syndrome, caused by heavy drinking during pregnancy. Certain rare diseases may also eventually provide clues to the biology of ADHD. Many of the symptoms were found in children who suffered brain damage during encephalitis epidemics in the 1920s. ADHD is also associated with a rare genetic disorder involving resistance to thyroid hormones. However, in most cases there is no obvious toxic influence, birth complication, or medical illness.

In the past, blame has been laid on food additives, sugar, vitamin deficiencies, allergies, radiation, lead, fluorescent lights, and even television. None of these theories have ever been con-

firmed, and they have little support today. All the evidence we have suggests that parents are not to blame either, although their responses can moderate or aggravate the symptoms.

Clues for the future

One focus of current neuroscience research relates to the development of brain circuits that are needed for self-control and planning ahead — what is sometimes called executive function. The brain scans of children with ADHD indicate a lower than average blood flow in the right front part of the brain (the prefrontal cortex), which governs planning, judgment, and problem-solving, and in the basal ganglia, which help to coordinate body movements and the sense of time. Some studies also show a lower than average volume of tissue in those regions. But these differences are subtle and are revealed only by statistical analysis.

Genetics also appears to play a role in the development of ADHD, as we discuss in Synapshot (*see page 5*). □

Larry King Leads Symposium on Stroke for HMNI

(Continued from page 1)

Larry King started off the symposium by asking the panelists to define what a stroke is and what causes it.

LK: What is a stroke and do we know what causes it?

Dr. Kaplan: A stroke is an injury to the vessels that supply blood to the brain. Every 58 seconds someone is having a stroke. This fact accounts for approximately 700,000 strokes every year in the United States.

Dr. Young: The majority of strokes are caused by small blood clots that dislodge from the heart or from the aorta, one of the major vessels coming out of the heart. These clots then lodge and clog the blood supply to the brain. An additional 25% of all strokes are caused by disease in small

blood vessels, mostly the result of high blood pressure (hypertension). The remaining 15% of strokes are caused by the build up plaque and other substances in the blood vessels that supply blood to the brain.

LK: If I were having a stroke, how would I know it?

Dr. Young: Symptoms include numbness or clumsiness of a limb; difficulty seeing, hearing or understanding. If you have such symptoms, don't go to bed. Go to the hospital!

LK: Have you seen patients actually recover from a stroke in a few hours?

Dr. Young: Absolutely and it's really quite spectacular. This is a direct result of some of the newer therapies that have been developed. For example, specially designed catheters (or tubes) have been used to break open

blood clots that have formed in the brain. The catheter is threaded into the clogged blood vessel and the clot is broken apart, just like one does to break apart clots in the heart. The brain, of course, is more complicated than the heart and the blood vessels are more convoluted, but this is still a very effective therapy. I have seen people who were comatose, due to a blood clot in the back of their brain, who after this therapy, were able to walk out of the hospital without any impairment.

LK: What are some of the recent advances used to treat stroke patients?

Dr. Kaplan: The most dramatic advance has been in our ability to give medications that dissolve clots in the brain once a stroke has begun and thus reduce the amount of damage.

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This medication (called tPA) can only be given for certain kinds of strokes, and must be given within 3 hours after the stroke, which is why we are starting to call strokes 'brain attacks'. In addition, we can now image the brain and its blood vessels with great accuracy. The goal is to target treatment based on each individual patient's needs and symptoms.

Dr. Young: Treatment is very individualized. For instance, we would prescribe a different treatment if the clot originated from the carotid artery (one of the major arteries that supplies blood to the brain) as opposed to the heart. In one instance you might do surgery; in the other, you might use the threadlike catheters we talked about earlier. There are also some very exciting new areas of research in which we're trying to find drugs that will actually protect the brain.

LK: Why is paralysis associated with stroke?

Dr. Bizzi: You experience paralysis if the blood supply is interrupted to the motor control region of the brain — the machinery that activates the muscles. The specific loss of function depends on where in the brain the clot or hemorrhage occurs. For instance, if the blood supply is interrupted to the auditory area of the brain, you get deafness. If the clot blocks supply to the visual region, there will be some defect in visual perception.

Dr. Kaplan: It is the very variety of symptoms that make it difficult for the average person to realize what is happening. You can have speech problems, memory loss, difficulty seeing, loss of balance and dizziness. The symptoms are quite heterogeneous.

We must start now to educate the public about the advances in the research and treatment of stroke, and about the ways to reduce the risk for having a stroke in the first place.
— Dr. Louis Kaplan



Dr. Louis Kaplan, Dr. Anne Young and Dr. Emilio Bizzi (from left to right)
Photo: Julie Skarratt

LK: Tell me about what can be done to help people who have had strokes — what do we know about rehabilitation?

Dr. Bizzi: I work with people who have had a stroke. Whether they can relearn is the core of my research. I do think that stroke patients can relearn.

LK: Can they relearn speech?

Dr. Bizzi: They can relearn speech to a certain extent. They can also relearn to move their body. There are two reasons why people can relearn. The brain is essentially malleable. That is, the capacity for learning exists in the brain even in later life. We can exploit this capacity for learning by recruiting new cells to do a task or trying to get cells that were doing something else learn new motor programs. These new programs can then do the job of the old ones that are now gone.

LK: Can we ever, in your opinion, completely cure strokes? Will we ever have a magic bullet?

Dr. Bizzi: There are new drugs that are being tested on animals and those are quite promising. One of the things

that happens with a stroke, is that the clot that blocks one artery causes the cells that used to get the oxygen from that blood vessel to die. But what happens afterwards, the following day, is that the death of those cells produce substances that damage additional cells. Now that damage probably can be prevented with drugs. Those drugs, so far, have been effective in animals. Right now they are too toxic in humans. But I am sure that sooner or later the right drug will be found.

Dr. Kaplan: We also try to prevent strokes by educating people about their individual risk. Factors that increase heart disease also increase risk for stroke. That means if you have high blood pressure, high cholesterol or diabetes, you are increased risk for stroke as well as heart disease.

LK: Now I'd like to take some questions from the audience.

Audience: With the convergence of biotechnology and what is called nanotechnology, bringing us closer to the day when small electronic devices can be worn, ingested or implanted, I was wondering if you could envisage a self sealing device that would thwart the stroke as it occurs.

Dr. Young: Researchers at Harvard and MIT are joining together to do research in this area. For instance, the technologies that were invented for national defense can now be used to make very tiny catheters, lasers and

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other potentially small sensors that can go not only into the small blood vessels of the brain and sense oxygen levels but may also have an effective function beyond that as well. So we are optimistic about the possibilities for the future.

Audience: Last spring I read about a study at the University of Alabama that used restraint therapy. Can you tell us something about that?

Dr. Bizzi: This study used a simple procedure to promote rehabilitation. They restricted the use of the good limb in a person with paralysis to make the other limb work harder. For example, they tied the functional arm of a stroke patient behind their back and forced him/her to use the paralyzed or semi-paralyzed arm. This approach was based on the well known fact that in order to reestablish motor skills you have to practice them. This is just a simple way to promote practice.

Audience: Can you tell us what we can do to help protect ourselves against stroke, especially if it runs in one's family.

Dr. Kaplan: You are correct that family history is important. It would be very important for you to know if your parents had a stroke, high blood pressure or diabetes. It would also be important for you to know what your cholesterol is and, of course, for you not to smoke. Other than that, just general health measures like staying thin, exercising, eating at the right times, are very helpful. The most important thing is for each person to know their own risk factors.

LK: Are you optimistic that strokes can be prevented?

Dr. Kaplan: Yes, very much so. I think we must start now though to educate the public about advances in the research and treatment of stroke, and about the things they can do to reduce their risk for having a stroke in the first place. □

SYNAPSHOT

Genetics and ADHD

There is considerable evidence that genes play a role in the development of ADHD. This is most clearly seen in studies of the relatives of children with the disorder. For instance, the parents, brothers, and sisters of children with the disorder have a rate of ADHD that is three to five times the average. The biological parents of adopted children with ADHD have a much higher rate of the disorder than do their adoptive parents, emphasizing that genetic transmission plays a role, above and beyond upbringing. Dr. Stephen Faraone and his colleagues at Harvard Medical School, were the first to demonstrate both a familial and a genetic basis of the disorder. Their study found that the way ADHD clusters in families is most consistent with the effects of a single major gene. Studies of twins provide even more evidence. In the largest study comparing identical and fraternal twins, investigators found that the heritability of ADHD (that is, the proportion of individual differences in susceptibility linked to genetic differences) was 80%.

Moreover, advances in genetic technology, have given researchers clues to some of the genes that may play a role in ADHD. In order to look for these genes, they collecting blood from families in which ADHD was common. A genetic marker is a bit of DNA (the chemical that makes up our genes) whose location on a gene is known. Thus, one way of looking for a gene, causing a disease such as ADHD,

is by seeing if family members with ADHD share a specific genetic marker. If this occurs across a number of families, then a gene involved with the development of ADHD is likely to reside nearby on the chromosome. This approach is called genetic linkage analysis. Using a series of markers, investigators can narrow down their search to a small region and eventually to a single gene.



Two genes related to the production of a chemical known as dopamine have been implicated by genetic research in families with ADHD. These genes are called the dopamine transporter gene (or DAT gene) and the dopamine D4 receptor gene (or DRD4 gene). They provide instructions for the synthesis, release, and reabsorption of dopamine. Interestingly, genetically engineered mice who lack the DAT gene show symptoms of hyperactivity. The DRD4 gene has been implicated in a personality trait related to ADHD, novelty seekers.

To better understand the genetics of ADHD, however, scientists will have to conduct more extensive studies, because different forms of the disorder — or perhaps different disorders with superficially similar symptoms — are found in different families. It is hoped that understanding the genetics of ADHD will permit the development of specialized medication and other individualized treatments — possibly even, some day, prevention of ADHD in children who are at high risk.

ADHD in Adulthood

Dr. Joseph Biederman, Professor of Psychiatry at Harvard Medical School and Chief of Pediatric Psychopharmacology at Massachusetts General Hospital, heads one of the largest ADHD programs in the world. He is an authority on both children and adults with ADHD. We spoke with him about ADHD, particularly as it appears in adulthood.



Joseph Biederman M.D.

Question: Does ADHD persist beyond childhood among most individuals?

JB: It may persist in about 50% of children. The reason that it has been assumed to dissipate is that the most visible symptoms, for example hyperactivity, tend to go away with age. Inattentiveness, however, tends to persist. So if you are inattentive but no longer fidget the assumption has been that your ADHD has disappeared.

Question: What factors do you believe cause ADHD to persist beyond childhood?

JB: We have identified three factors from our research. One is family history of ADHD. The second factor concerns psychiatric problems, particularly those related to mood, anxiety and disruptive disor-

ders. The third factor is psychosocial adversity, such as one finds more frequently among individuals who are poor. Each one of these factors increase the odds about twofold that one will have ADHD. If you have all three factors together the risk increases about seven fold.

Question: What are the most successful methods of treating ADHD in adults?

JB: The most effective method in children is also useful in adulthood — stimulant medications. Drugs like Ritalin and Dexedrine that help children with ADHD also help adults. In fact, every drug that has been shown to help children with ADHD, also works in adults. So drugs, at the moment, are the most effective method we have for treating adults. Interestingly, drugs that are only mildly effective in children (such as some anti-depressants) are only mildly effective in adults as well.

Question: Are there adults who don't realize that they have ADHD?

JB: Absolutely. We estimate that ADHD may be a very common unrecognized condition, affecting 1–2% of adults.

Question: Is it possible to have ADHD as an adult with no prior history of ADHD as a child?

JB: All adults with ADHD have had the same problems as children. However, many people seek treatment for the first time as adults. This can occur for a number of reasons. In some instances the condition was mild in childhood and only becomes a problem in specific circumstances. One gets the impression that very bright people are somehow better able to handle the symptoms associated with ADHD — up to a certain point in life. I have many patients with graduate degrees, doctors and lawyers that, by society standards, are doing pretty well. They have problems, however, in specific situations in the workplace. On the other hand, sometimes ADHD has been a considerable lifelong problem, but was just not identified in childhood. Adults with this background will have difficulty with

anything that has to do with managing multiple tasks. Studies have shown that adults with ADHD do not advance as fast as adults without the disorder given the same education and cognitive levels, particularly if it is unrecognized.

Question: What is the most common reason for an adult to seek treatment for the first time?

JB: Most commonly it is when their child has been diagnosed with ADHD. The second most common reason is when someone is doing surprisingly badly at work, even though they have a good intelligence.

Question: Is the diagnosis of ADHD more complicated in adults than in children?

JB: I don't think that the diagnosis is more complicated in adults. What one looks for is a group of symptoms that occurred in childhood. In clinical research, we look to see if these symptoms were evident starting at about age seven. This is not because we think the symptoms began then, but it is difficult for people to accurately recall their behavior before that.

Question: What symptoms does one typically see in an adult with ADHD?

JB: In general, an ADHD adult will have trouble sitting still in conferences. If you bring an adult with ADHD to staff meetings, for example, they have a terrible time. Unstructured time and boring situations are their places of greatest weakness. For example, an adult who does not know what to do with themselves on the weekend may have ADHD.

Question: Are people usually upset if they receive the diagnosis of ADHD for the first time as adults.

JB: Quite the contrary. Many patients have a tremendous sense of release when they understand the problem. As a group they are very grateful, because they finally understand their problem and because we have effective treatments. □

From the Director

Honoring Larry King

As Director of the Harvard Mahoney Neuroscience Institute (HMNI) I was most pleased that Larry King was chosen by our Council as the recipient of the Fourth David Mahoney Prize. The award, which was given to Larry King by Hillie Mahoney at a dinner in New York on October 23, 2000, is exceedingly well deserved.

The prize was established by in 1995 by David and Hillie Mahoney to recognize individuals who have helped increase public awareness about brain science and about disorders of the nervous system. Through his famous Emmy award winning show Larry King Live, Larry has hosted a number of shows on disorders related to the brain, including stroke, migraine and depression. The visibility of this show, which is CNN's highest rated program,

has helped people around the world understand more about brain disorders and their treatment. Larry King joins a list of distinguished recipients of the David Mahoney Prize, which includes: Former President Ronald Regan and his wife Nancy; Mike Wallace, interviewer and co-editor of the CBS television news program 60 Minutes; and Roone Arledge, former Chairman of ABC News.

Before the award dinner, Larry King moderated a symposium on stroke, which is excerpted in this issue. There was doubt to everyone in attendance why he has been called the "most remarkable talk-show host on TV — ever". Larry led the three panelists, who were excellent, through all aspects of stroke, from symptoms and cause to treatments and prevention. The symposium was lively, challenging, and fun.

I would like to thank you for this award tonight in honor of one of the greatest men I ever met in my life, David Mahoney. I loved David and to receive a prize in his name is one of the treasures of my life.

- Larry King



Larry King receiving the David Mahoney Prize from Hildegarde E. Mahoney, Chairman of the Harvard Mahoney Neuroscience Institute. Photo: Julie Skarratt

Through my involvement with HMNI, I have attended many public events about brain science around the county and I have never seen such a superlative job of making brain science both fascinating and fun.

The quality of the symposium would have made David Mahoney, co-founder of HMNI along with his wife Hillie, very proud. Though he died a year ago, David had a passionate belief that if the public understands more about brain disorders and the research related to them, this will ultimately lead to better treatment. The award to Larry King and the symposium he led is the best example of what David envisioned.

In accepting the award Larry also honored David. "I would like to thank you for this award tonight in honor of one of the greatest men I ever met in my life, David Mahoney. I loved David and to receive a prize in his name is one of the treasures of my life."

David's accomplishments have also been honored by the fact that Caroline Kennedy Schlossberg has agreed to become a Council Member of the Harvard Mahoney Neuroscience Institute. Her visibility and commitment to improving the welfare of others should greatly benefit the mission of the Institute in the coming years. □

Dr. Marilyn S. Albert



Shown above are the Harvard Mahoney Neuroscience Institute Council Members with Larry King. From the left, Herbert J. Siegel, Carla J. Shatz, PhD, Joseph B. Martin, MD, PhD, Marilyn S. Albert, PhD, Larry King, Hildegarde E. Mahoney, Edward F. Rover, Daniel C. Tosteson, MD. Not included in the photograph is Caroline Kennedy Schlossberg. Photo: Julie Skarratt

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