

**PROFESSOR:** All right. So brain mechanisms and sleep. We were talking about sleep pathologies and irregularities in sleep patterns last time. We defined these different things. And I think I hurriedly told you about these two phenomena of sleep wake activity, not wave, night terror and somnambulism.

After the class, Robert Thomas, who was in the class with us, volunteered to tell us a little bit about his work on sleep problems. He's an MD, and he's been attending the class. So I think before we continue with this, we will ask him to talk. He'll tell us a little bit about these.

**ROBERT THOMAS:** So part of what we do is to record sleep studies on patients. The technical term is a polysomnogram. It just means multiple recorded variables during sleep. And I'll first show you a few slides on what normal sleep looks like and then some snapshots of disease. And I will send to Dr. Schneider a whole set of expanded descriptions of disease and normals, which he can put up on the site and you can look at it.

So if you record sleep, you record breathing, you record oxygen levels indirectly through what's called oxygen saturation-- a little finger probe which uses infrared light to look at the absorption spectra differences between oxy and deoxyhemoglobin. So if you hold your breath and you allow your oxygen levels to drop, which is actually quite hard to do when you're awake, you will change the amount of oxygenated hemoglobin. And if you have abnormal breathing during sleep, then that is one of the reflections of pathology.

How do we record sleep? You record EEG, electroencephalography activity, by what is called cross-cranial montage. It says they're actually C382. There's a standard convention of recording EEG. And what that means is you're recording from a central site on the left side-- the odd numbers are on the left side-- to the ear on the right side. So you're measuring the average brain activity across the brain.

It does it. When these systems were developed in the '60s, there weren't too many EEG channels. So they had to minimize the number of leads put on the head, and it turned out this worked well enough. So you're sampling from a distance. This is C4A1, right side to left ear.

This is an occipital O182. It turns out that the alpha rhythm, which I'll show in a moment, which is at rest baseline fast activity, is best seen on the occipital leads. And then you have eye moment left and right. These are offset so that when you move your eyes up or down, the channels show a pattern, which you will see in a moment. And this is EMG, electromyogram, measuring from the chin.

So this should be wake. This is what wake EEG looks like. You see this rhythm here. Each of the vertical lines. Now, each of the vertical lines is one second. And if you look at an area such as this, there are about 10 little squigs across in that second. And there's also some degree of waxing and waning of the rhythm. And this is the altruism-- this person is awake.

As a person falls asleep, you see that there are less squigs in any given area. So if you just count the number of waves between here and here, you have 1, 2, 3, 4, 5. That's going to what is called a theta range. And this is stage one sleep.

Or that was stage two. Right, sorry. This is-- OK. Back to the beginning.

This wake. In stage one sleep, you see a drop out of the faster alpha, and you start seeing what are called theta waves. So in any given second, there will be about four to six, four to seven waves. And then you have what are called k-complexes, which sticks out like a thumb. And you have spindles. These are faster activities which look like a spindle in its morphology.

You see a k-complex or you see a spindle, it's stage two sleep. And as an amount of slower wave start getting larger and larger, these are slower waves. As you can see, they take up almost a second. And if they turn out to be a certain amplitude, don't worry about the actual number, it's a delta wave. And if 20% to 50% of sleep has so-called big, chunky, slow waves, delta waves, it stage three sleep. If it's more than 50%, it's stage four.

This is stage four sleep, where more than 50% have these larger wave forms. This is fairly arbitrary, but it seems to work fairly well. They could have chosen 60%. Why 50? It doesn't have any specific biological significance. But once you use it as a standard, it works fairly well.

Now REM sleep is completely different. Now, this is REM sleep. You can see these eye movements. So when the eyes flicker up or down, forwards, or to the side, you have these eye movements. The EMG tone, the chin tone, is very low. There is very little EMG activity. It's called atonia-- lack of tone.

The breathing muscles continue, the eye muscles continue, and it turns out the middle ear muscle also has activity. But much of the other muscles are paralyzed. The EEG looks very much like you're in a light sleep. That's why it was called paradoxical sleep. And these are the features of stage REM.

Now, in disease-- don't worry with the captions. I'll send you more precise details later. In disease, things tend to get pretty messy, and we measure more things. So these are the same channels. You have EEG, you have eye movements, you have chin.

Thermistor is a thermal-based breathing sensor. It's put under the nose, and when you breathe out, the air is warmer. When you breathe in, the air is cooler. So that's a signal as you breathe in and breathe out.

The nasal here is a nasal pressure transducer. You put what looks like a little cannula in through the nose, and you measure the fluctuations in air pressure. So when you take a big breath and let it out, you have a bigger fluctuation than when you take a little breath.

So if you just look here, you have a reduction that's a signal. You have a reduction, and then you have an increase-- an abrupt increase. These are two effort bands. It's measuring the effort of breathing.

And this is your oxygen level. So you can see that it is fluctuating. That's about normal, and that's decreased. This is an example of what's called sleep apnea, which Dr. Schneider mentioned. It's a very common disease of sleep where you have a range of abnormal breathing behaviors.

And I'll show you another sample of what could happen if a person goes into REM sleep. You see that eye movement there. You see the tone. The tone is, well, pretty low. The EEG looks like the person is in light sleep.

This is your airflow trace. There is no breathing at all. And then there is this big gasp and recovery, causing an arousal. Think of like a splatter of ink. And see the oxygen is almost going off the trace.

You can do this hundreds of times on an average night and be very sick medically. Sleepy, tired, unable to concentrate, have levels of depression, attention deficit disorder. They cause hypertension, strokes, heart attacks when it's really very severe. So it's pretty serious stuff.

And we treat diseases like this predominantly by using air pressure through a mask, and the air pressure keeps the airway open. And it actually prevents much of this. The lucky few have large tonsils, something similar, and you can do surgery and open up the airway.

And then there's just many other samples showing different features of abnormal breathing. You can see here the oxygen is fluctuating. You have a good ongoing breathing effort. Flow is decreased. This is the recovery, something like-- [GASPS]. And you have a smattering of ink out there, which is essentially a transient intrusion of wakefulness into sleep.

So if you imagine someone's clapping their hands loudly by your ear once every minute, you would not feel very well. And if this goes on day after day nonstop, I mean for years and years, these patients are very sick. I mean they are really hurt.

So I think I'll stop there. And what I'll do is to send a collection of slides with simple details. And I'll annotate what the different things mean. I can put it up there, and it'll be pretty useful and interesting if nothing else.

**PROFESSOR:** Thank you very much for that. The sleep apnea that he's talking about, as he mentioned that some cases can be cured by surgery on the throat, that's obstructive apnea. But there are also cases of central apnea, where something is wrong in the nervous system control. And I am not sure what they do now. Do they have drugs to help with that?

**ROBERT** [INAUDIBLE] the air pressure [INAUDIBLE] the air pressure [INAUDIBLE] patients. [INAUDIBLE].  
**THOMAS:**

**PROFESSOR:** OK. How is the air pressure applied?

**ROBERT** [INAUDIBLE] mask [INAUDIBLE] and it's [INAUDIBLE] mask [INAUDIBLE] pressure.  
**THOMAS:**

**PROFESSOR:** OK. So these people actually wear the mask all night then. Obviously, it's very serious. You could see the oxygen levels-- sorry, CO2 levels going way up. Obviously dangerous. If it goes too far, they would start losing brain cells.

All right. Now we mentioned narcolepsy before, and we found out that there are a few kids in the class that have some signs of it. Mild narcolepsy is pretty common. I also have it, like the sleep onset REM. But it becomes accentuated when I am hypoglycemic.

Totally compatible with normal function. But on the other hand, severe narcolepsy can cause a lot of problems. I'll describe one phenomenon that I've experienced in hypoglycemia. I can be having a conversation with you, I'm understanding each sentence, but I'm not putting one sentence together with the next. And I experience little microsleeps it's called.

I literally go to sleep while I'm talking to you or listening to you, and then I wake up. You say, well, that happens to me all the time when people are talking to me. They're boring, and I-- but this is different. This is genuinely you literally lose consciousness, but you don't fall over. It's a very interesting phenomenon.

It's called excessive daytime sleepiness. But that's a symptom of narcolepsy. And actually, what I just described can happen to you also if you're just sleep deprived. All right.

What happens in diabetes is that if the blood sugar is very high or very low, it just accentuates the effects of sleep deprivation a lot. So it's very important for diabetics to get adequate sleep because of this. I'm not sure how many physicians know this, but I can give them a detailed report.

All right. Narcolepsy has been found in animals to have a genetic basis. In fact, in narcoleptic dogs they find a defective gene in this flex 2 receptor, and the ligand is Oxyren. So they took that the gene for that and knocked it out in mice in a study. Actually, they were studying body weight regulation, but then they discovered that these mice did have frequent behavioral arrests that resemble cataplexy-- that is during their waking periods. And it was triggered while they were interacting with other mice, so it's quite possible that it's very similar to what we see in both dogs and humans with narcolepsy.

If someone can ask Bob to bring the video down, I'll continue with the lecture. But when he gets it set up, I will show you a film that'll show you a little more. It'll show cataplexic person. There's also a person with apnea. OK.

And the rest of the time, we're going to be talking about brain systems and sleep. The focus has been on the action of these wide axons with very widespread distributions, the serotonin axons that come from the raphe nuclei in the hindbrain, the norepinephrine axons that also come mainly from the hindbrain, the locus coeruleus, and also acetylcholine axons, which are widespread in the forebrain, and they come from large neurons in the basal forebrain. So while Bob's setting this up, let's talk a little bit about some of the early studies-- two of the early studies-- gross transections of the brain and then [INAUDIBLE] early studies.

Transection produce two kinds of cat preparations, the *cerveau isolé* and *encéphale isolé*. And I've gotten the textbook illustrations, and then I'll show you on the Shmoo brain exactly where these are. *Encéphale isolé* is a transection basically between the spinal cord and brain, the lower end of the hindbrain or medulla oblongata. Remember, the lower end of the hindbrain is the medulla oblongata. And if you make a transection there, the body shows no spontaneous behaviors, but the brain shows indications of a cycle of sleep and waking.

It shows wakefulness, slow wave sleep, and REM sleep, even though the body is not connected with the brain. If you make the transection way up here, you have what they call *cerveau isolé*. Now, that's right through the middle of the midbrain. And in this case, the brain-- that is the forebrain here-- including all of the neocortex, seems to show constant slow wave sleep. And yet the body, still, of course, connected with the whole brain stem now, shows alternating periods of muscle atonia, indicating that it's going into paradoxical sleep.

These are where those transactions are on your Shmoo diagram. Actually, we shouldn't call this the Shmoo. This is really a [? totipotent ?] embryonic brain. So there's the *encéphale isolé*. There's the *cerveau isolé*. So these effects focused attention on the hindbrain in the search for mechanisms controlling REM sleep and the muscle atonia that accompanies it.

Let's review now this study also here-- another early study. Professor Nauta-- this is long before he came to MIT. He came here in 1961. When he was working on his PhD, he took rats with an interest in studying sleep, and he made two kinds of lesions. I never asked him how many rats it used in finding lesions that would work, but he made lesions of the anterior hypothalamus and posterior hypothalamus.

Now, these were pretty large lesions. They found drastically different effects on sleep and waking. Remember, the transection studies focused attention on the hindbrain. These were studies in the forebrain, in the hypothalamus. The anterior hypothalamic lesions made rats show insomnia. They never went to sleep.

In fact, if he kept them alive for long enough, it became actually more and more difficult to keep them alive. And he claim that some of them would start to die. The posterior hypothalamic lesions made them sleep most of the time. And these were just hypothalamic lesions. So we know that hypothalamus is probably involved in the regulation of the sleep cycle.

So people have tried stimulating, electrically, these same regions. And if you stimulate that anterior hypothalamic region, what we call the preoptic area, in front of the optic chiasm and the anterior hypothalamic nucleus, first of all, if you have the cat doing a behavior where he's running, he will slow down. And if he's normally just walking around a cage or a room, and you start stimulating there, you will get fixed action patterns that cats show when they're preparing for sleep. They will clear a little area, they will curl up, assume a sleep posture, and so forth in a pretty natural manner.

But if you stimulate the posterior hypothalamic area, you get opposite effects. You speed up running behavior and you get increased alertness. You get sympathetic arousal effects. OK?

Now, remember, we said that you can get these insomnia and hypersomnia effects from stimulating lesioning in the hypothalamus. Well, there's a related effect from the raphe nuclei to midbrain and hindbrain. The raphe nuclei are the cells that contain serotonin. They're the source of widely projecting serotonin axons.

And if you make lesions there, you also get insomnia. In fact, the severity of the insomnia is directly related to the number of serotonin-- the amount of reduction of serotonin cells. The size of the lesion in other words.

So you begin to see that regulation of sleep is a complicated business. It involves hindbrain and forebrain. And I am going to mention one more study relevant to what we're talking about, and then we'll show a video of some of these sleep pathologies. I don't have too much to say about these other things, but we'll say a little bit.

The locus coeruleus region-- now, this is a region in the hindbrain. In this textbook diagram, it's right there below the cerebellum. I've circled it there. It's not circled on your textbook like this, but I'm pointing to that region.

If you make a lesion in the vicinity of the locus coeruleus, that may not be those cells, but they're near there, you get a very interesting effect in cats. And it's been seen now in rare human patients who have lesions in that area. Why do you think we don't get many human cases with such lesions? Because usually if you have a lesion in that area, you die.

But with a cat, it's possible to be very selective and make a small lesion in that region. And the cat appears to be pretty normal, and he goes to sleep. When he enters REM sleep, he doesn't get the muscle atonia. Instead, he moves around.

He lacks the atonia. So with the active forebrain, and corticospinal tract, and cortex behind brain mechanisms, you get the behavior that would cause. And the cat appears to be hallucinating-- acting out his dream, so to speak. And people-- these rare patients with that. I don't know of more than, I think, two cases that I've read about. You do get similar things.

While he's doing that, are there questions about any of this? There were some questions last time, some of which I didn't get to. Yes.

**STUDENT:** [INAUDIBLE].

**PROFESSOR:** The locus coeruleus, is it related to sleepwalking? That's a very good question. Because I just described a cat that when he's asleep will get up and run around. But no, when you lesion the locus coeruleus region and get this activity during REM sleep, it's very different from sleepwalking. Because in sleepwalking, we're not in REM sleep. We're in a slow wave sleep. Have some amblyopia or sleepwalking. OK. Yes.

**STUDENT:** [INAUDIBLE].

**PROFESSOR:** No, they seem to have the effects of sleep. They don't become neurotic and crazy. They just have this abnormality. Of course we keep them in padded areas where they can't hurt themselves. They, of course, could hurt themselves in that kind of situation.

OK. Now this is actually a *Donahue* show on TV, where because of the popular interest in these things, he has a narcoleptic dog brought on his show. And he has a woman who has cataplexic attacks and narcolepsy. You'll see her with her daughter. And they have a little video that the family took of her where she collapsed in a chair, and then they revive her.