STRESS!!!

What are stressors?

Stressors are environmental or internal events that tax adaptive resources…they interfere with our day to day stuff…for example, encountering a vicious dog on your daily walk is a stressor, taking an exam in N-12 is a stressor, and so is any disease state! Obviously, these sorts of things happen all the time, so the body adapts in various ways.

How do we adapt to stressors?

First, it is important to note that the body responds to physical stress and psychological stress the exact same way.

- SNS: enhancement of the SNS causes the release of epi and norepi for increased vigilance and alertness. If you're out hunting wildabeast, you're going to be super vigilant if you hear the sounds of a saber-toothed tiger nearby.
- Corticotropin Releasing Factor (CRF) released from the PVN of the hypothalamus. This factor stimulates the pituitary to relase ACTH (corticotropin) which, in turn, signals the adrenals to secrete glucocorticoid. This occurs in 30 minutes and is cleared hours after the stress is over…so it hangs around for a bit.
- Other adaptive measures:
    - Pancreas secretes glucagon (which converts glycogen to glucose for energy)
    - An initial burst of growth hormone with a subsequent release of somatostatin (growth hormone inhibiting hormone). Why the quick negation of GH? In times of stress, the body only needs GH to do one part of it's job (converting fat in cells to free fatty acids that are available for the muscles to use as energy). If GH actually were allowed to stick around and actually cause growth, then the body would be wasting energy on growing when it really just needs to focus on survival.
    - Pituitary secretes prolactin…
    - Pituitary secretes antidiuretic hormone (ADH, aka Vasopressin… remember that vasopressin vasoconstricts arteries to increase TPR which increases BP so that the blood can get where it needs to go. It also causes the tubule cells of the kidney to reabsorb more water from urine which also increases blood volume and increases BP.
    - Pituitary and brain secrete morphine-like substances called endorphins and enkephalins…this comes in handy if you've got a broken leg but need to still get away from the saber-tooth tiger.

So, how do body systems adapt?

Various body systems adapt to the stress response, and this is typically a useful adaptation when the stress is infrequent and acute. However, when it is turned on a LOT, or just never turned off (as in the case with Peter Pan author), then the risk of getting disease

goes up. The body just can't handle it. Note that it doesn't seem to matter if the body is dealing with a physiological stress or psychological stress.

How metabolism adapts to stress
EPINEPHRINE antagonies insulin…remember that insulin "takes up" glucose in the blood stream. If insulin is antagonized, then it's not going to do it's job, so the sugar is going to stay in the blood stream where it is needed for energy in times of stress.

GLUCAGON increases…remember that glucagon is responsible for the transformation of glycogen to glucose in the liver…so this also increases blood sugar!

GLUCOCORTICOID block's insulin's transport of nutrients into fat cells (gotta keep the nutrients available), decreases insulin secretion, breaks down triacylglycerides to free fatty acids (muscles can use these!) and stimulates gluconeogenesis in the liver.

Inhibition of the PNS causes a decrease in energy storage…why store it when you need to use it NOW??? Remember, that the PNS stimulates the GI system to store nutrients.

Proteins are broken down for amino acids (only proteins in nonexercising muscle), which are then converted to glucose in the liver…BS goes up!

What happens if metabolism can't adapt? The exhaustion phase!
For starters, with all that glucose running around in the system, one has to think about diabetes. Epi and glucocorticoid make cells less sensitive to insulin so the pancreas decreases production and you end up with *Insulin-Resistant Diabetes* (Type 2)

Fatigue occurs for several reasons. The biggie is that each time nutrients change between storage and useful forms then a <u>little bit of energy loss</u> occurs. Over time and with a lot of "stress on", "stress off" kind of activity you end up with a cumulative loss and fatigue worsens. Also, too much SNS activity causes <u>sleep disorders</u> by interfering with the good ol' Reticular Activating System. (recall that the RAS detects new and novel stimuli and can help you "tune out" repetitive noises). CRF causes <u>appetite suppression</u> which can lead to malnutrition. <u>ASVD</u> also comes into play, but we'll talk about that more in the cardiovascular section.

How does the cardiovascular system adapt to stress?
The SNS INCREASES HR and BP, and epinephrine makes platelets stickier in case you need to clot a wound. The SNS also VASODILATES to skeletal muscle so it gets all the blood and nutrients needed for "fight or flight."

Pituitary increases RELEASE OF ADH, which increases water retention by the kidneys, keeping BP and BV up there, baby!

The glucocorticoids increase platelets, increase BS and increase fat being mobilized for energy. Yay glucocorticoids! Sugar is used by the brain, and fat/sugar is used by muscle.

Incontinence empties bladder…think of it as getting rid of excess weight so you can run.

What happens if the CV system can't adapt and exhaustion sets in?
Arteriosclerotic Vascular Disease is caused by chronic high blood pressure, high glucose and high free fatty acids. Hmm….so if the stress isn't resolved, these things are going to continue to happen for longer than what is therapeutic. The turbulence at birfucation of vessels leads to the deposition of fatty acids, glucose and calcium…vessel is damaged ☹
Note that decreases in estrogen also accelerate artherosclerosis….not sure why.

Also, an aging CV system does not respond well to epi/norepi, so older adults who are exercising are actually getting less "maximal cardiac output". Even in a resting state, the elderly secrete more epi and glucocorticoid than do young people. It is thought that the epi may be responsible for some of the increased instances of hypertension in the elderly.

How does the gastrointestinal system adapt to stress?
The inhibition of the PNS causes digestion to be inhibited. Why digest when you may not even live to need the nutrients? You also don't need to carry around a bunch of poo, so note that the SNS increases motility in the tract…get rid of it!

The SNS increases various digestive enzymes…

CRF (corticotropin releasing factor) suppresses appetite. Note that glucocorticoids stimulate appetite…this explains why sometimes you eat when stressed, and other times you don't eat at all.

What happens with the GI system can no longer adapt? Exhaustion.
The loss of protective mucosal lining permit HCl to damage the gut leading to GI bleeding and ulcers. You also get things like colitis and irritable bowel…note that with repeated stress, recovery from decreased UGI motility and increased LGI motility may not occur simultaneously. (is this b/c SNS affects one and PNS another?)

Some people also lose weight while others gain weight. How is this possible? Well, CRF clears rapidly after the stressor goes away, leaving a longer appetite stimulant effect of glucocorticoid. Interesting. So…would constant stress cause weight loss while repeated short-term stressors cause weight gain? Looks like it!

How growth is affected by stress…adaptive response.
One of the ways the body adapts to stress is to simply not grow…why be a bigger target and why use up your nutrients for growth when you need them to run away from a deranged ax murderer. So, what you'll see first is an initial burst of growth hormone,

which frees up cell fats into free fatty acids the muscles can use. BUT WAIT! We don't actually want to grow now…so the body quickly realeases somatostatin, which inhibits the growth effect of GH. Whew!

Also, glucocorticoid (there it is again!) decreases GH, and decreases the sensitivity of target cells for GH by 2-3x…so what little GH there is in the body isn't being used. This is often seen in the arrested development of asthmatic children who used to be put on systemic glucocorticoids in the "olden days."

Glucocorticoid also inhibits bone growth by decreasing calcium uptake from the intestines and accelerating resorption of bone.

The stimulation of the SNS also causes decreased absorption of nutrients from the gut…is this because it speeds up motility of the LGI?

Rx: Note that glucocorticoid is given as a DRUG for hypercalcemia

What happens when growth can't occur due to exhaustion from stress?
Dwarfism, though rare, can occur…one would have to have some seriously severe levels of glucocorticoids to suppress GH that much. Also, osteoperosis and bone fractures result from decreased calcium uptake from the intestines and increased absorption from bone. Dr. Van notes that this is probably not significant, though. And finally…there is a likelihood that stress causes delays in wound healing.

How does the reproductive system adapt to handle stress?
In general, the body does not care about sex when it's about to be hacked up into little pieces by a psychopath. When stress occurs, the SNS releases endorphins and enkephalines…now these guys decrease LHRH (leutenizing hormone releasing hormone) in the brain, and this leads to a decreases in LH and FSH being secreted from the pituitary. **In males**, this results to decreases in testosterone and sperm production. This also happens to people who have a lot of endorphins in their system such as "super jocks", or those who have a lot of opiates in their system (addicts).

The stress also causes an increased release of prolactin from the pituitary which decreases the sensitivity to LHRH, and you have the same situation as outlined above.

Inhibition of the PNS causes less penile blood flow for erections…but note that the SNS is responsible for ejaculation.

To sum up…**in males**, stress causes lowered sex drive, increased impotence and premature ejaculation…not a good combo!

For the **ladies**, adaptation and exhaustion are less clearly separated…it depends on if you're pro woman or pro baby, I guess. For example, if a miscarriage is a stress response to save the mother's life, is this adaption or exhaustion? It's a fuzzy area.

More specifically, stress causes those endorphins and enkephalines to be released which reduces LH and FSH release form the pituitary…this leads to decreased estrogen, decreased ovulation and decreased progesterone. Decreased estrogen leads to decreased stimulation of estrogen receptors in the brain and genitals for a lowered sex drive (though for women, sex drive isn't just about hormones, it's about psychological and emotional stuff, too.)

Women under stress have increased prolactin, which leads to decreases in LHRF.

Glucocorticoid also blocks pituitary sensitivity to LHRH, and it inhibits ovarian sensitivity to LH, so there is less estrogen secreted from the ovaries.

Prolactin interferes with progesterone's activity to maintaining the uterine lining for implantation. You can guess what happens to the lining when prolactin is on the job. No implantation, no preganancy, no baby. (no baby = no stress…ha!)

The SNS vasoconstricts organs that are not vital for the mother's survival, so it can cause increases in fetal death and miscarriages by decreasing blood flow to the uterus/fetus.

Super jocks, anorexics and those starving may have delayed puberty due to lower estrogen levels. Enzymes in fat cells (which these people don't have) convert androgesn to estrogen. Since they have no fat cells, the androgens stay "male" and estrogen levels are relatively lower…mustache wax anyone?

How does the immune system adapt to stress?
Immunity is suppressed during stress…not very well understood as of yet. We do know that the thymus atrophies when glucocorticoid levels are high. (not sure why this happens or what the implications are…too tired to look it up). Lymphocytes decrease and there is decreased communication among WBCs.

However, some compoments of the immune system are *stimulated by stress.* Mild elevations of gluco may stimulate the immune system possibly due to suppression of immune suppressor cells. Also, WBCs that should be functioning (but are not) leads to a higher neutrophil count because they're floating around in the blood stream where they can get drawn…if they were functioning, they would not be floating around. They would be sticking to the vessel wall like they're supposed to in order to be able to get out to the site of tissue infection or trauma.

What happens when the immune system can't adapt? Exhaustion.
One of the biggies is cancer. Substantial evidence shows that stress accelerates ca growth, but probably does not initiate it.

- The glucocorticoid levels usually seen in stress aid the development of blood vessels to the tumor (tumor now has a way to get nutrients)
- Glucocorticoids suppress lymphocytes that normally detect and kill cancer cells
- Glucocorticoids provide higher BS, which is nutrition for the tumor

Autoimmune disease can also occur. Note that stressful periods often precede the onset of immune-related diseases such as diabetes, multiple sclerosis and lupus.

How does the neuro system adapt to stress?
When you are faced with a stressor you go onto high alert and get done whatever it is you need to get done (escape from a predator, take a test or do CPR on a plane!)

- The SNS increases alertness
- Endogenous morphine (endorphins & enkephalins) blunt pain perception

What happens with neuro can't adapt? Exhaustion.
Stress depletes norepi transmitter in the limbic system of the brain. Recall that the limbic system is involved with emotion, so a lot of people with chronic stress are also very sad. Depressed learning, coping and motivation are all associated with "learned helplessness." People with learned helplessness have an external locus of control and are the most vulnerable for this. "There's just nothing I can do."

Aging also comes into play. The loss of glucocorticoid feedback regulating cells in the hippocampus area of the brain. Recall that the hippocampus is involved with memory! Research tells us that increased exposure to glucocorticoid causes neurons to lose their ability to re-branch effectively. This explains why stress can accelerate memory loss with aging.

How do people manage stress? COPING!
Note that coping may or may not be functional…for example, if I go for a run or do breathing exercises when I am faced with stress, then I am probably coping pretty well. If I get drunk every night, then my coping is dysfunctional!

Coping Mechanisms

- Anxiety can be useful if it is mild and accompanied by increased alertness and vigilance This is the type of anxiety that is helpful when you take an exam, but you wouldn't want it to be so high that your brain freezes.
- Taking action to reduce the stressor or minimize its impact. This can be done by simply eliminating the stressor (get a divorce if your husband stresses you out) or displacing major worry onto something more manageable…you yell at your husband but you're actually angry with Dr. Van's test questions.

- Depression is definitely a dysfunctional way of coping. Gluco levels are elevated in many depressed people, and Dr. Van poses the question "Could some people be more vulnerable to insufficient replacement of stress-depleted limbic norepi?"… I'd say that older people would be at risk for this?
- Helplessness and hopelessness (not functional)
- Alcohol and drug use (not functional)
- Seek social support (great idea!)
- Denial (can be useful for short-term to help us get on with life)

Stress reduction/adaptation therapies
One of the best things you can do for someone who is stressed is give then the perception of control or the ability to predict when stressors will occur. If you KNOW you're going to get a shot every day for the rest of your life you know when to expect it and it's no big deal. If the nurse tells you, "I'm going to be giving you a shot sometime in the next week", then you're going to stress about it the entire week…better to know and better to be predictable!

Examples of ways to accomplish this in a clinical setting:
- Call light…find out if the pt is worried we won't respond right away. If so, he may be pressing the call light in anticipation of FUTURE needs. If we always respond, he knows that he only needs to press the button when he actually needs something. He has control!
- PCA is associated with less medication need. Yay!
- Choice or room décor, meals, activities, etc…definitely key with nursing home residents.

Focus on giving control only when the outcome is actually controllable and not something horrible. It can be too much responsibility and too stressful…which is why family members don't do the actual plug pulling!

Focus on giving control over future course of disease and not mulling over poor choices made in the past. Don't berate the pt for smoking…talk to them about how they can cease smoking and improve their health.

When the outcome is good, give the pt all the credit…"GOOD JOB! You walked all the way around the nursing station…way to go!" If the outcome is not good (pt has to sit down, can't make it all the way)…then you take the blame. "We'll try this again after I get some more fluids into you."

Sharing Knowledge: Basically, just be aware that you give the right amount of information…too much can be stressful as can too little. You can also assist the pt in determining the significance of stressors and maximize the pt's ability to DO SOMETHING ABOUT IT!!!! The first thing you should think (Primary Appraisal) is

"What is the significance of these events to my well being? Is the situation getting better or worse? Is it a 1x event or likely to continue?" When this assessment is made appropriately, the pt is likely to have an appropriate stress response. The Secondary Appraisal is "What resources and options are available to me for coping?"

Touch: Touch can be very therapeutic, but you have to watch for the pt's response in order to know if it is something they are comfortable with. One study showed that rats handled during the first few weeks of life secrete LESS gluco and age more successfully as adults.

Moderate Exercise: Exercises lowers BP and resting HR while increasing lung capacity. Yay for exercise! It also releases those morphine-like substances that make us feel fantastic!

Hostility Management: If your patient is hostile or angry, LISTEN to them. Let them talk! Note that hostility is associated with increased incidence of CVD…no bueno.

Social Support: Several studies have shown a relationship between fewer social relationships and shorter life expectancy…this factor appears to be at least as important as smoking, obesity and sedentary lifestyle. Make some friends!

Other therapeutic/adaptation mechanisms:

- Provide outlet for frustration
- Relaxation techniques (listen to music, breathing exercises)
- Spiritual rationalization of stressor

Fatigue

Fatigue is a sensation of exhaustion that may or may not be related to activity.

Chronic fatigue is fatigue for a duration of 6 months or more.

Chronic fatigue syndrome is severe but has no known etiology and always occurs with other symptoms. Almost 2.2 million American adults suffer from CFS-like illness. Exercise can help decrease fatigue, but it may be difficult to get pt to try…it works better when combined with education and antidepressants.

Fatigue
Depression
Stress
Often are interrelated!

Biochemistry of Fatigue
The RAS (reticular activating system) of the brain keeps you alert, but you need to replenish neurotransmitters. If you run short of NTs, then you have fatigue. At the cellular level, the substrate (which can be a fat, protein or CHO) a cell needs to do its job has to get to the cell in the first place. Now, enzymes break down substrates which produce energy when the bonds are broken, and heat is released as a byproduct. The heat is dissipated to the environment as blood perfuses skin. If the heat is not perfused, then the temperature is too high for the enzymes to do their job. Recall that enzymes use various vitamins and electrolytes to trigger reactions and won't be able to do this unless within the right temp, pH and oxygen levels.

Fatigue Assessment

1. "Do you have more fatigue when you first wake up?" If yes, think about depression and psychologically related fatigue.
2. "Do you have more fatigue after activity?" If yes, think about metabolic related fatigue.
3. Evaluate meds for possible side effects of fatigue. This includes hypnotics, muscle relaxants, antidepressants and narcotics)
4. Duration of fatigue
5. Impact on quality of life…can they work? Have fun?

Therapy

- Assist pt to meet unmet needs, focus on the most important first! (ABCs, Maslow's, etc..)
- Identify most important things for pt to expend energy on
- Provide specific Tx as indicated (i.e. may be anemic, may need sleep apnea mask)
- Replace nutrients and restore healthy cellular environment (O2, fluids, iron/ erythropoietin, electrolytes, energy source, BP, body temp, etc…)
- Antidepressants, possibly stimulants
- Cognitive behavioral therapy (help pt. learn how to cope)
- Exercise

Cancer and Fatigue

- Some evidence shows that exercise benefits women with breast cancer (not adequately studied).
- Bone marrow transplant pts who exercised for 30 mins/day x 6 weeks reported less fatigue
- Prevalence of fatigue in pts with advanced cancer is 50-70%.
- Fatigue in the caregiver is also a factor…mainly relates to how much the care impacts their day-to-day life

Fatigue effects about 7% of the general population.

Fatigue is higher with many diseases and conditions such as cancer and MS.

Anemia and Fatigue

- Low Hgb associated with fatigue, but not with postnatal depression.
- Iron may be helpful in menstruating women…those who benefited had low ferritin stores and were not anemic.

AIDS and Fatigue

- AIDS meds cause many side effects. Exercise is most popular therapy.

Depression and Fatigue

- Depression and chronic fatigue are risk factors for each other.

Sleep Deprivation and Fatigue

- Psychological fatigue is related to prolonged and irregular work hours, not necessarily related to energy expenditure (truckers)
- Shift workers must be able to adapt to changes in schedule and control schedule
- Napping during night shifts reduces fatigue (lunch break, etc…)

Respiratory Disease & Obstructive Sleep Apnea and Fatigue

- Nasal positive pressure ventilation improves daytime energy in pts with respiratory failure related to neuromuscular weakness
- 5-15% of population has OSA. Positive pressure airway mask prevents apnea!

Renal Failure and Fatigue

- Acupoint massage reduced fatigue and depression in patients on dialysis

Lupus & Erythematosus and Fatigue

- Teaching pts and families coping mechanisms helped reduce fatigue

Epi antagonizes insulin… and stress raises BS. This is why a diabetic pt will need MORE insulin when hospitalized (stressed).

Heat and Fatigue

- High core temp can cause fatigue due to heat/stress
- When hot weather, give enough fluids to permit loss of heat

from increased metabolism in exercise (work)…don't exercise during the hottest times of day!

MS and Fatigue

- Higher levels of helplessness correlate with more fatigue in MS pts…cognitive behavioral therapy would work well here
- Some find stimulants helpful, other studies do not

Spinal Cord Injury and Fatigue

- Pts with OH were given midodrine…fatigue after standing improved!

Brain Attack and Fatigue

- Fatigue is common and debilitating after a stroke…more studies need to be done regarding intervention.