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SP.236 / ESG.SP236 Exploring Pharmacology
Spring 2009

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Big Molecules

Agenda:

Quick review of action potentials

- Alcohol, continued
- Epilepsy
- Local anesthetics
- Shock therapies

Big Molecules:

- G-Protein Coupled Receptors
- Transport Proteins
- Metabolic Enzymes

Big molecules, in action:

- Antidepressant Mechanisms

Choose your adventure:

We may not have time for everything, so which of these are you more interested in:

- Alcohol substitutes debate
- More info on alcohol safety
- Shock therapies
- Local anesthetics
- Antidepressants (we will cover these eventually, but how about sooner rather than later?) (This option could be paraphrased as: “Don’t fall behind the syllabus!”)

Ion concentrations in and around axons:

Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out:In	E_{ion} (at 37 C, in mV)
K+	5	100	1 : 20	-80
Na+	150	15	10 : 1	+62
Ca ⁺⁺	2	0.0002	10,000 : 1	+123
Cl-	150	13	11.5 : 1	-65

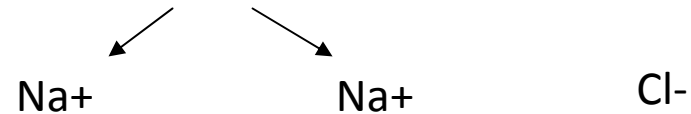
Types of channels

- There are a few types of ion channels:
 - Leak channels: These are always open, there are a number of K^+ leak channels and they are responsible for the resting potential
 - Voltage-gated: Open or close at specific voltages, very important for action potentials
 - Ligand-gated: Open or close when exposed to chemicals
 - Second-messenger-gated: Similar to ligand-gated, these open or close depending on chemicals called second messengers inside the cell, or they open or close when phosphorylated or dephosphorylated
 - Combined type: NMDA receptors have multiple agonists that must bind simultaneously for opening, PLUS they only open when the membrane is depolarized

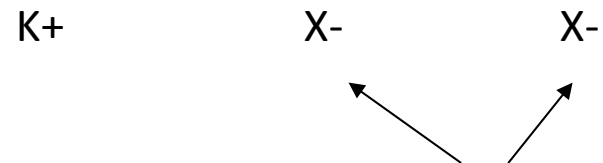
A neuron's cell membrane:

The abundance of sodium ions causes an overall positive charge outside the cell

These ions are concentrated outside the cell:



These ions are concentrated inside of the cell:



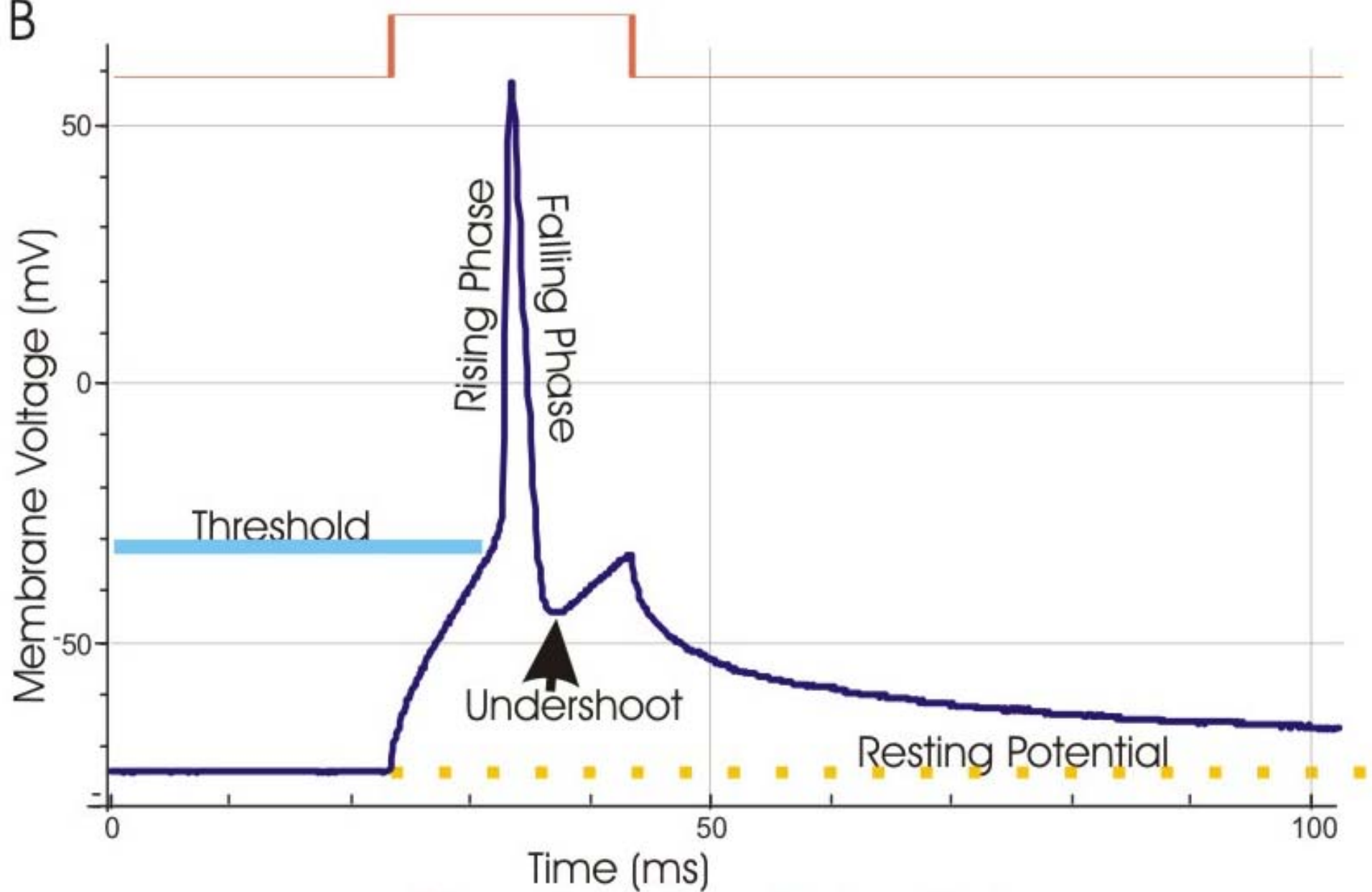
The abundance of random negative ions causes an overall negative charge inside the cell

Action potentials

An action potential (an electrical signal in a neuron) gets fired (sent) when the negative potential of the cell membrane is weakened. When the potential, which is normally negative, rises above a certain threshold, sodium floods into the cell and the membrane potential changes dramatically and becomes positive. This is the action potential. Shortly after the sodium floods into the cell, potassium flows out of the cell, and this causes the membrane potential to be negative again, just as it was in the resting neuron, before the action potential was fired.

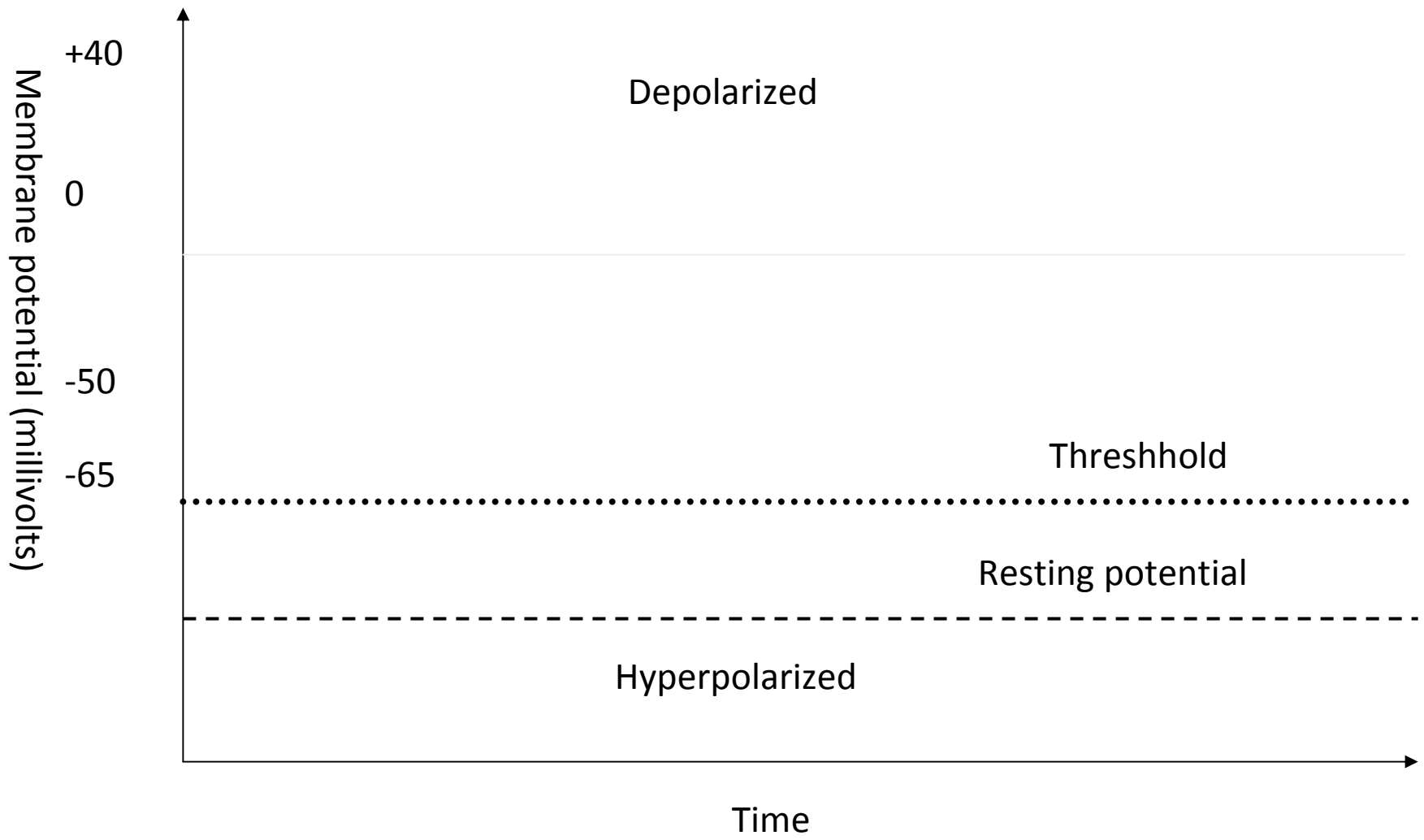
“Schematic” Action Potential

[Click here to view a graph of “schematic” action potential.](#)

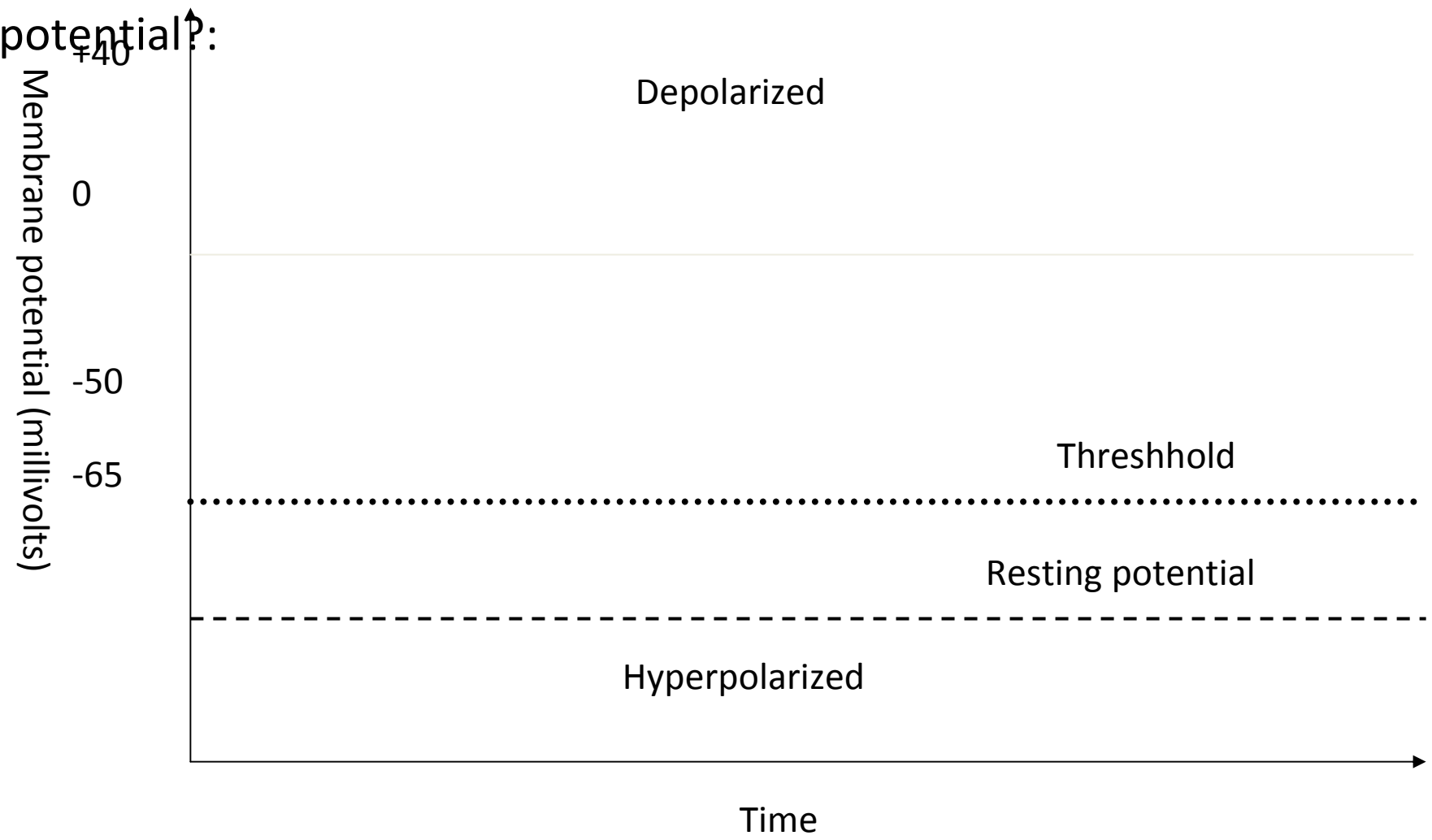
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“Real” Action Potential

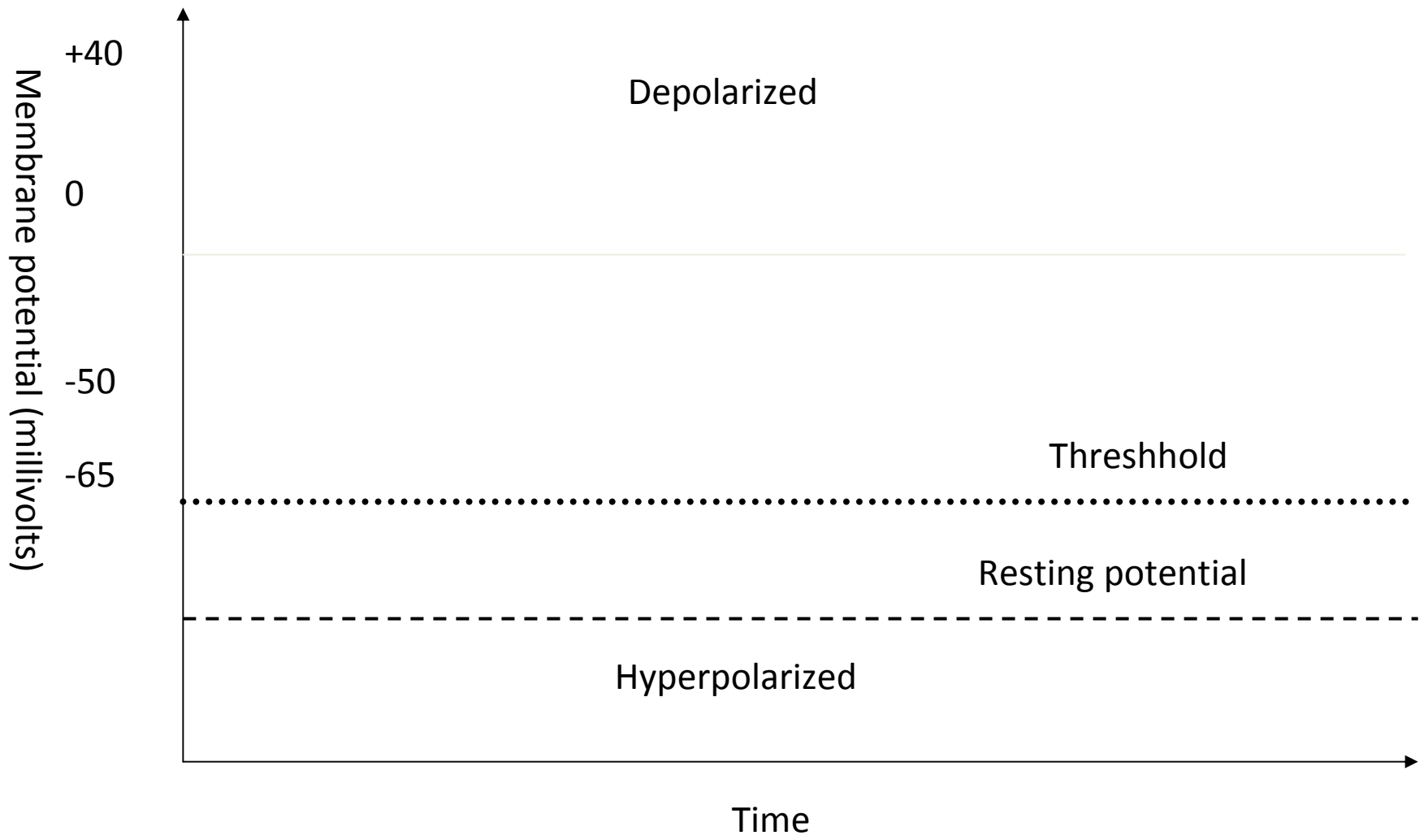
Draw a graph of membrane potential that might occur if you applied an excitatory input to a neuron (such as the neurotransmitter glutamate), but the depolarization caused by the excitatory signal is not quite great enough to trigger an action potential:



Draw a graph of membrane potential that might occur if you applied an inhibitory input to a neuron, such as the neurotransmitter GABA. GABA causes negatively charged chloride ions to enter the neuron, so the inside of the neuron (the membrane potential) becomes more negative. How does this affect the amount of excitatory signal needed to fire an action potential?



Draw a graph of membrane potential that might occur if you drank a glass of wine, and the ethanol in it caused positively charged potassium ions to leak out of the neuron:



Now the fun stuff:

- Epilepsy and anticonvulsants
- Local anesthetics
- Alcohol and alcohol antagonists
- Shock therapies

Alcohol

In many ways, alcohol is the most dangerous drug I will talk to you about.

CDC: 76,000 Americans a year die because of alcohol (conservative estimate)

NIAAA: 110,000 Americans per year die because of alcohol (commonly cited estimate)

Alcohol causes car accidents, violence, exacerbates other conditions, breaks up families,

Alcohol

How does alcohol work?

It is not understood which mechanisms are important, and alcohol does many things to the brain. Here are a few things it does:

- Opens BK potassium channels

- Closes SK potassium channels, which are found on DA-releasing cells in the VTA

- Activates GABA_A and GABA_B receptors

- Lets calcium into cells, causing cell death

Alcohol

BAC and effects:

- .03 Mild euphoria, relaxation, talkativeness, decreased inhibition, coordination and judgment impaired
- .06 Reflexes, senses, and reasoning impaired
- .10 Emotional swings, staggering, slurred speech
- .20 Memory blackout, possible unconsciousness, highly impaired thought, movement, and perception, gag reflex is suppressed
- .30 Unconsciousness, impaired breathing and heart rate, death possible
- .40 Death likely if untreated

Gender and alcohol tolerance

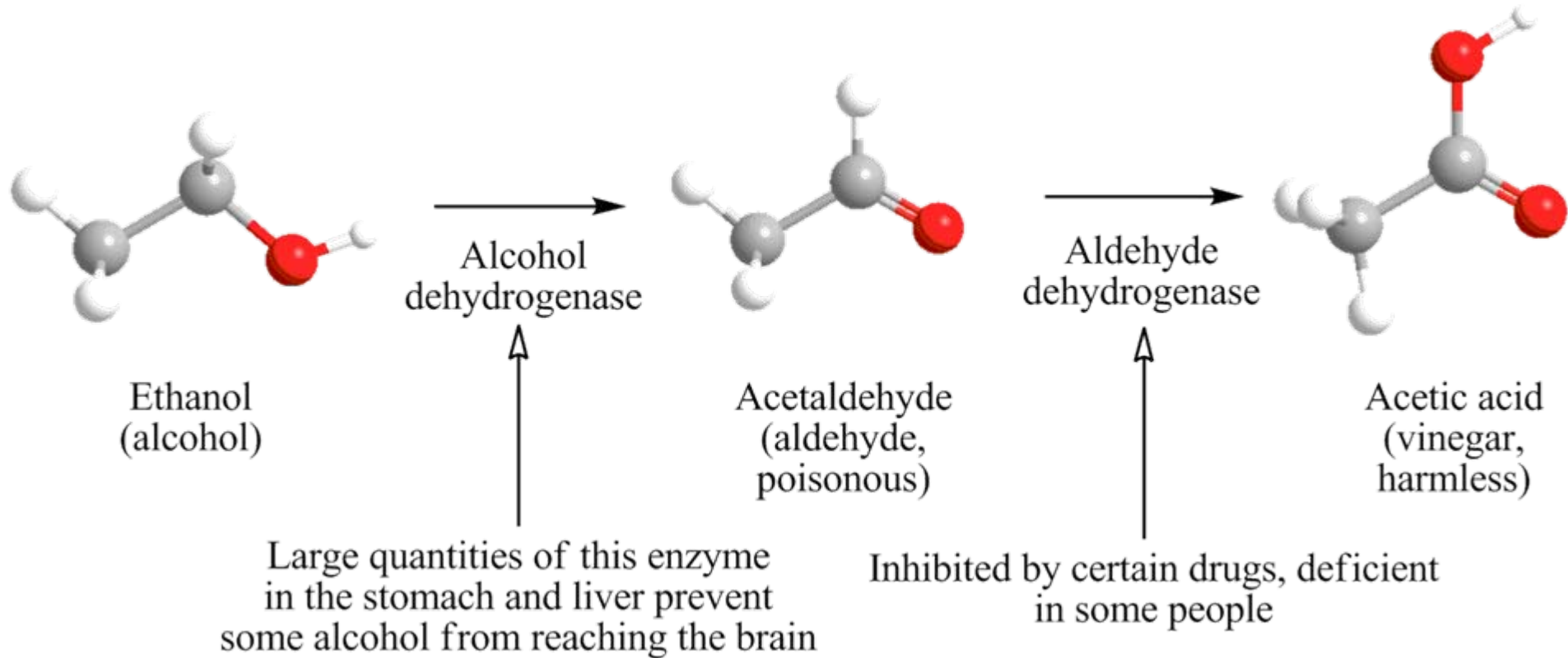
Alcohol

Hilarious study correlating alcohol consumption to enjoyment.

Recent study from Northumbria and Kent universities shows that 3 or 4 days after having 4 or 5 shots of alcohol or nothing, the young adults who had alcohol remembered one third fewer items from a video/list than the non-alcohol subjects

University of Tokyo finds that drinking after a bad day will actually reinforce the memory – you have to start drinking BEFORE an event to forget it, getting hammered after being fired or dumped will only make your psychological pain and memories worse.

Alcohol metabolism



Alcohol

Why does it make you nauseous?

How do Antabuse and Temposil work?

How can you avoid nausea and improve bioavailability?

- Other routes of administration (bad idea)
- Become an alcoholic and destroy your GAD and liver (also a bad idea, especially since it masks the development of tolerance which would have otherwise required larger doses, and it removes the disincentive to drinking caused by nausea and hangovers)

Alcohol

Why does it cause brain damage?

What else does it cause?

- Cancer from the lips to the anus, hepatitis, pancreatitis, gastritis, anxiety, depression, phobias, sleep disorders, liver cirrhosis, Korsakoff's syndrome, Wernicke's encephalopathy, alcoholic dementia, heart disease, epilepsy, polyneuropathy, malnutrition, and sexual dysfunction

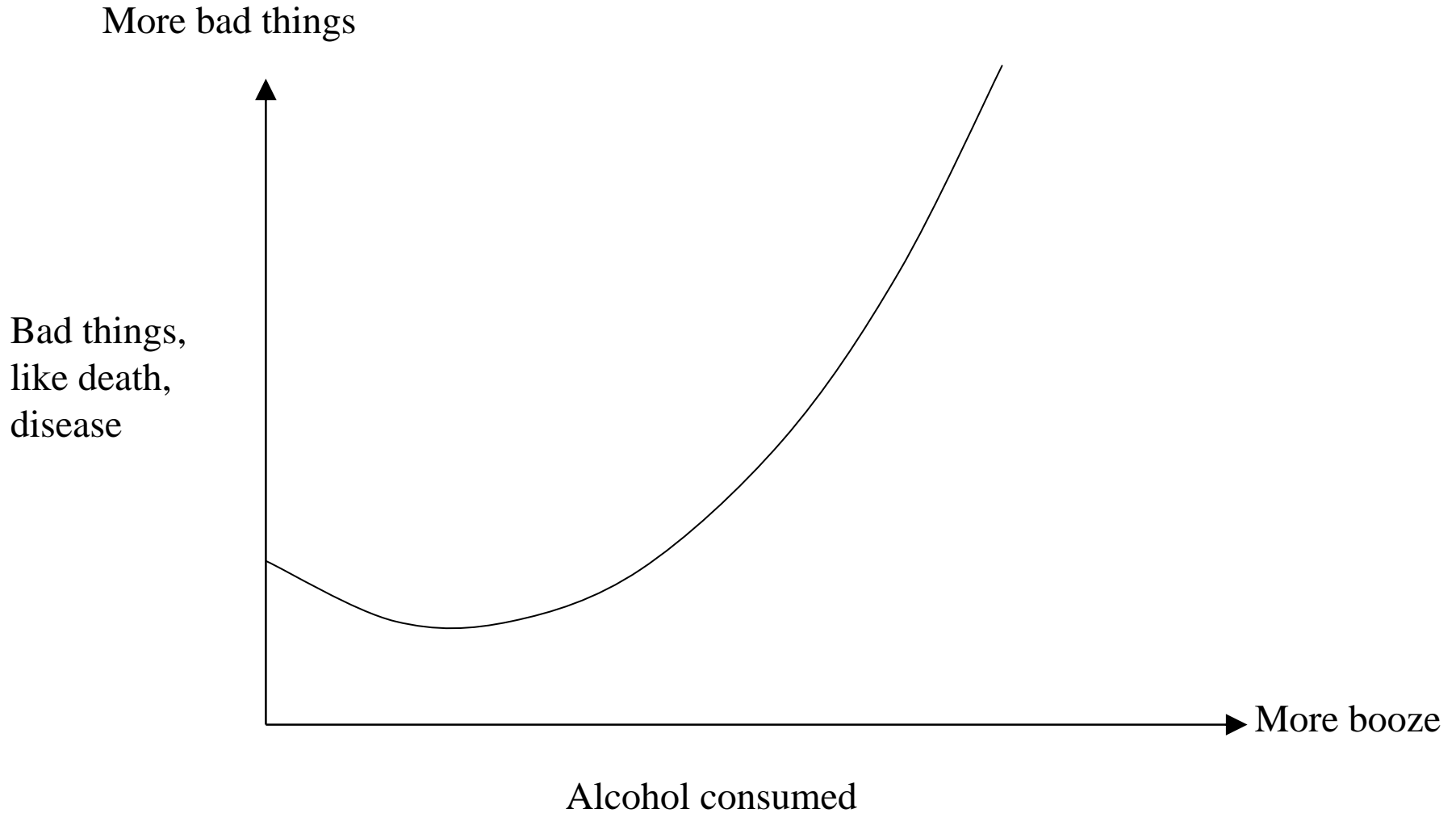
What blocks the effects of alcohol?

What is the alternative?

To what extent is it OK to drink alcohol?

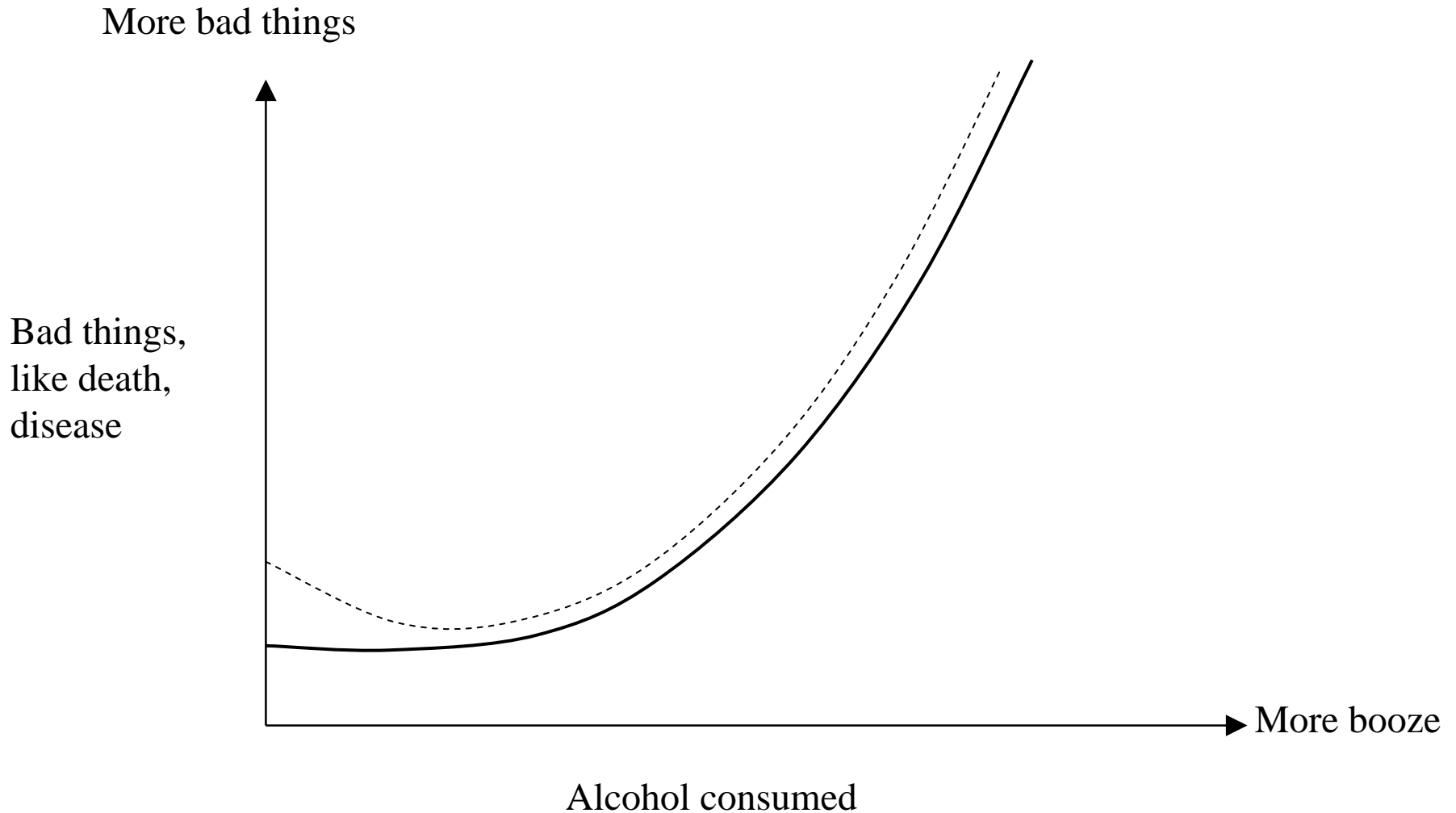
- All but the most fanatical of scientists and doctors agree that healthy adults with no history of addiction can have up to 7 drinks a week, ideally spread out.
- Some sources say up to 14 drinks a week, or up to 14 drinks a week for women and 21 drinks a week for men. (Or 10 for women, 14 for men)
- Despite what people may say about “teaching kids to drink, like they do in France,” it is a bad idea. There are a lot of alcoholics in France, and in every country where kids start drinking young. The longer you wait, the safer you are.

Is alcohol good for you?



A number of studies produced graphs like this, but there was a problem...

Is alcohol good for you?



If you exclude people who are already sick, alcohol doesn't look so beneficial. This is because many sick people avoid alcohol.

Is alcohol good for you?

What kinds of people drink zero alcohol:

- Religious people
- People who have some moral or scientific objection to alcohol
- People who get nauseous when they drink
- Former alcoholics
- Former drug addicts
- People with mental health disorders
- People on medication that might interact with alcohol
- Very old people
- People with various diseases (liver disease, kidney disease, AIDS)

Reasons for not drinking which often indicate poor health are in **RED**.

There were other confounding factors as well:

- Red wine is full of good stuff, like antioxidants, but so is grape juice
- Beer is full of good stuff, like vitamins, but so is oatmeal
- Clear vs. dark liquors

Is alcohol good for you?

A recent study (Medical University of Southern Carolina) helped to clear up this question, it included only people who began drinking for the first time during the course of the study. Beginning to drink between the ages of 45 and 64 was beneficial because it reduced coronary heart disease, but starting to drink at an earlier age was not good. Before the age of 45, the risk of heart attack is low and cannot be significantly reduced by alcohol, while the risk of alcoholism and long-term alcohol-related damage is higher.

Is alcohol good for you?

An even more recent study

(<http://jnci.oxfordjournals.org/cgi/content/abstract/djn514> Journal of the National Cancer Institute) used a population of 1.3 million UK women, and found that drinking just 4 glasses of alcohol a week (even if it was all wine) caused an absolute increase in the risk of cancer by 1.5%. Of 1,000 women, 15 more of them will get cancer in any time period if they drink 4 glasses a week.

(Notice that they define a “unit” of alcohol as 10 grams, which is less than one glass. I have converted to 17 gram glasses for you.)

Risk of cancer at baseline seems to be 12.5% in the lifetime by age 75, and it seems to increase 1.5% for each 4 glasses of alcohol. I may be interpreting this wrong.

Epilepsy

- Seizures are caused by excessive and disorganized action potentials
- Seizures are treated with anticonvulsants:
 - Phenytoin and carbamazepine help inactivate sodium channels (these drugs put channels in the refractory state). In small doses, this ensures that rapid sequences of spikes can't occur
 - Phenobarbital (a barbiturate), benzodiazepines, and valproate (Depakote) increase GABA-mediated inhibition in various ways

More anticonvulsants

- Gabapentin (Neurontin) probably inhibits voltage-gated Ca^{++} channels. This drug was marketed using very sleazy and aggressive practices.
- Lamotrigine (Lamictal) unknown mechanism. Possibly similar to phenytoin and carbamazepine (voltage-gated Na^{+} channel inactivation). Often used off-label for bipolar disorder, other psychiatric disorders.

Local anesthetics

- Mechanism: They completely plug up the voltage-gated sodium channel (similar to anticonvulsants but a much more complete blockage)
- Cocaine was the first, but it has other effects too.
- Then came procaine, marketed as Novocaine. It is now deprecated for safety reasons.
- Today dentists and doctors use: lidocaine, xylocaine, benzocaine

Shock therapies

History:

Motivation: Perhaps fever is beneficial, and syphilis patients who don't have fevers might improve if they could have a fever.

1917: Dr. Julius Wagner von Jauregg intentionally gives neurosyphilis patients malaria to cause a very high fever. He notices that if they have febrile seizures, they get less crazy and less depressed. He wins the 1927 Nobel Prize for this work.

Shock therapies

Motivation: Maybe crazy people's brain cells are tired and need to rest. Let's induce a coma to provide that rest.

1927: Dr. Manfred J. Sakel gives schizophrenic patients insulin to induce coma, many of them are improved upon waking. Those who have seizures along with their coma improve the most.

Shock therapies

Motivation: I've never seen a schizophrenic epileptic, therefore the diseases must be mutually antagonistic. (This theory is dead wrong and Dr. Meduna's observations were due to coincidence)

1934: Dr. Ladislaus von Meduna gives schizophrenic patients various convulsants to induce seizure. He tried camphor, strychnine, thebaine, pilocarpine, and pentylenetetrazol (metrazol).

Shock therapies

Motivation: Dr. Meduna's drug-induced seizures are incredibly dangerous. Let's try using electricity instead.

1937: Dr. Ugo Cerletti uses electric shocks to induce seizures in schizophrenic patients.

Shock therapies

Over several decades:

- It was noticed that shock therapy is completely ineffective for schizophrenia, but it is very effective for depression
- Paralytics (including succinyl choline and vecuronium) were introduced to relax the muscles and prevent broken bones
- General anesthesia was administered before the seizure to prevent panic and pain
- The electric shock was applied only to one half of the head, or only to the front, to minimize memory loss