The Ballad of Ira Hayes

With the onset of new variants of sars-cov-2 a better understanding of this virus's biological function would do some benefit.

I have found several links between liver metabolism at CP450 and sars-cov-2. This is a lot of information and I have done my best to compile it in an accurate manner so please bear with me.

There seems to be a link between the metabolism of xenobiotics and cytochrome P450. Cytochrome p450 (CP450) is a major liver enzyme involved in the metabolism of many drugs. CYP enzymes have been identified in every kingdom of life: animals, plants, fungi, protists, bacteria, and archaea. This is the same enzyme that does not mix well with grapefruit juice (some medications specifically say to avoid grapefruit juice). The efficiency of this enzyme is mainly based on one's genetic makeup which varies by ethnicity and geography.

CP450 enzymes were first discovered in 1955 in rat liver microsomes. The highest concentration of these enzymes is found in the liver and small intestine.

When you take a medication, your body need to utilize that drug. It does this by utilizing enzymes to break down the molecular structure of the drug. The enzyme called cytochrome P450 2C19 (CYP2C19) helps to process some medications including hydroxychloroquine, codeine, tramadol, and many commercial antidepressants. This means that from individual to individual these medications will have different effects based on the genetic variation of the patient. We have broken down the metabolism efficiency at CP450 into the following categories.

Genetics of CYP2D6		
Genetic Type	**CYP2D6 Activity**	**Ethnic Differences (Approximate)**
Poor metabolizers	None	Caucasians 6%-10%
		Mexican Americans 3%-6%
		African Americans 2%-5%
		Asians ~1%
Intermediate metabolizers	Low	Not established
Extensive metabolizers	Normal	Most people are extensive metabolizers
Ultrarapid metabolizers	High	Finns and Danes 1%
		North Americans (white) 4%
		Greeks 10%
		Portuguese 10%
		Saudis 20%
		Ethiopians 30%

Poor Metabolizer (no CYP2D6 activity)

- Caucasians (6-10%)
- Mexicans (3-6%)
- African Americans (2-6%)
- Asians (1%)

Intermediate Metabolizer (LOW CYP2D6 activity)

- Not established

Extensive Metabolizer (Normal CYP2D6 activity)

- Most people are extensive metabolizers

UltraRapid Metabolizer (High CYP2D6 activity)

- Finns and Danes (1%)
- North Americans (white) 4%
- Greeks (10%)
- Portuguese (10%)
- Saudis (20%)
- Ethiopians (30%)

4% of Caucasians (North America) classify as UltraRapid metabolizers while they also represent 6-10% of poor metabolizers alongside Mexicans

and African Americans. Asians are not well represented as poor metabolizers.

This creates a wide variation of possible effects from drugs that rely on this enzyme for metabolism. The discovery of CP450 was a major milestone as it led to the development of better and more efficient therapeutics.

One particularly interesting drug that was developed by German scientist is called Tramadol or oddly enough Ultram. Ultram was first developed shortly after the discovery of CP450 by Kurt Flick from the German pharmaceutical company Grunenthal. This drug was marketed similar to Oxycontin as a less addictive alternative for pain management. Ultram is quite a revolutionary medication as it is metabolized at CP450 from tramadol to a more potent opioid o-desmethyltramadol.

Ultram was popularized by Nazi sympathizer Ernst-Gunther Schenck in 1977. During WW2, Schenck served as a doctor for the SS. Captured by the Soviets at the end of the war. He was never prosecuted as a war criminal and his participation is unclear. He went on to work for Grunenthal after the war and helped commercialize Ultram.

The purpose of pointing this out is to emphasize that shortly after the discovery of these enzymes in 1955 they were shortly utilized to develop better medicines in the 1960's. However, Ultram didn't really become popularized till 1977.

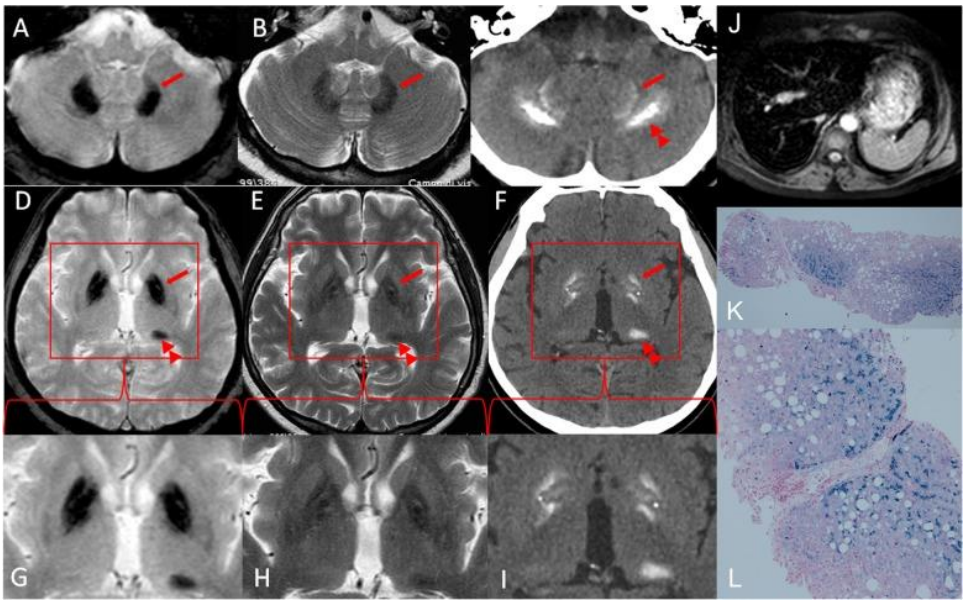
It is theorized that the variation of metabolizers was brought on by crisis such as famine. This concept works by the principle that if resources were low, individuals who could rapidly and more efficiently metabolize nutrients would then have higher rates of survival. Interesting case study I would like to mention is that of the Celtic curse found in Ireland during The Great Irish Potato Famine.

This was known as hemochromatosis a genetic mutation that causes the over absorption of Iron. This is important because it shows that a mutation was advantageous to the survival of a set population. Individuals who over metabolized Iron needed less from their diet which was nutrient-lacking.

Hemochromatosis also known as the “Celtic curse” a mutation of a specific gene that causes organ damage. This causes the body to absorb excessive amounts of Iron.

The iron is deposited in various organs including the liver, heart, pancreas, and the joints causing iron overload.

In one case it was reported that iron deposits were found in the brain from this condition. This was until previously not well reported due to the fact the blood-brain-barrier is relatively affective at filtering. A brain computed tomography (CT) was performed to better characterize the suspected and unexplained brain iron accumulation. Brain-MRI showed the presence of bilateral T2GRE hyperintensities within the globus pallidus, substantia nigra, dentate nucleus, and left pulvinar.



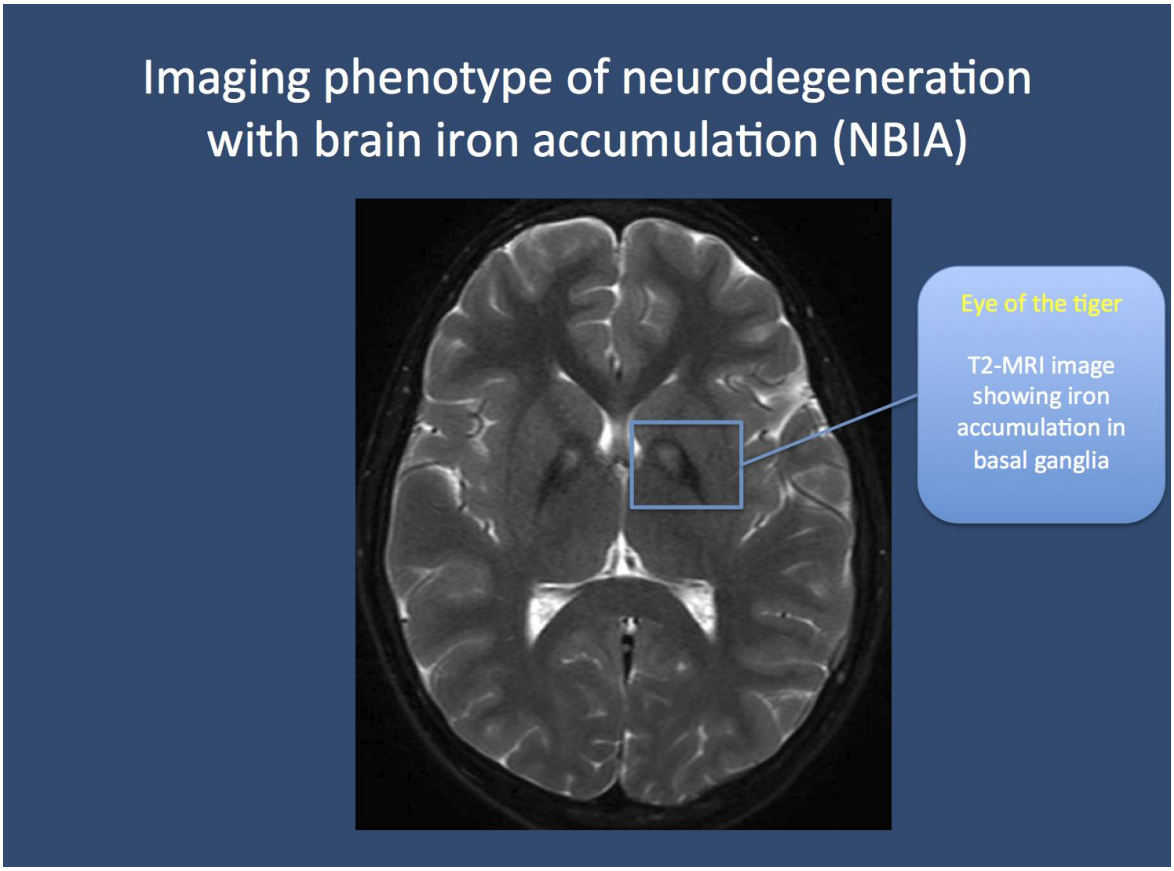
T Brain-MRI T2-weighted images shown in (E) above show the presence of bilateral hyperintensities within the globus pallidus very similar to Hallervorden-Spatz syndrome.

The symptoms can include extreme tiredness, joint pain, and in extreme cases it can cause damage to vital organs. This metabolic disorder

affects more than 1 million Americans. Complications can include the following cirrhosis, diabetes, infertility, arthritis, arrhythmia, or even fatal organ failure.

Different geographical locations, environment, and mitigating factors all are crucial in determine how the metabolism at CP450 could positively or negatively affect a certain population over time.

Furthermore, another interesting rare condition I would like to point out is Hallervorden-Spatz Syndrome. This is known as the Eye of the Tiger sign on MRI brain scans. It shows buildup of iron deposits in key centers of the brain involved in many important functions.



http://epilepsygenetics.net/2013/06/05/the-eye-of-the-tiger-brain-iron-and-the-beta-propeller/

The eye of the tiger sign shows symmetric bilateral abnormal low signal on T2-weighted MRI from accumulation of Iron in globus pallidus.

This was first identified by Nazi scientists during the Holocaust. The name of the condition has been changed to Pantothenate kinase-associated neurodegeneration (PKAN). Essentially a neurogenerative disorder involved in specific regions of the CNS.

https://en.wikipedia.org/wiki/Julius_Hallervorden

Juluis Hallervorden was a German physician and neuroscientist. In 1938, he became the head of the Neuropathology Department of the Kaiser Wilhelm Institute for Brain Research. He was a member of the Nazi party, and admitted to knowingly performing much of his research on the brains of executed prisoners and participated in the action T4 euthanasia program.

He was even quoted saying this horrifying statement.

Hallervorden: “Look here now, boys. If you are going to kill all those people, at least take the brains out so that the material can be utilized. “They asked me, “How many can you examine?” and so I told them...the more the better. “

Hallervorden and Spatz are credited with the discovery of the eye of the tiger condition. After WW2, Hallervorden became President of the German Neuropathological Society and continued his research at the Max Planck Institute in Giessen, Germany. He was never charged with war crimes.

Nuremberg Code:

1. Voluntary informed consent
2. Fruitful result for the good of society
3. Prior experimentation on animals and prior knowledge of the problems
4. Avoidance of unnecessary physical or mental injury
5. Banning of known lethal or disable procedures
6. Degree of risks should exceed benefits
7. Proper preparation and proper facilities to prevent injury or death
8. Performance of experiments only bt scientifically qualified persons
9. Participants may freely end the experimentation
10. The experimentation must stop if it proves too dangerous

Nuremberg Code (1948)

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disability injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Autopsies revealed brown discolorations in different areas of the brain. (Globus pallidus/substantia nigra). It is hypothesized that the disorder originated in central Europe, that was then reinforced with clinically and genetic evidence.

Symptoms include weakness, abnormal posture, movements, and tremors. Diagnostics include MRI scans and genetic testing. MRI shows a buildup or iron deposits in the basal ganglia. This is what then looks like tiger eyes on an MRI. The purpose of introducing this rare disorder is to link metabolism inefficiency with the possible buildup of Iron in key regions of the brain.

In Germany, many of these patients examined for this rare disorder were that of the mentally unfit and handicapped. Prior to Hitler's final solution they ran programs that focused on undesirables. In Germany, during WW2, more than 120,000 handicapped children and adults were murdered for the convenience of the state. To gain scientific knowledge, the brains of many of these patients were examined by German neuropathologists.

https://pubmed.ncbi.nlm.nih.gov/17551614/

Some 698 of these brains were examined by Julius Hallervorden, whose career is reviewed together with that of his superior, Hugo Spatz.

Hallervorden also oversaw the examination of cases of mental handicapped patients targeting those individuals with significant intellectual or physical disabilities in chronic-care facilities for experimentation.

The Nazi program was designed to not only eradicate a whole population but to attempt to enhance scientific discovery simultaneously. This euthanasia program gave the Nazi's a quick opportunity to have unprecedent access to pathological materials and patients. This should provide us today with a cautionary tale on how one's involvment in the advancement of technology could have devestating consequences for humanity.

We have also found interesting data showing cognitive decline in patients with sars-cov-2. Roughly 30% of patients with dementia progressed into the more severe stage. This indicates that sars-cov-2 may be linked to cognitive decline. The mechanism for this is not established but I would like to hypothesize that it could be related to the impact of metabolism at CP450.

Variations of metabolizing ability at cytochrome P450 could be causing disruption in the mineral absorption possibly causing toxicity to these select areas of the brain.

The variation in the genetics gives rise to polymorphisms. (6-8%) Caucasians, and very low percentage of Asian, have little or no activity and are "poor metabolizers".

https://academic.oup.com/ijnp/article/11/5/727/968967

Iron is classified as a transition metal. Transition metals include Zinc, Iron, Nickel, and Copper. These all have major biological important but I will focus mainly on Iron for simplicity.

Iron is vital to plant and animal life. Iron is the active part of the hemoglobin molecule found in our blood. This is important because hemoglobin is what shuttles oxygen around in the body. Iron is absolutely essential to survival.

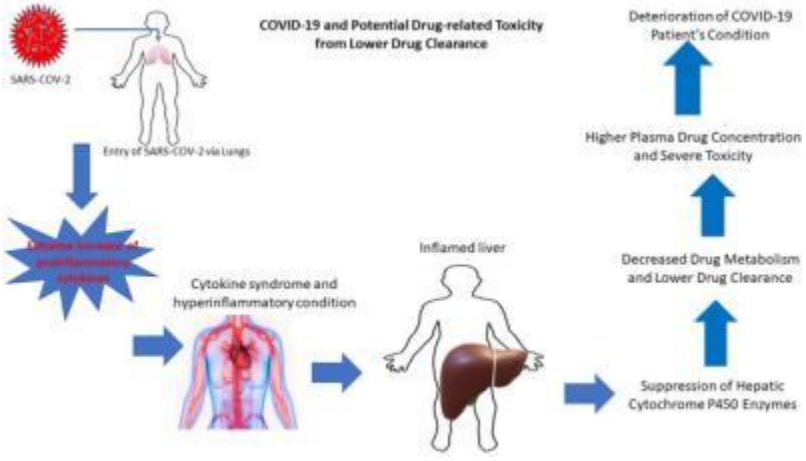
Many people are familiar with anemias and their impact on the body. Anemias are generally regarded as the bodies inability to properly utilize iron. Anemic patients lack sufficient amounts of Iron thus need iron

supplementation. This is a very delicate balance and any external factors will have a great impact on iron metabolism. Free iron reacts with peroxides to form free radicals which damage DNA, proteins, lipids, and other cellular tissues.

Iron is also essential in the development of the brain. I have not dug deep into this but I have speculated myself that Iron absorption might have played a key role in the evolution of man. Humans are capable of complex emotions and somewhere down the lines our brains expanded at an astounding rate. Many theories have been put forward and they are quite fascinating. The stoned aped theory, ability to communicate (rapidly), and enhanced nutrient uptake.

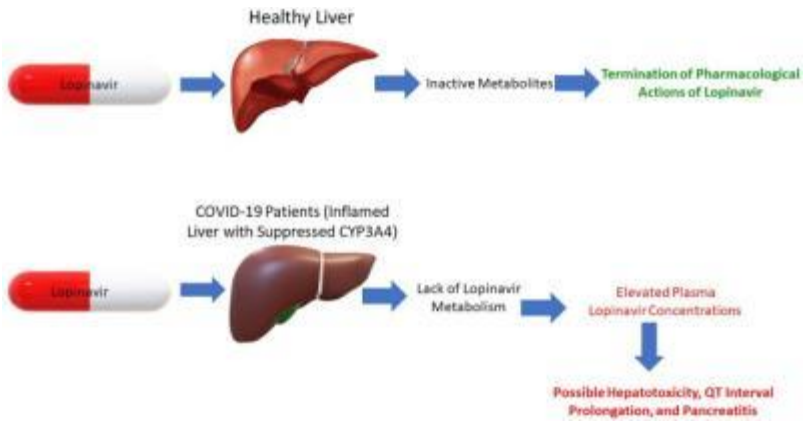
Iron is found in very high levels on meats. The discovery of fire may have made it safe and more practical for humans to eat meat. This would drastically increase the iron intake of that subspecies.

Studies were done to show irons impact on people suffering from sars-cov-2. 60 days after admission 30% of patients presented with iron deficiency and 9% were full blown anemic. This was mainly classified as anemia of inflammation. Inflammation of the blood usually induced by infection and over activation of the immune system. This causes inflammation-inducible cytokines and the regulation of iron hemostasis via hepcidin. The major effects of this are in erythrocytes (blood cells).



This flow chart shows the introduction of sars-cov-2 and how it negatively impacts metabolism. Something to note is that Hydroxychloroquine must be metabolized at CP450. Not all people can metabolize drugs efficiently at this site. Thus this is not a practical medication for all patients. Redemsivir

is another medication that bypasses liver metabolism as it is given via intravenous injection.



The liver is the powerhouse of protein synthesis and of course the primary location of CP450. The slightest disruption of liver function has the ability to impact the clearance of xenobiotics.

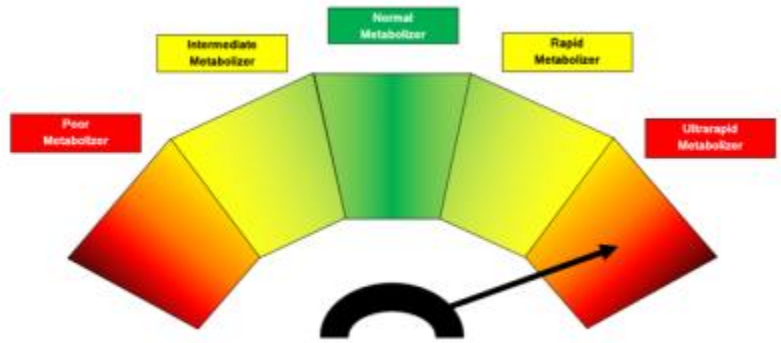
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211730/

Extreme increases in cytokines levels are common in sars-cov-2 infection known as cytokine storms. CYP enzymes can be suppressed by an infection-related cytokine increase and inflammation.

Individuals classified as Ultra metabolizers would be able to clear xenobiotics better. Incomplete detoxification in organisms in the food chain may determine the extent of human exposure to environmental toxins.It has been recognized that xenobiotic metabolism could modify the pharmacological properties of drugs or even activate inert chemical into biologically reactive species.

This then complicates the drug disease interaction of several key medications for sars-cov-2. Overall, it is important to understand a patient's liver metabolism so dosage can be adjust based on the individual.

UltraRapid metabolizers have 2 copies of a CYP2C19 gene with increased activity. This results in very high CYP2C19 activity. About 5 out of 100 people have this gene status.



Different people metabolize drugs so quickly that after they take a normal dose, drug levels in the blood never become high enough for the drug to have any effect.

The major biological significance of these differences has now been deciphered with regard to drug metabolism, action and toxicity, as well as disposition of endogenous substrates, including neuroactive compounds. It is absolutely vital to do more research on CP450/CYP2D6 and its biological role in sars-cov-2 with a view to optimize and standardize the metabolic efficiency.

‘I wish I could be beside you now mother, to bring you the glass of water. All these years I have spent in the service of mankind brought me nothing but insults and humiliation”. - Nikola Tesla’s last letter to his mother.