

ISONIAZID



*“Skirmish in the Wilderness”, oil on canvas, 1864, Winslow Homer,
New Britain Museum of American Art*

When Grant began his spring campaign of '64, he took what they called “the heavies”, the heavy artillerymen, out of the forts in Washington and put them in the field. Many had been in the army two or three years and never heard a shot fired in anger and as these units marched into camp, they were so much larger than combat regiments that soldiers alongside the road used to say, “What division is that?” there was so many of them. But they had some fierce things. The first time they'd go into combat, they'd have a mangled corpse, an artillery casualty, with a blanket over him. As the new green regiments came abreast of them, they'd whisk the blanket off and say, “This is what's waiting for you up ahead!”Not a very pleasant story.

(Shelby Foote, Civil War Historian)

“To get possession of Lee’s army was the first object. With the capture of his army, Richmond would necessarily follow. It was better to fight him outside his stronghold than in it”

(Ulysses S. Grant)

“This advance by General Grant inaugurated the seventh act in the “On to Richmond” drama played by the armies of the Union”

(General John B. Gordon).

“That man Grant will fight us every day and every hour till the end of the war”.

(General James Longstreet).

Grant’s plan called for four simultaneous blows. William Tecumseh Sherman had orders to strike out from Chattanooga for Atlanta. Franz Sigel would advance up the Shenandoah Valley. Benjamin Butler was to lead an army up from the James River, and George Meade was to lead the army of the Potomac, 110,000 strong, south against Lee “Wherever Lee goes, you will go also”, Grant told Meade. And Grant would come along too.

Lee’s strategy was unchanged - destroy the Union resolve to wage war. He would refuse to fight Grant in the open, force him to attack fortified Confederate positions, and thereby offset Grant’s superior numbers. The bloody cost of trying to force the South back into the Union at gunpoint would bolster antiwar sentiment in the North.

“If we can break up the enemy’s arrangements early and throw him back, he will not be able to recover his position or his morale until the presidential election is over and then we shall have a new president to treat with”

(General James Longstreet)

“April 1, 1864. The President came down to Culpeper to review the army. The president was mounted on a fractious horse. Soon after the march began, his tall hat fell off. His pantaloons slipped up to the knees, showing his white homemade draws, which presently slipped up also, revealing a long hairy leg. While we were inclined to smile, we were very much chagrined to see our poor President compelled to endure such torture”.

(Washington Roebling)

“On the morning of May 4, 1864, we, with the entire grand army of the Potomac, were in motion toward the Rapidan. The dawn was clear, warm, and beautiful as the almost countless encampments were broken up, with bands in all directions playing lively airs, banners waving, regiments, brigades, and divisions falling into line, the scene, even to eyes long familiar with military displays, was one of unusual grandeur”

(Chaplain A.M Stewart).

Lee’s 60,000 men were waiting for Grant in the tangled thicket known as the Wilderness, in which they had trapped the army under Joseph Hooker only a year before.

“Covered by a dense forest almost impenetrable by troops in line of battle the undergrowth was so heavy that it was scarcely possible to see more than 100 yards in

any direction. The movements of the enemy could not be observed until the lines were almost in collision”

Advance units of the Union army camped for the night on the old Chancellorsville battlefield, where winter rains had washed open the shallow graves.

“In glades they meet skull after skull where pine cones lay - the rusted gun, green shoes full of bones, the moldering coat and cuddled-up skeleton and scores of such. Some start as in dreams, and comrades lost bemoan. By the edge of these wilds Stonewall had charged - but the year and the man were gone”

“It grew dark, and we built a fire. The dead were all around us. Their eyeless skulls seemed to stare steadily at us. The trees swayed and sighed gently in the soft wind”
(Private Frank Wilkeson)

The Battle of the Wilderness began in chaos. Units got lost, fired on their own comrades. Officers tried to navigate by compass. But on the second day Union forces drove through the Confederate center. As a worried Lee watched, General John Gregg’s Texans hurried to plug up the hole.

“Scarce had we moved a step when General Lee, in front of the whole command, raised himself in his stirrups, uncovered his gray hairs, and with an earnest voice exclaimed, “Texans always move them!”

“Never before in my lifetime did I ever see such a scene as was enacted when Lee pronounced these words. A yell rent the air that must have been heard for miles around. A courier riding by my side, with tears coursing down his cheeks, exclaimed, “I would charge hell itself for that old man !”.
(Confederate soldier)

The Texans held the position until reinforcements came. By the end of the day, the Confederates had smashed Grant’s right, seized two generals and 600 prisoners, and come close to cutting the Union supply line. Grant received these reports without comment.

Right in the middle of the Battle of the Wilderness, all staff men who had been fighting in the east all this time - and he had just come from the west - kept talking about Bobby Lee. Bobby Lee, he’s going to do this and going to do that. And Grant finally told them, “I’m tired of hearing about Bobby Lee; you think he’s going to do a double summersault and land in our rear!? Quit thinking about what he’s going to do to you and think about what you’ll do to him. Bring some guns up here!” , things like that. Grant...he’s wonderful!
(Shelby Foote, Civil War Historian)

The Wilderness is probably not the bloodiest battle in the war, but the most terrible battle in the war in many ways. Grant in two days loses more men than Hooker did at Chancellorsville. But in the Wilderness, the leaves from the previous year cover the ground, and using the type of weapon they used in the Civil War, you have lots of lint and linen smoldering, falling into the leaves, and it will set these leaves afire. And men

who've been shot badly through the bowels, with broken legs, will not be able to move as the fire starts burning towards them and large numbers of wounded men will perish in the flames.

(Ed Bearss, Civil War Historian)

Grant's first move had been a disaster. The Wilderness had cost 17,000 men. That night brush fires raged through the woods. 200 wounded federal soldiers burned alive while the entrenched armies listened to their screams.

"I am holding my breath in awe at the vastness of the shadow that floats like a pall over our heads. It is come that man has no longer an individual existence, but is counted in thousands and measured in miles".

(Clara Barton, Civil War Nurse).

In the Wilderness, surgeons amputated limbs without letup for more than 100 hours and sent back behind the lines 2,000 wounded men each day. "As a wounded man was lifted on the table, often shrieking with pain, as the attendants handled him, the surgeon quickly examined the wound and resolved upon cutting off the wounded limb. Some ether was administered. The surgeon snatched his knife from between his teeth, wiped it rapidly once or twice across his bloodstained apron, and the cutting began. The operation accomplished, the surgeon would look around with a deep sigh then... "Next"
(Carl Schurz)

"The Wilderness was a useless battle fought with great loss and no result"

(Union soldier, Washington Roebling)

Grant, in the Wilderness, after that first night in the Wilderness, went to his tent and broke down and cried very hard. Some of the staff members said they'd never seen a man so unstrung. Well he didn't cry until the battle was over, and he wasn't crying when it began again the next day.

(Shelby Foote, Civil War Historian)

What was different about Grant became clear the next morning when he gave the order to march. For the first time after a defeat, the army of the Potomac was moving forward!

"May 7. If we were under any other general except Grant, I should expect a retreat, but Grant is not that kind of soldier"

(Elisha Hunt Rhodes).

"Our spirits rose", one Union man remembered. "We marched free. The men began to sing out "Ulysses", another soldier said, "Don't scare worth a damn".

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

After three years of bloody fighting, the North, and despite by now it's overwhelming superiority in men, had not been able to subdue the South in the eastern theatre - the "main game" of the Civil War. Indeed Robert . E. Lee had invaded the North twice, almost securing victory in the second at Gettysburg. Both times ultimately however, he

was driven back to the South. Six times, the North tried to invade the South with massive armies under Irvin McDowell, George McClellan, John Pope, George McClellan again, Ambrose Burnside, and Joseph Hooker, but each time they were bloodily repulsed. By May 1864 it seemed neither side could gain the critical victory they needed on the other's soil. Lincoln knew he had the men, industry, and the material, to ensure ultimate victory, but what he had lacked was a commander that could match it with Robert E. Lee, but now the most famous General, North or South of the Potomac, indeed of the world. But by now Lincoln realized he may have his General. He looked to one not from the east, but from the far western theatre of the Mississippi, the victor of Fort Donelson, Shiloh, Vicksburg and Chattanooga - his name was Ulysses S. Grant. Though often accused of not caring about the cost of his victories, Lincoln at least knew that he had someone who would fight. When Grant was summoned to Washington, a number of his commanders who had come with him, retailed eastern commanders with stories of Grant's impressive in the west. But eastern commanders remained unimpressed - "That all may be so", one of them mumbled, "But you haven't met Bobby Lee!"

Grant was now in command of the all armies of the North, and at a combined strength of over one million men, it was the biggest army in history. He would lead the greatest Northern army yet, into the South and finally crush the Confederate States of America. But Lee would be waiting with his army in a primal untamed part of Virginia, known only as the "Wilderness". Here within the dense forest, Grant would not have the advantage of numbers and heavy artillery. As Grant's army moved through the area on its way to Richmond, Lee struck in massive ambush. Grant in two days lost more men than Hooker did at Chancellorsville, 17,000 casualties. The North, who finally thought they had their hero was shocked at the news. Robert E. Lee had defeated Ulysses S. Grant! Grant had not been so badly shaken since Shiloh. At one point he was reported to have wept uncontrollably, the only time he lost control of himself in the war. On previous occasions, Northern commanders had retreated back to Washington following a major defeat. All eyes now turned to Grant to see what he would do. But Grant was a fighter indeed, as Lincoln had observed. He still had the men. There would be no retreat. Despite the huge losses he thundered to his men the familiar refrain, "On to Richmond!" If we were under any other general except Grant, I should expect a retreat, but Grant is not that kind of soldier", Elisha Hunt Rhodes exclaimed. He resorted the confidence of his shaken troops. "Our spirits rose", one Union man remembered. "We marched free. The men began to sing out "Ulysses!". For the first time in the war the Unionists cheered a commander as Southerners had repeatedly done so for Lee and Stonewall Jackson. But instead of heading directly for Richmond, he would try to outflank the Confederates. But Lee always had a genius of knowing the mind of his adversaries. "General Grant is not going to retreat", he said. "He will move his army to Spotsylvania. I'm so sure of his next move that I have already made arrangements". The next day Grant marched for Spotsylvania.

The mycobacterial species are a most intractable enemy. Despite our best efforts it defeats all of our conventional antibiotics. It is clear we need a real fighter for this enemy. And in this regard we have our General in isoniazid! But we must recall the titanic battles Grant fought with Robert E. Lee. Victory will not come easily, and nor will it be swift!

ISONIAZID

Introduction

Isoniazid, also known as **iso-nicotinyl-hydrazide** (INH), is an **anti-mycobacterial** antibiotic primarily used in the treatment and prevention of tuberculosis in combination with other agents.

Because resistance can develop within a few weeks to isoniazid used alone, it is usually given together with one or more of the other anti-tubercular agents.

Pyridoxine is also taken with isoniazid, to reduce the risk of peripheral neuropathy, especially for people at risk.

Isoniazid is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

Isoniazid is potentially lethal if taken in overdose.

See also separate documents on:

- **Isoniazid Overdose (in Toxicology folder)**
- **Pyridoxine (in Drugs folder)**

History

Isoniazid was first synthesized in the early 20th century, but its activity against tuberculosis was not reported until the early 1950s. It was introduced into clinical practice in 1952. This marked one of the most significant landmarks in the history of medicine - for the first time it seemed that a cure for tuberculosis was possible.

Isoniazid was first tested at "Many Farms", an American Indian **Navajo** community. There was a high incidence of tuberculosis among the tribe. Additionally none had been previously treated with streptomycin, which was the principle tuberculosis treatment at that time.

Chemistry

Isoniazid is **iso-nicotinyl-hydrazide** (INH)

It is structurally related to pyridoxine, nicotinic acid and NAD.

Physiology

Pyridoxine (vitamin B6) is metabolized to pyridoxal - 5 - phosphate (or P5P, the active form of vitamin B6).

P5P is a ubiquitous cofactor for over a 100 cellular biochemical enzyme reactions.
Pyridoxine → pyridoxal - 5 - phosphate

Pyridoxine (i.e vitamin B6) deficiency is sometimes observed in adults treated with high doses of isoniazid. This is thought to be due to its competition with pyridoxal - 5 - phosphate for the enzyme apo-tryptophanase.

Classification

The anti-mycobacterial drugs are those that have specific anti-mycobacteria activity and include:

1. Anti- tuberculosis agents

Examples include:

- Streptomycin
- **Isoniazid**
- Rifampicin
- Ethambutol
- Pyrazinamide

2. Anti-leprosy agents:

Examples include:

- Dapsone
- Rifampicin
- Clofazimine

Preparations

Isoniazid as

Tablets:

- 25 mg
- 100 mg

Ampoules:

- A parenteral formulation has been developed, but is not available in Australia.

Mechanism of Action

Isoniazid is thought to inhibit the synthesis of mycolic acids, which is important constituents of the mycobacterial cell wall.

It is bactericidal against actively dividing *M. tuberculosis*

It is bacteriostatic against resting bacteria.

It is active against both intra and extracellular organisms.

Pharmacodynamics

Isoniazid only has antibacterial activity against **mycobacteria**.

It is s one of the first line chemotherapeutic agents used in treating tuberculosis, however, because resistance may develop within just a few weeks to isoniazid used alone, it is given together with one or more other anti-tubercular agents.

Treatment (in combination with other agents) must be prolonged to effect cures - (6 - 9 months) .

Pharmacokinetics

Absorption:

- Absorption is rapid and complete following oral administration.
- Peak serum levels occur within 1-2 hours.

Distribution:

- Isoniazid is distributed into all tissues and fluids. CSF concentrations of the drug are reported to be up to 90 - 100% of concurrent plasma concentrations.
- The volume of distribution is 0.6 L/kg.
- Protein binding is variable at 4 - 30 %
- Isoniazid can cross the human placenta.
- Small amounts are excreted in human breast milk.

Metabolism and elimination:

- Isoniazid undergoes hepatic metabolism by:

♥ Acetylation → acetyl - isoniazid.

Or

♥ Hydrolysis by cytochrome P450 → hydrazine derivatives.

- Some of the drug is excreted unchanged in the urine.
- There are **fast** and **slow acetylators** so that elimination half lives may vary from 1- 4 hours.

The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and are more susceptible to toxic reactions.

Indications

Isoniazid is used in combination with other anti-tuberculous drugs for

1. The treatment of active tuberculoses
2. The treatment of latent tuberculosis

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Previous severe adverse reaction including:
 - Immediate hypersensitivity reactions to isoniazid (contraindicated).
 - Skin reactions (contraindicated).
2. Epilepsy (caution):
 - Isoniazid may cause seizures; ensure adequate control.
3. Those at *risk* of developing peripheral neuropathy with isoniazid (caution):
 - Severe malnutrition
 - Diabetes

- HIV infection
- Alcoholism
- Renal impairment
- Pregnancy

Use pyridoxine 25 mg daily as prophylaxis.

4. Renal impairment:

- As above, there is a greater risk of peripheral neuropathy (use pyridoxine 25 mg daily as prophylaxis).

5. Hepatic impairment:

Isoniazid is contraindicated in **acute** liver disease.

Risk of hepatotoxicity may increase in patients with hepatic impairment; use cautiously and monitor liver function closely. Do not start treatment if ALT concentration is > 2 - 3 times upper normal limit.

The risk increases with:

- Alcoholism or treatment with other hepatotoxic drugs increases risk of hepatotoxicity (hepatitis is common when taken with rifampicin).
- Age > 35 years
- Women, especially postpartum and those > 60 years.

6. Food interactions:

Caution with tyramine rich foods:

- Isoniazid has some weak MAOI action and so serotonin levels may be raised with excessive tyramine intake (tyramine is the dietary precursor of serotonin). This may lead to serotonergic symptoms.

Caution with histamine rich foods:

- Histamine is also metabolized by MOA and so excessive histamine rich foods may result in histamine related symptoms.

Pregnancy

Isoniazid is classified as a category A drug with respect to pregnancy.

Category A drug are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Isoniazid is considered safe to use during pregnancy, although pyridoxine supplementation is also recommended to reduce the risk of peripheral neuropathy.

Breast feeding

Small amounts of isoniazid are excreted into breast milk, but it is unlikely to cause harm to the breastfed infant.

However, observe the breastfed infant for signs of jaundice, fatigue, weakness and vomiting.

Maternal and infant pyridoxine supplementation is recommended during isoniazid therapy.

Adverse Effects

1. Hypersensitivity reactions
2. Lethargy /malaise.
3. Neurological reactions:

These are due to pyridoxine deficiency and may include:

- **Peripheral neuropathy:**

The principle adverse neurological reaction is peripheral neuropathy

Peripheral neuropathy is dose related and is uncommon with doses of isoniazid less than 5 mg/kg.

Patients receiving larger than usual doses or with pre-existing peripheral neuritis should receive 100 to 300 mg of pyridoxine daily.

Risk factors for the development of peripheral neuropathy include the following:

- Severe malnutrition
- Diabetes
- HIV infection

- Alcoholism
- Renal impairment
- Pregnancy

To prevent the development of peripheral neuropathy **pyridoxine 25 mg daily is given.**

Less commonly:

- Seizures (**seen in particular with overdose**).
- Toxic encephalopathy (memory impairment, toxic psychosis).
- Optic neuritis and atrophy

4. Pyridoxine (i.e vitamin B6) deficiency:

Pyridoxine (i.e vitamin B6) deficiency *in more general form* is sometimes observed in adults treated with high doses of isoniazid.

This is thought to be due to its competition with pyridoxal - 5 - phosphate for the enzyme apo-tryptophanase.

5. Hepatitis:

Increases in serum aminotransferases:

- 10 - 20% of people in the first few months of treatment
- It may however occur less commonly after this period

This *usually* resolves despite continuation of drug.

However, it can sometimes progress to more serious hepatic dysfunction sometimes without obvious symptoms (and so monitoring is required).

Risk factors for hepatitis include:

- Age:
 - ♥ 35 - 50 years - 1.2%
 - ♥ > 50 years - 2.3%
- Excessive alcohol use

- Use with other hepatotoxic drugs (hepatitis is common when taken with rifampicin).

Dosing

Because resistance can develop within a few weeks to isoniazid used alone, it is usually given together with one or more other anti-tubercular agents.

Pyridoxine 25 mg with each dose of isoniazid is recommended to reduce the risk of peripheral neuropathy, especially for people at risk

In general terms:

Tuberculosis:

Use for **6 months**, as part of the 6-month **multidrug** regimen.

Adults

- *Daily regimen*, oral 5 mg/kg (maximum 300 mg) once daily.
- *Three times a week regimen*, oral 15 mg/kg (maximum 900 mg) 3 times each week.

Child >1 month

- *Daily regimen*, oral 10 mg/kg (maximum 300 mg) once daily.
- *Three times a week regimen*, oral 15 mg/kg (maximum 900 mg) 3 times each week.

Latent tuberculosis:

Adults:

- Oral 300 mg once daily for 6 - 9 months.

Child >1 month:

- Oral 10 mg/kg (maximum 300 mg) once daily, preferably for 9 months.

Monitoring:

Monitor aminotransferase concentrations at baseline and then **each month** as serious hepatotoxicity can occur without symptoms

Stop isoniazid if:

- Aminotransferase concentrations increase to > 5 times ULN without symptoms.
- Aminotransferase concentrations increase to >3 times ULN with symptoms.
- The bilirubin concentration rises

Also stop isoniazid if symptoms of hypersensitivity occur

References

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