THE NORTHERN HOSPITAL

PENICILLIN

"The Crisis", oil on canvas, 1891, Sir Frank Dicksee.

On March 14, 1942, thirty one year old Anne Miller lay in New Haven Hospital dying of blood poisoning. She had developed a bacterial infection following a miscarriage a month before, a then common complication that quickly could turn fatal. For all those weeks her temperature swung between 103 and 106 degrees F (39.4 and 41.1 degrees C), often leaving her delirious as her condition worsened and her body wasted away from

her inability to eat. Blood transfusions, surgery, and many doses of the recently developed sulpha drugs all failed to kill the streptococcus that had colonised her blood.

Her doctor, John Bumstead of the Yale Clinical Faculty, was about out of hope for her when he remembered a passing conversation with Dr John Fulton, another of his patients, who was lying ill in a nearby room. Fulton and his wife were friends of Howard Florey, an Oxford University scientist who headed the group that was developing an almost unknown substance called penicillin, which was many times more powerful against bacteria than any known drug. The devastation and the crippling of industry caused by World War II made further production and testing in England difficult, so in 1941 Florey and his colleague Norman Heatley had come to the United States to try to persuade American drug companies to work on this potentially miraculous but still unproven medicine. Heatley had even stayed on to help the New Jersey pharmaceutical company Merck manufacture penicillin.

Bumstead beseeched Fulton to help him get some of the drug for Mrs Miller. Fulton, a champion of Florey's research, knew the chairman of the Committee on Chemotherapy in Washington D.C, which controlled all important medicines during World War II; after Fulton's call he authorized Merck to release 5.5 grams of penicillin - about a teaspoon full. It was half of the entire amount in the United States.

The tiny cache of raw antibiotic was soon delivered to Mrs Miller's room, where it was passed through an extrafine filter to remove impurities and dissolved in a saline solution. No one was certain of the appropriate dose, so a small one was injected by an intern, at three PM.

Her doctors waited for a possible negative reaction, but when after four hours there was none, a larger dose was administered. When the second dose also caused no harmful reaction, all other medication was discontinued and penicillin was injected every four hours. by midnight her temperature was down to 100 degrees. By nine A.M the next day, it was normal for the first time in a month. She began to eat hearty meals, again for the first time in weeks. Within twenty-four hours, the deadly bacterial growth in her blood had disappeared. After a month-long convalesce, during which Mrs. Miller received more penicillin manufactured by Merck, she went home and lived until she died in 1999, at age ninety.

Four patients in Oxford had been cured by penicillin several months earlier, but Anne Miller as arguably the first patient pulled back from death's door by the drug. Her reclaimed life marks a revolution in Medicine that has touched virtually everyone on Earth.

Eric Lax, "The Mould in Dr Florey's Coat", 2004.

By 1942 other patients had been treated with penicillin before Anne Miller - it's not entirely certain who has claim to be the first person treated by it - (though one thing is for certain - it wasn't Winston Churchill!). What can be said is that the initial patients were not suffering from life threatening conditions - Anne Miller was. She was the first person whose life was saved by penicillin.

It is difficult in the 21st century to appreciate just how feared a diagnosis of pneumonia was in the days before antibiotics. No treatment humanity could devise was effective. It was a common cause of death among the elderly (the "old person's friend") - but tragically it also frequently took the lives of the young and the very young. Physicians were completely powerless to do anything about it and it was left to the individual's own immune defenses to fight it. Physicians although they were powerless were excellent at reading the signs of a patient's progress, and many could, if not treat the patient, then at least make astonishingly accurate predictions about whether or not they would survive. The greatest contribution they could make in addition to their empathy and support was their almost oracle-like ability to predict the outcome between life and death. It is fascinating to read some of these accounts on clinical pictures we no longer see today. Young people suffering from "typical" pneumococcal pneumonia would become very unwell, until such time that they reached a crossroads where they would either die or survive. Interestingly many would herald quick recovery by a process that was designated as "crisis"- this was characterized by profuse sweating followed by a rapidly falling temperature (presumably due to release of pyrogens from bacteria naturally killed by the patient's immune system) - others sometimes showed a more gradual response - termed "lysis". People that did not show signs of the typical "crisis"- were essentiality doomed. Doctors would wait by the bedside of sick patients all night - looking for the signs - relatives and loved ones would wait in the next room tearfully awaiting the pronouncement of the doctor that the crises had arrived or it had not. We may be bemused a this from the vantage point of the 21st century however many physicians were extremely skilled in this prognostication - a skill that no longer exists amoung physicians today.

The great Sir William Osler in his 1892 Textbook of Medicine provided a dramatic picture of the much feared pneumonia describing in intricate graphs the course of the disease in terms of the evolving pattern of the patient's respiration, pulse and temperature. He demonstrated the truth of the crisis - that was so dramatically portrayed in those days in novels and on the stage and in the visual arts.

Cecil Russell in his 1947 Textbook of medicine, described the crisis as follows....

"Pneumonia may terminate by crisis or lysis. The typical crisis of pneumonia is one of the most striking features of the disease. The patient, struggling against a virulent infection, often appears on the verge of collapse. The whole organism seems to be affected by the toxemia. Suddenly the patient begins to perspire freely; there is a rapid drop in temperature to normal or subnormal, accompanied by a corresponding fall in the respiratory and pulse rate. In a few hours the entire clinical picture is changed. The patient looks and feels much better and drops off into a quiet sleep…In many cases there is no definite crisis, but the patient's temperature comes down gradually by lysis…"

He goes on to describe the course of pneumonia should crisis (or lysis) not be observed - death by hypoxia and overwhelming sepsis.

PENICILLIN

Introduction

Penicillin is the archetype beta-lactam antibiotic.

It is a **narrow spectrum** antibiotic with cover against **gram positive bacteria.**

The principle forms of penicillin include:

1. **Phenoxymethyl-penicillin (**also commonly known as **Penicillin V)**:

    - This is an **orally** active form of penicillin.
    - It is intrinsically **less active** than benzylpenicillin.

2. **Benzyl-penicillin** (also commonly known as **penicillin G** or trade name **BenPen**):

    - The intravenous form of penicillin.

3. **Procaine penicillin** (or procaine benzylpenicillin or trade name **Cilicaine**):

    - This is an **intramuscular depot** preparation that is often used as an alternative to benzylpenicillin when intravenous therapy cannot be administered (e.g. in rural and remote areas where hospitalisation is delayed).
    - It can maintain an effective blood concentration for up to **24 hours** after a single dose.

4. **Benzathine penicillin** (or trade name **Bicillin**):

    - This is a **long acting intramuscular depot** preparation that results in low concentrations of benzylpenicillin for up to **4 weeks.**

Benzathine and procaine penicillins are hydrolysed to benzylpenicillin

Narrow-spectrum penicillins are mainly active against Gram-positive organisms, but are inactivated by beta-lactamase enzymes.

Due to its *narrow* spectrum, **benzylpenicillin** (penicillin G) remains the treatment of choice for *susceptible* infections (such as pneumococcal pneumonia).

The penicillins have a very wide therapeutic index.

The principle adverse reactions are allergic including life threatening anaphylaxis.

History

In **1897** the French physician, **Ernest Duchesne** (1874 - 1912) at the École du Service de Santé Militaire in Lyons, published a medical thesis entitled *Contribution à l'étude de la concurrence vitale chez les micro-organismes : antagonisme entre les moisissures et les microbes* (Contribution to the study in vital competition in microorganisms: antagonism between molds and microbes). In this work he noted the ability of *Penicillium glaucum*, a fungus, used in the making of some types of blue cheeses, to inhibit the growth of some bacteria. The stunning implications of his thesis were completely unappreciated and it was largely ignored.

The Scottish biologist, pharmacologist and botanist, **Alexander Fleming**, (1881 - 1955) is credited with the discovery (or rediscovery) of penicillin in **1928**, when he noticed that the fungus, ***Penicillium notatum*** which had accidently contaminated a plate culture of staphylococcus, appeared to be inhibiting the growth of the staphylococcus. From this observation he isolated the fungal substance penicillin in the form of a crude culture "broth" - essentially the discovery of the world's first antibiotic. However, somewhat astonishingly, he then did virtually nothing with his discovery.

It would be left to the brilliant **Australian** scientist **Howard Florey** (1898 - 1968) and his research team, (most notably Ernst Boris Chain and Norman Heatley) at Oxford University, to isolate pure penicillin, demonstrate the miraculous "in-vivo" ability of penicillin to kill pathogenic bacteria, demonstrate its safety in vivo, and to then actually produce it in large enough quantities to be used as an effective therapeutic agent in humans in the early 1940s. Penicillin would be responsible for saving not only many civilian lives, but also countless lives of soldiers then fighting in the Second World War, lives that in the conflicts of previous ages would most certainly have been lost from infectious complications of their wounds and their surgery.

Howard Florey, Alexander Fleming and Ernst Boris Chain shared the 1945 Nobel Prize for Physiology or Medicine.

Chemistry

Penicillin is the archetype beta-lactam antibiotic.

The **beta-lactam antibiotics** are structurally related via their central **beta lactam** moiety. Side chains determine antibacterial, pharmacological and pharmacokinetic properties.

The beta-lactam antibiotics include:

1. Penicillins
2. Cephalosporins
3. Carbapenems
4. Monobactams

Classification

The penicillins are classified into 5 principle groups:

1. Narrow-spectrum penicillins:

   These are **narrow spectrum** antibiotics with cover against **gram positive bacteria.**

   Examples include:

   - **Phenoxymethyl-penicillin (Penicillin V).**
   - **Benzyl-penicillin (Penicillin G)**

2. Narrow-spectrum penicillins with antistaphylococcal activity:

   These are stable to beta-lactamase enzymes produced by some bacteria such as staphylococci.

   Examples include:

   - **Dicloxacillin**
   - **Flucloxacillin**

3. Moderate-spectrum penicillins:

   These have better activity than benzylpenicillin against *some* Gram-negative organisms (e.g. *Escherichia coli*, *Haemophilus influenzae*),

   They are however inactivated by strains that produce beta-lactamase enzymes.

   Examples include the aminopenicillins:

   - **Amoxycillin**
   - **Ampicillin**

4. Broad-spectrum penicillins (beta-lactamase inhibitor combinations):

   The beta-lactamase enzyme inhibitors **clavulanate** and **tazobactam** have little inherent antibacterial activity.

   They inhibit the enzymes produced by *Staphylococcus aureus, Bacteroides fragilis* and *H. influenzae,* and also some of the beta-lactamase enzymes produced

by *E. coli* and *Klebsiella* species and so can *significantly* extend the spectrum of activity of penicillin antibiotics when used in combination.

Examples include:

- **Amoxycillin and clavulanate**
- **Ticarcillin and clavulanate**
- **Piperacillin and tazobactam**

5. Broad-spectrum penicillins with antipseudomonal activity:

These penicillins have extended activity against *Pseudomonas aeruginosa*, though high doses are required.

These drugs are only available in combination with a beta-lactamase enzyme inhibitor

Examples include:

- **Piperacillin**
- **Ticarcillin**

Preparations

Tablets:

- Phenoxymethylpenicillin: 250 mg, 500 mg.

Ampoules/ syringes:

- Benzylpenicillin ampoules (powder for reconstitution):
  - ♥ 600mg, 1.2 grams, 3.0 grams.
- Procaine penicillin:
  - ♥ 1.5 grams / 3.4 ml syringe.
- Benzathine penicillin:
  - ♥ 900 mg (viscous, opaque aqueous suspension) in 2.3 ml prefilled syringe.

Confusingly penicillin doses are sometimes quoted in terms of "**units**":

- 600 mg of benzylpenicillin = 1 million units.

- 1 gram of procaine penicillin = 1 million units.
- 900 mg of benzathine penicillin = 1.2 million units.

Mechanism of Action

The penicillins are **bactericidal** agents.

They interfere with **bacterial cell wall peptidoglycan** synthesis during the stage of active multiplication, thereby leading to cell lysis and death.

The penicillins are inactivated by **bacterial beta-lactamases.**

Pharmacodynamics

Narrow-spectrum penicillins are mainly active against **Gram-positive** organisms, principally:

- Staphylococci (except penicillinase-producing strains).
- Streptococci
- Pneumococci.
- Clostridium perfringens

Also:

- Corynebacterium diphtheriae
- Treponema pallidum

There is *some* Gram negative cocci susceptibility such as:

- Gonococci (though most strains are now resistant).
- Meningococci.

They are however **inactivated by beta-lactamase enzymes** and so are not active against the penicillinase producing bacteria, which include many strains of staphylococci.

Due to its *narrow* spectrum, **benzylpenicillin** (penicillin G) remains the treatment of choice for *susceptible* infections (such as pneumococcal pneumonia).

Pharmacokinetics

Absorption:

- **Phenoxymethylpenicillin** (penicillin V) is acid-stable and so can be given **orally.**

- **Benzylpenicillin** (Penicillin G) is given **intravenously**. Benzylpenicillin can also be given **intramuscularly**, though **intravenously is preferred.**

- **Procaine penicillin** and **Benzathine penicillin** are both given intramuscularly. These must *not* be given IV.

  The **procaine salt** has low solubility and is administered intramuscularly as a suspension of crystalline procaine penicillin. These particles dissolve slowly after administration, so that absorption from the injection site takes place over a prolonged period. Because absorption continues for up to 24 hours, injection may be given only once or twice daily, or as an initial treatment. A peak serum level is reached in about 2 hours.

  Intramuscular **benzathine benzylpenicillin** is absorbed **very slowly** into the bloodstream from the intramuscular site and converted by hydrolysis to benzylpenicillin. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Distribution

- Benzylpenicillin crosses the placental barrier

- Benzylpenicillin is excreted in breast milk.

- Benzylpenicillin has poor penetration into the cerebrospinal fluid through intact healthy meninges, however it does have good penetration in inflamed meninges.

- About 60% of benzylpenicillin is bound to serum proteins.

Metabolism and excretion:

- **Benzathine and procaine penicillins are hydrolysed to benzylpenicillin**

- Benzylpenicillin is 70% excreted through the kidneys (10% of this by glomerular filtration and 90% of it by tubular secretion).

  The renal tubular secretion of benzylpenicillin can be partly blocked by **probenecid** (and so lead to an increase in blood benzylpenicillin levels).

  About 25% is metabolized by the liver,

Around 5% is is excreted in the bile.

Indications

Infections due to susceptible / likely susceptible bacterial organisms.

Conditions include:

1. Bacterial sore throat:
    - Pharyngitis and/or tonsillitis
2. Impetigo
3. **Mild early** cellulitis and erysipelas
4. Acute rheumatic fever
5. Early syphilis (and other spirochete infections).
6. Valve endocarditis (in combination with other agents).
7. CAP:
    - Uncomplicated community acquired pneumonia in the immunocompetent, who are not severely unwell (often in combination with other agents).
8. Dental infections (in combination with other agents).

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:

- Contraindicated with a history of severe or immediate allergic reaction to penicillin.
    - ♥ Including urticaria, anaphylaxis, interstitial nephritis to a penicillin (seek specialist advice if using a penicillin is critical).
- Caution in those with a history of an allergic reactions to other beta lactam antibiotics such as a carbapenem or a cephalosporin:

- ♥ As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.

- Procaine and benzathine penicillins must **not** be administered IV.

  - ♥ There have been reports of inadvertent intravenous administration of the procaine and benzathine formulations which have been associated with severe neurovascular complications.

- Peripheral nerve injury:

  - ♥ Injection of **benzathine** penicillin **into or near** a nerve may result in permanent neurological damage.

Pregnancy

Penicillin is classified as a class A drug with respect to pregnancy.

Class A drugs 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.

Breast feeding

Safe in breast feeding.

Adverse Effects

All the beta lactams including the penicillins have a **wide therapeutic index** and are not associated with significant adverse effects, apart from hypersensitivity reactions..

Adverse reactions include:

1. Allergic reactions

   - Including serious and *fatal* **anaphylactic** reactions.

     Anaphylaxis is more frequent following **parenteral** therapy, but it has also occurred in patients on oral therapy

2. GIT upset (oral penicillin)

Less commonly:

3. Pseudomembranous colitis:

- Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening.

  Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

4. Jarisch-Herxheimer reaction:

   - This is fever, chills, hypotension due to release of pyrogens from the killed organisms occurring shortly after starting to treat syphilis and other spirochete infections.

     Prednisolone may be used to minimise likelihood of reaction in cardiovascular syphilis or neurosyphilis where this can be dangerous.

Rarely:

5. Dermatological hypersensitivity reactions.

   - Usually mild, but occasionally can be severe e.g. exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

6. Interstitial nephritis

7. Hepatic:

   - Hepatitis

   - Cholestatic jaundice

8. Neurotoxicity (rare):

   - Usually only with high doses, e.g. drowsiness, hallucinations, confusion, seizures.

Dosing

Exact dosing and the duration of dosing depends on the condition being treated as well as the severity of the condition and illness.

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

In *general* terms:

Phenoxymethylpenicillin (Penicillin V) :

- Usual dosing is **500 mg orally, 6 hourly.**

Benzylpenicillin (Penicillin G):

- **1.2 grams - 2.4 gram IV 4 - 6 hourly.**

  Children generally 30 - 50 mg / kg (to as maximum of 2.4 grams) 4- 6 hourly

- Higher and more frequent dosing is used for more serious infections, e.g. in patients with meningitis use 2.4 grams 4 hourly.

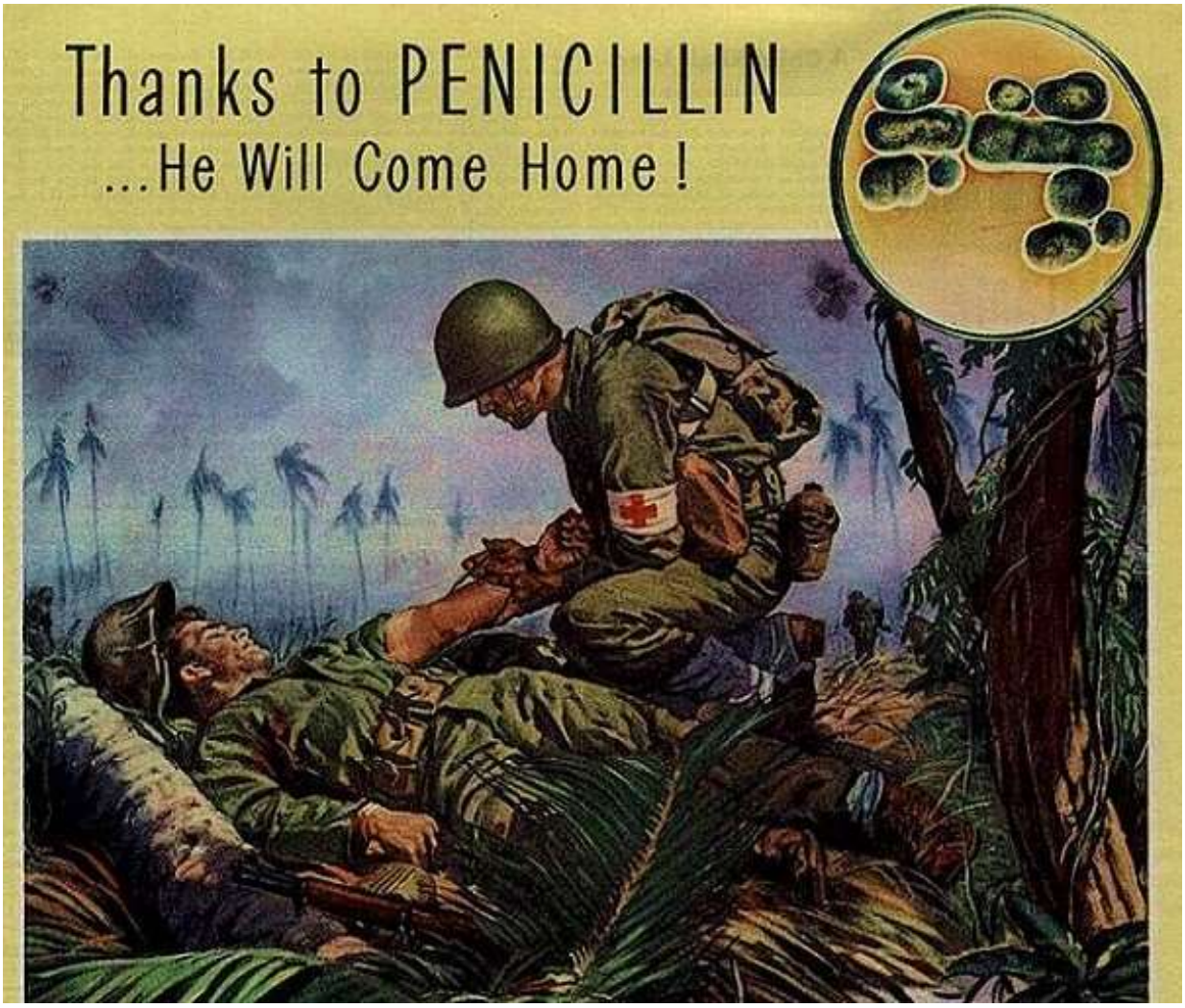
Procaine penicillin:

- Usual dosing is **1.5 grams daily.**

- Child: 50 mg/kg up to 1.5 grams daily.

Benzathine penicillin:

- Usual dosing is **900 mg - 1.8 grams IM 3-4 weekly.**



Penicillin Poster Advertisement of August 1944 from Schenley Laboratories, Time-Life.

References

1. eTG Complete - November 2014.

   - Antibiotic Therapeutic Guidelines, 15th ed 2014.

2. Penicillin in Australian Medicines Handbook, accessed February 2015.

3. Penicillin in MIMs 1 May 2007.

Further Reading:

Eric Lax, The Mould in Dr Florey's Coat, the remarkable true story of the penicillin miracle. Little Brown, 2004.

Howard Florey, Alexander Fleming and the Fairy Tale of Penicillin. Peter D Goldsworthy and Alexander C McFarlane, MJA February 2002; 176: 178-180.

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7 February 2015.