[Template:For](/wiki/Template:For" \o "Template:For) [Template:Pp-move-indef](/wiki/Template:Pp-move-indef) [Template:Use mdy dates](/wiki/Template:Use_mdy_dates) [Template:Drugbox](/wiki/Template:Drugbox) **Penicillin** (**PCN** or **pen**) is a group of [antibiotics](/wiki/Antibiotic) which include [penicillin G](/wiki/Benzylpenicillin) ([intravenous use](/wiki/Intravenous_therapy)), [penicillin V](/wiki/Phenoxymethylpenicillin) (oral use), [procaine penicillin](/wiki/Procaine_benzylpenicillin), and [benzathine penicillin](/wiki/Benzathine_benzylpenicillin) ([intramuscular use](/wiki/Intramuscular_injection)). Penicillin antibiotics were among the first medications to be effective against many [bacterial infections](/wiki/Bacterial_infection) caused by [staphylococci](/wiki/Staphylococcus) and [streptococci](/wiki/Streptococcus). Penicillins are still widely used today, though many types of bacteria have developed [resistance](/wiki/Antibiotic_resistance) following extensive use.

About 10% of people report that they are [allergic](/wiki/Allergy) to penicillin; however, up to 90% of this group may not actually be allergic.<ref name=Al2015/> Serious allergies only occur in about 0.03%.<ref name=Al2015>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> All penicillins are [β-lactam antibiotics](/wiki/Beta-lactam_antibiotic).

Penicillin was discovered in 1928 by Scottish scientist [Alexander Fleming](/wiki/Alexander_Fleming).[[1]](#cite_note-1) People began using it to treat infections in 1942.[[2]](#cite_note-2) There are several enhanced penicillin families which are effective against additional bacteria; these include the [antistaphylococcal penicillins](/wiki/Antistaphylococcal_penicillins), [aminopenicillins](/wiki/Aminopenicillin) and the [antipseudomonal penicillins](/wiki/Antipseudomonal_penicillins). They are derived from [*Penicillium*](/wiki/Penicillium) fungi.[[3]](#cite_note-3)

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## Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]

The term "penicillin" is often used generically to refer to [benzylpenicillin](/wiki/Benzylpenicillin) (penicillin G, the original penicillin found in 1928), [procaine benzylpenicillin](/wiki/Procaine_benzylpenicillin) (procaine penicillin), [benzathine benzylpenicillin](/wiki/Benzathine_benzylpenicillin) (benzathine penicillin), and [phenoxymethylpenicillin](/wiki/Phenoxymethylpenicillin) (penicillin V). Procaine penicillin and benzathine penicillin have the same antibacterial activity as benzylpenicillin but act for a longer period of time. Phenoxymethylpenicillin is less active against [gram-negative](/wiki/Gram-negative) bacteria than benzylpenicillin.[[4]](#cite_note-4)[[5]](#cite_note-5) Benzylpenicillin, procaine penicillin and benzathine penicillin are given by injection (parenterally), but phenoxymethylpenicillin is given orally.[Template:Citation needed](/wiki/Template:Citation_needed)

### Susceptibility[[edit](/index.php?title=(none)&action=edit&section=2)]

While the number of penicillin-resistant bacteria is increasing, penicillin can still be used to treat a wide range of infections caused by certain susceptible bacteria, including Streptococci, Staphylococci, Clostridium, and Listeria genera. The following list illustrates [minimum inhibitory concentration](/wiki/Minimum_inhibitory_concentration) susceptibility data for a few medically significant bacteria:[[6]](#cite_note-6)[[7]](#cite_note-7)\* *Listeria monocytogenes*: from less than or equal to 0.06 μg/ml to 0.25 μg/ml

* *Neisseria meningitidis*: from less than or equal to 0.03 μg/ml to 0.5 μg/ml
* *Staphylococcus aureus*: from less than or equal to 0.015 μg/ml to more than 32 μg/ml

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=3)]

Common [adverse drug reactions](/wiki/Adverse_drug_reaction) (≥ 1% of people) associated with use of the penicillins include [diarrhoea](/wiki/Diarrhoea), [hypersensitivity](/wiki/Hypersensitivity), [nausea](/wiki/Nausea), rash, [neurotoxicity](/wiki/Neurotoxicity), [urticaria](/wiki/Urticaria), and [superinfection](/wiki/Superinfection) (including [candidiasis](/wiki/Candidiasis)). Infrequent adverse effects (0.1–1% of people) include fever, vomiting, [erythema](/wiki/Erythema), [dermatitis](/wiki/Dermatitis), [angioedema](/wiki/Angioedema), [seizures](/wiki/Seizures) (especially in people with [epilepsy](/wiki/Epilepsy)), and [pseudomembranous colitis](/wiki/Pseudomembranous_colitis).[[8]](#cite_note-8) About 10% of people report that they are [allergic](/wiki/Allergy) to penicillin; however, 90% of this group are not actually allergic.<ref name=Al2015/> Serious allergies only occur in about 0.03%.<ref name=Al2015/>

Pain and inflammation at the injection site is also common for [parenterally](/wiki/Parenteral#Parenteral_by_injection_or_infusion) administered benzathine benzylpenicillin, benzylpenicillin, and, to a lesser extent, procaine benzylpenicillin.

Although penicillin is still the most commonly reported [allergy](/wiki/Allergy), less than 20% of people who believe that they have a penicillin allergy are truly allergic to penicillin;[[9]](#cite_note-9) nevertheless, penicillin is still the most common cause of severe allergic drug reactions. Significantly, there is an immunologic reaction to Streptolysin S, a toxin released by certain killed bacteria and associated with Penicillin injection, that can cause fatal cardiac syncope.[[10]](#cite_note-10) Allergic reactions to any [β-lactam antibiotic](/wiki/Β-lactam_antibiotic) may occur in up to 1% of patients receiving that agent.[[11]](#cite_note-11) The allergic reaction is a [Type I hypersensitivity](/wiki/Type_I_hypersensitivity) reaction. [Anaphylaxis](/wiki/Anaphylaxis) will occur in approximately 0.01% of patients.[[8]](#cite_note-8) It has previously been accepted that there was up to a 10% cross-sensitivity between penicillin-derivatives, cephalosporins, and carbapenems, due to the sharing of the β-lactam ring.[[12]](#cite_note-12)[[13]](#cite_note-13) Assessments in 2006 found no more risk for cross-allergy for second-generation or later cephalosporins than the first generation. However, as a general risk, research shows that all beta lactams have the intrinsic hazard of very serious hazardous reactions in susceptible patients. Only the frequency of these reactions vary, based on the structure.[[14]](#cite_note-14)[[15]](#cite_note-15) Papers in 2006 showed that a major feature in determining frequency of immunological reactions is the similarity of the side chains (e.g., first generation cephalosporins are similar to penicillins); this is why the β-lactams are associated with different frequencies of serious reactions (e.g., anaphylaxis).[[16]](#cite_note-16)

## Mechanism of action[[edit](/index.php?title=(none)&action=edit&section=4)]

[Template:Refimprove section](/wiki/Template:Refimprove_section) [Template:Main](/wiki/Template:Main) [upright|Bacteria that attempt to grow and divide in the presence of penicillin fail to do so, and instead end up shedding their cell walls.|thumb|right|600px](/wiki/File:Penicillin_spheroplast_generation_horizontal.svg) [thumb|upright|right|Penicillin and other β-lactam antibiotics act by inhibiting](/wiki/File:Penicillin_inhibition.svg) [penicillin-binding proteins](/wiki/Penicillin-binding_proteins), which normally catalyze cross-linking of bacterial cell walls.

Bacteria constantly remodel their [peptidoglycan](/wiki/Peptidoglycan) cell walls, simultaneously building and breaking down portions of the cell wall as they grow and divide. [*β*-Lactam antibiotics](/wiki/Beta-lactam_antibiotic) inhibit the formation of peptidoglycan [cross-links](/wiki/Cross-link) in the bacterial [cell wall](/wiki/Cell_wall); this is achieved through binding of the four-membered *β*-lactam [ring](/wiki/Cycloalkane) of penicillin to the [enzyme](/wiki/Enzyme) [DD-transpeptidase](/wiki/DD-transpeptidase). As a consequence, DD-transpeptidase cannot [catalyze](/wiki/Catalysis) formation of these cross-links, and an imbalance between cell wall production and degradation develops, causing the cell to rapidly die.

The enzymes that [hydrolyze](/wiki/Hydrolyze) the peptidoglycan cross-links continue to function, even while those that form such cross-links do not. This weakens the cell wall of the bacterium, and osmotic pressure becomes increasingly uncompensated—eventually causing cell death ([cytolysis](/wiki/Cytolysis)). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the cell wall's peptidoglycans. The small size of the penicillins increases their potency, by allowing them to penetrate the entire depth of the cell wall. This is in contrast to the [glycopeptide antibiotics](/wiki/Glycopeptide_antibiotics) [vancomycin](/wiki/Vancomycin) and [teicoplanin](/wiki/Teicoplanin), which are both much larger than the penicillins.[[17]](#cite_note-17) were grown in the appropriate substrate, it would exude a substance with antibiotic properties, which he dubbed penicillin. This [serendipitous](/wiki/Serendipity) observation began the modern era of antibiotic discovery. The development of penicillin for use as a medicine is attributed to the Australian Nobel laureate [Howard Walter Florey](/wiki/Howard_Walter_Florey), together with the German Nobel laureate [Ernst Chain](/wiki/Ernst_Chain) and the English biochemist [Norman Heatley](/wiki/Norman_Heatley).<ref name=Bud2009>[Template:Cite book](/wiki/Template:Cite_book)</ref>

Fleming recounted that the date of his discovery of penicillin was on the morning of Friday, September 28, 1928.[[27]](#cite_note-27) The traditional version of this story describes the discovery as a fortuitous accident: in his laboratory in the basement of [St Mary's Hospital](/wiki/St_Mary's_Hospital,_London) in London (now part of [Imperial College](/wiki/Imperial_College)), Fleming noticed a Petri dish containing [Staphylococcus](/wiki/Staphylococcus) that had been mistakenly left open was contaminated by blue-green [mould](/wiki/Mould) from an open window, which formed a visible growth.<ref name=Lax2004>[Template:Cite book](/wiki/Template:Cite_book)</ref> There was a halo of inhibited bacterial growth around the mould. Fleming concluded that the mould released a substance that repressed the growth and caused [lysing](/wiki/Lysing) of the bacteria.<ref name=Bud2009/>

Once Fleming made his discovery he grew a pure [culture](/wiki/Cell_culture) and discovered it was a [*Penicillium*](/wiki/Penicillium) mould, now known to be [*Penicillium notatum*](/wiki/Penicillium_notatum). Fleming coined the term "penicillin" to describe the [filtrate](/wiki/Filtrate) of a broth culture of the *Penicillium* mould. Fleming asked C. J. La Touche to help identify the mould, which he incorrectly identified as [*Penicillium rubrum*](/wiki/Penicillium_rubrum) (later corrected by [Charles Thom](/wiki/Charles_Thom)). He expressed initial optimism that penicillin would be a useful disinfectant, because of its high potency and minimal toxicity in comparison to antiseptics of the day, and noted its laboratory value in the isolation of *Bacillus influenzae* (now called [*Haemophilus influenzae*](/wiki/Haemophilus_influenzae)).<ref name=Lax2004/><ref name=Fleming1929>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Fleming was a famously poor communicator and orator, which meant his findings were not initially given much attention.<ref name=Lax2004/> He was unable to convince a true chemist to help him extract and stabilize the antibacterial compound found in the broth filtrate. Despite the lack of a true chemist, he remained interested in the potential use of penicillin and presented a paper entitled "A Medium for the Isolation of Pfeiffer's Bacillus" to the [Medical Research Club](/wiki/Medical_Research_Club) of London, which was met with little interest and even less enthusiasm by his peers. Had Fleming been more successful at making other scientists interested in his work, penicillin for medicinal use would possibly have been developed years earlier.<ref name=Lax2004/>

Despite the lack of interest of his fellow scientists, he did conduct several experiments on the antibiotic substance he discovered. The most important result proved it was nontoxic in humans by first performing toxicity tests in animals and then on humans. His following experiments on penicillin's response to heat and pH allowed Fleming to increase the stability of the compound.<ref name=Fleming1929/> The one test that modern scientists would find missing from his work was the test of penicillin on an infected animal, the results of which would likely have sparked great interest in penicillin and sped its development by almost a decade.<ref name=Lax2004/>

### Medical application[[edit](/index.php?title=(none)&action=edit&section=8)]

[thumb|Florey (pictured), Fleming and Chain shared a Nobel Prize in 1945 for their work on penicillin.](/wiki/File:Howard_Walter_Florey_1945.jpg) In 1930, Cecil George Paine, a [pathologist](/wiki/Pathologist) at the [Royal Infirmary](/wiki/Sheffield_Royal_Infirmary) in [Sheffield](/wiki/Sheffield), attempted to use penicillin to treat [sycosis barbae](/wiki/Sycosis_barbae), eruptions in beard follicles, but was unsuccessful. Moving on to [ophthalmia neonatorum](/wiki/Neonatal_conjunctivitis), a gonococcal infection in infants, he achieved the first recorded cure with penicillin, on November 25, 1930. He then cured four additional patients (one adult and three infants) of eye infections, and failed to cure a fifth.[[28]](#cite_note-28)[[29]](#cite_note-29)[[30]](#cite_note-30) In 1939, Australian scientist [Howard Florey](/wiki/Howard_Walter_Florey) (later Baron Florey) and a team of researchers ([Ernst Boris Chain](/wiki/Ernst_Boris_Chain), [Arthur Duncan Gardner](/wiki/Arthur_Duncan_Gardner), [Norman Heatley](/wiki/Norman_Heatley), M. Jennings, J. Orr-Ewing and G. Sanders) at the Sir William Dunn School of Pathology, [University of Oxford](/wiki/University_of_Oxford) made progress in showing the [*in vivo*](/wiki/In_vivo) bactericidal action of penicillin. In 1940 they showed that penicillin effectively cured bacterial infection in mice.<ref name=ClarkBook>[Template:Cite book](/wiki/Template:Cite_book)</ref>[[31]](#cite_note-31) In 1941 they treated a policeman, [Albert Alexander](/wiki/Albert_Alexander), with a severe face infection; his condition improved, but then supplies of penicillin ran out and he died. Subsequently, several other patients were treated successfully.[[32]](#cite_note-32)

### Mass production[[edit](/index.php?title=(none)&action=edit&section=9)]

[thumb|left|A technician preparing penicillin in 1943](/wiki/File:Penicillin_Past,_Present_and_Future-_the_Development_and_Production_of_Penicillin,_England,_1943_D16959.jpg) By late 1940, the Oxford team under Howard Florey had devised a method of mass-producing the drug, but yields remained low.<ref name=SW/> In 1941, Florey and Heatley traveled to the U.S. in order to interest pharmaceutical companies in producing the drug and inform them about their process.<ref name=SW/>

Florey and Chain shared the 1945 [Nobel Prize in Medicine](/wiki/Nobel_Prize_in_Physiology_or_Medicine) with Fleming for their work.

The challenge of mass-producing this drug was daunting. On March 14, 1942, the first patient was treated for streptococcal septicemia with US-made penicillin produced by [Merck & Co.](/wiki/Merck_&_Co.)[[33]](#cite_note-33) Half of the total supply produced at the time was used on that one patient. By June 1942, just enough US penicillin was available to treat ten patients.[[34]](#cite_note-34) In July 1943, the [War Production Board](/wiki/War_Production_Board) drew up a plan for the mass distribution of penicillin stocks to Allied troops fighting in Europe.<ref name=JParas/> The results of fermentation research on [corn steep liquor](/wiki/Corn_steep_liquor) at the [Northern Regional Research Laboratory](/wiki/National_Center_for_Agricultural_Utilization_Research) at Peoria, Illinois, allowed the United States to produce 2.3 million doses in time for the [invasion of Normandy](/wiki/Invasion_of_Normandy) in the spring of 1944. After a worldwide search in 1943, a mouldy [cantaloupe](/wiki/Cantaloupe) in a [Peoria, Illinois](/wiki/Peoria,_Illinois) market was found to contain the best strain of mould for production using the corn steep liquor process.[[35]](#cite_note-35)Large-scale production resulted from the development of deep-tank fermentation by [chemical engineer](/wiki/Chemical_engineer) [Margaret Hutchinson Rousseau](/wiki/Margaret_Hutchinson_Rousseau).<ref name=ChemH>[Chemical Heritage](http://www.chemheritage.org/women_chemistry/med/rousseau.html) Manufacturing a Cure: Mass Producing Penicillin</ref> As a direct result of the war and the War Production Board, by June 1945, over 646 billion units per year were being produced.<ref name=JParas>[Template:Cite book](/wiki/Template:Cite_book)</ref>

[thumb|Penicillin was being mass-produced in 1944.](/wiki/Image:PenicillinPSAedit.jpg) G. Raymond Rettew made a significant contribution to the American war effort by his techniques to produce commercial quantities of penicillin.[[36]](#cite_note-36)During [World War II](/wiki/World_War_II), penicillin made a major difference in the number of deaths and amputations caused by infected wounds among [Allied](/wiki/Allies_of_World_War_II) forces, saving an estimated 12%–15% of lives.[Template:Citation needed](/wiki/Template:Citation_needed) Availability was severely limited, however, by the difficulty of manufacturing large quantities of penicillin and by the rapid [renal clearance](/wiki/Clearance_(medicine)) of the drug, necessitating frequent dosing. Methods for mass production of penicillin were patented by [Andrew Jackson Moyer](/wiki/Andrew_Jackson_Moyer) in 1945.[[37]](#cite_note-37)[[38]](#cite_note-38)[[39]](#cite_note-39) Florey had not patented penicillin, having been advised by Sir [Henry Dale](/wiki/Henry_Hallett_Dale) that doing so would be unethical.[[32]](#cite_note-32) Penicillin is actively excreted, and about 80% of a penicillin dose is cleared from the body within three to four hours of administration. Indeed, during the early penicillin era, the drug was so scarce and so highly valued that it became common to collect the urine from patients being treated, so that the penicillin in the urine could be isolated and reused.<ref name=Silverthorn2004>[Template:Cite book](/wiki/Template:Cite_book)</ref> This was not a satisfactory solution, so researchers looked for a way to slow penicillin excretion. They hoped to find a molecule that could compete with penicillin for the organic acid transporter responsible for excretion, such that the transporter would preferentially excrete the competing molecule and the penicillin would be retained. The [uricosuric](/wiki/Uricosuric) agent [probenecid](/wiki/Probenecid) proved to be suitable. When probenecid and penicillin are administered together, probenecid competitively inhibits the excretion of penicillin, increasing penicillin's concentration and prolonging its activity. Eventually, the advent of mass-production techniques and semi-synthetic penicillins resolved the supply issues, so this use of probenecid declined.<ref name=Silverthorn2004/> Probenecid is still useful, however, for certain infections requiring particularly high concentrations of penicillins.<ref name=AMH2006>[Template:Cite book](/wiki/Template:Cite_book)</ref>

After World War II, Australia was the first country to make the drug available for civilian use. In the U.S., penicillin was made available to the general public on March 15, 1945.[[40]](#cite_note-40) [thumb|left|Dorothy Hodgkin determined the chemical structure of penicillin.](/wiki/File:Dorothy_Hodgkin_Nobel.jpg)

### Structure determination and total synthesis[[edit](/index.php?title=(none)&action=edit&section=10)]

[thumb|Dorothy Hodgkin's model of penicillin's structure.](/wiki/File:Molecular_model_of_Penicillin_by_Dorothy_Hodgkin_(9663803982).jpg) In 1945 the [chemical structure](/wiki/Chemical_structure) of penicillin was determined using [X-ray crystallography](/wiki/X-ray_crystallography) by [Dorothy Crowfoot Hodgkin](/wiki/Dorothy_Hodgkin), who was also working at Oxford.[[41]](#cite_note-41) She later received the Nobel prize for this and other structure determinations.

Chemist [John C. Sheehan](/wiki/John_C._Sheehan) at the [Massachusetts Institute of Technology](/wiki/Massachusetts_Institute_of_Technology) (MIT) completed the first chemical [synthesis](/wiki/Total_synthesis) of penicillin in 1957.<ref name=Sheehan1957>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=Sheehan1959>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=NAPSheehan>[Template:Cite web](/wiki/Template:Cite_web)</ref> Sheehan had started his studies into penicillin synthesis in 1948, and during these investigations developed new methods for the synthesis of [peptides](/wiki/Peptides), as well as new [protecting groups](/wiki/Protecting_group)—groups that mask the reactivity of certain functional groups.[[42]](#cite_note-42)<ref name=ArtTotalSyn>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Although the initial synthesis developed by Sheehan was not appropriate for mass production of penicillins, one of the intermediate compounds in Sheehan's synthesis was [6-aminopenicillanic acid](/wiki/6-APA) (6-APA), the nucleus of penicillin.[[42]](#cite_note-42)<ref name=MITSheehan>[Template:Cite news](/wiki/Template:Cite_news)</ref>[[43]](#cite_note-43)[Template:Page needed](/wiki/Template:Page_needed) Attaching different groups to the 6-APA 'nucleus' of penicillin allowed the creation of new forms of penicillin.

### Developments from penicillin[[edit](/index.php?title=(none)&action=edit&section=11)]

The narrow range of treatable diseases or "spectrum of activity" of the penicillins, along with the poor activity of the orally active phenoxymethylpenicillin, led to the search for derivatives of penicillin that could treat a wider range of infections. The isolation of 6-APA, the nucleus of penicillin, allowed for the preparation of semisynthetic penicillins, with various improvements over [benzylpenicillin](/wiki/Benzylpenicillin) (bioavailability, spectrum, stability, tolerance).

The first major development was [ampicillin](/wiki/Ampicillin) in 1961. It offered a broader spectrum of activity than either of the original penicillins. Further development yielded β-lactamase-resistant penicillins, including [flucloxacillin](/wiki/Flucloxacillin), [dicloxacillin](/wiki/Dicloxacillin), and [methicillin](/wiki/Methicillin). These were significant for their activity against β-lactamase-producing bacterial species, but were ineffective against the [methicillin-resistant *Staphylococcus aureus*](/wiki/Methicillin-resistant_Staphylococcus_aureus) (MRSA) strains that subsequently emerged.[Template:Citation needed](/wiki/Template:Citation_needed)

Another development of the line of true penicillins was the antipseudomonal penicillins, such as [carbenicillin](/wiki/Carbenicillin), [ticarcillin](/wiki/Ticarcillin), and [piperacillin](/wiki/Piperacillin), useful for their activity against [Gram-negative](/wiki/Gram-negative) bacteria. However, the usefulness of the β-lactam ring was such that related antibiotics, including the [mecillinams](/wiki/Mecillinam), the [carbapenems](/wiki/Carbapenem) and, most important, the [cephalosporins](/wiki/Cephalosporin), still retain it at the center of their structures.[[44]](#cite_note-44)

## Production[[edit](/index.php?title=(none)&action=edit&section=12)]

[thumb|A 1957 fermentor (bioreactor) used to grow *Penicillium* mould.](/wiki/File:Penicillin_bioreactor.jpg) Penicillin is a [secondary metabolite](/wiki/Secondary_metabolism) of certain species of [*Penicillium*](/wiki/Penicillium) and is produced when growth of the fungus is inhibited by stress. It is not produced during active growth. Production is also limited by feedback in the synthesis pathway of penicillin.[Template:Citation needed](/wiki/Template:Citation_needed)

[α-ketoglutarate](/wiki/Alpha-Ketoglutaric_acid) + [AcCoA](/wiki/Acetyl-CoA) → [homocitrate](/wiki/Homocitric_acid) → [L-α-aminoadipic acid](/wiki/Alpha-Aminoadipic_acid) → [L-lysine](/wiki/Lysine) + [β-lactam](/wiki/Beta-lactam)

The by-product, [Template:Smallcaps](/wiki/Template:Smallcaps)-lysine, inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.

The *Penicillium* cells are grown using a technique called [fed-batch](/wiki/Fed-batch) culture, in which the cells are constantly subject to stress, which is required for induction of penicillin production. The available carbon sources are also important: [Glucose](/wiki/Glucose) inhibits penicillin production, whereas [lactose](/wiki/Lactose) does not. The [pH](/wiki/PH) and the levels of nitrogen, lysine, phosphate, and oxygen of the batches must also be carefully controlled.[Template:Citation needed](/wiki/Template:Citation_needed)

The [biotechnological](/wiki/Biotechnology) method of [directed evolution](/wiki/Directed_evolution) has been applied to produce by mutation a large number of *Penicillium* strains. These techniques include [error-prone PCR](/wiki/Polymerase_chain_reaction), [DNA shuffling](/wiki/DNA_shuffling), [Template:Abbr](/wiki/Template:Abbr), and strand-overlap PCR.

Semisynthetic penicillins are prepared starting from the penicillin nucleus [6-APA](/wiki/6-APA).

### Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=13)]

[thumb|Penicillin G biosynthesis](/wiki/Image:Penicillin-biosynthesis.png) Overall, there are three main and important steps to the biosynthesis of [penicillin G](/wiki/Penicillin_G) (benzylpenicillin).

* The first step is the condensation of three amino acids—L-α-aminoadipic acid, L-cysteine, L-valine into a [tripeptide](/wiki/Tripeptide).[[45]](#cite_note-45)<ref name=Molecular>

[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[46]](#cite_note-46) Before condensing into the tripeptide, the amino acid L-valine must undergo epimerization to become D-valine.<ref name=Fern> [Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[47]](#cite_note-47) The condensed tripeptide is named δ-(L-α-aminoadipyl)-L-cysteine-D-valine (ACV). The condensation reaction and epimerization are both catalyzed by the enzyme δ-(L-α-aminoadipyl)-L-cysteine-D-valine synthetase (ACVS), a [nonribosomal peptide synthetase](/wiki/Nonribosomal_peptide) or NRPS.

* The second step in the biosynthesis of penicillin G is the [oxidative](/wiki/Redox) conversion of linear ACV into the [bicyclic](/wiki/Bicyclic_molecule) intermediate isopenicillin N by [isopenicillin N synthase](/wiki/Isopenicillin_N_synthase) (IPNS), which is encoded by the gene *pcbC*.[[45]](#cite_note-45)<ref name=Molecular/> Isopenicillin N is a very weak intermediate, because it does not show strong antibiotic activity.<ref name=Fern/>
* The final step is a [transamidation](/wiki/Transamidation) by [isopenicillin N N-acyltransferase](/wiki/Isopenicillin_N_N-acyltransferase), in which the α-aminoadipyl side-chain of isopenicillin N is removed and exchanged for a [phenylacetyl](/wiki/Phenylacetic_acid) side-chain. This reaction is encoded by the gene *penDE*, which is unique in the process of obtaining penicillins.[[45]](#cite_note-45)

## Members[[edit](/index.php?title=(none)&action=edit&section=14)]

### Natural penicillins[[edit](/index.php?title=(none)&action=edit&section=15)]

* [Penicillin G](/wiki/Penicillin_G)
* [Penicillin V](/wiki/Penicillin_V)

### β-lactamase-resistant[[edit](/index.php?title=(none)&action=edit&section=16)]

* [Methicillin](/wiki/Methicillin)
* [Nafcillin](/wiki/Nafcillin)
* [Oxacillin](/wiki/Oxacillin)
* [Cloxacillin](/wiki/Cloxacillin)
* [Dicloxacillin](/wiki/Dicloxacillin)

### Aminopenicillins[[edit](/index.php?title=(none)&action=edit&section=17)]

* [Ampicillin](/wiki/Ampicillin)
* [Amoxicillin](/wiki/Amoxicillin)
* [Pivampicillin](/wiki/Pivampicillin)
* [Hetacillin](/wiki/Hetacillin)
* [Bacampicillin](/wiki/Bacampicillin) [Metampicillin](/wiki/Metampicillin) [Talampicillin](/wiki/Talampicillin) [Epicillin](/wiki/Epicillin)

### Carboxypenicillins[[edit](/index.php?title=(none)&action=edit&section=18)]

* [Carbenicillin](/wiki/Carbenicillin)
* [Ticarcillin](/wiki/Ticarcillin)

### Ureidopenicillins[[edit](/index.php?title=(none)&action=edit&section=19)]

* [Mezlocillin](/wiki/Mezlocillin)
* [Piperacillin](/wiki/Piperacillin)

## See also[[edit](/index.php?title=(none)&action=edit&section=20)]

* [Medicinal molds](/wiki/Medicinal_molds)
* [Penicillinase](/wiki/Penicillinase)

## Notes[[edit](/index.php?title=(none)&action=edit&section=21)]

[Template:Reflist](/wiki/Template:Reflist)

## References[[edit](/index.php?title=(none)&action=edit&section=22)]

* [Template:Cite book](/wiki/Template:Cite_book)
* [Template:Cite journal](/wiki/Template:Cite_journal)
* [Template:Cite journal](/wiki/Template:Cite_journal)

## External links[[edit](/index.php?title=(none)&action=edit&section=23)]

[Template:Commons category](/wiki/Template:Commons_category)

* [Model of Structure of Penicillin, by Dorothy Hodgkin et al., Museum of the History of Science, Oxford](http://users.ox.ac.uk/~jesu1458/)
* [Template:YouTube](/wiki/Template:YouTube).
* [Penicillin](http://www.periodicvideos.com/videos/mv_penicillin.htm) at [*The Periodic Table of Videos*](/wiki/The_Periodic_Table_of_Videos) (University of Nottingham)
* [Penicillin Released to Civilians Will Cost $35 Per Patient](https://books.google.com/books?id=PN8DAAAAMBAJ&pg=PA47&dq=popular+science+antitank+1941&hl=en&ei=ZIiZTObfGcufnAe9kdWsDw&sa=X&oi=book_result&ct=result&resnum=7&ved=0CEAQ6AEwBjgK#v=onepage&q&f=true) *Popular Science*, August 1944, article at bottom of page

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[Template:Authority control](/wiki/Template:Authority_control)

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