Painful progress

~2000 BC

Mesopotamians and Egyptians recognize different types of pain, such as burning and stabbing. Where there is no obvious injury, pain is attributed to demons, ghosts or gods.

Mesopotamians think that these attack by touching or striking the body; Egyptians say that the spirits enter the body through the ears and nostrils. Physicians sometimes use narcotics such as opium or the poisonous plant henbane (*Hyoscyamus niger*) to relieve pain, but treatment consists mainly of spells or prayers.

~410 BC

Greek physician Hippocrates and his followers dismiss supernatural causes of pain, arguing that it is a symptom of disease. Hippocratic medicine considers pain to be a useful clue to what is wrong with the patient. Among the texts known as the Hippocratic Corpus are instructions in the art of diagnosis. High on the list of questions that physicians were to ask patients are the familiar "Are you in pain?" and "Where does it hurt?"

1664

French philosopher René Descartes proposes specific pain pathways from the point of origin to the brain; the concept holds for 300 years. He illustrates the mechanism in his book *Treatise of Man* — a boy with his foot near a flame is hit by "particles of fire", which speed along a nerve to the spinal cord and on to the brain, where his soul lies. The soul transforms the signals to a perception of pain, releasing "animal spirits" that course through the nerves to the leg, prompting it to move. The book is published posthumously so that Descartes can avoid the wrath of the Church, which teaches that pain is a gift from God.

1798

English chemist Humphry Davy tests the effects of inhaling nitrous oxide. It makes him giggly and dizzy, but also eases the agony of an erupting wisdom tooth. "The pain always diminished after the first four or five inspirations," he says. Later, Davy reports how a mix of nitrous oxide and oxygen produces reversible unconsciousness in animals. He suggests that the gas "may probably be used with advantage during surgical operations", although the idea of gaseous anaesthesia languishes until the 1840s.

1805

German pharmacist Friedrich Sertürner isolates morphine, the active ingredient of opium. The milky gum tapped from unripe seed pods of poppies (pictured) had been used to deaden pain since prehistoric times, but despite improved preparations (such as laudanum) the variable potency of plant products made their effects unpredictable. Morphine proves ten times as potent and more reliable than opium, making it a mainstay of pain relief.

-6000 BC LEAF RELIEF

People of the Nanchoc Valley in Peru are the earliest known users of cocaine. Archaeological evidence suggests that they chewed coca leaves (pictured) with quicklime to speed the release of the drug — a traditional painkiller in parts of South America.

-2250 BC EARLY WORMS

A Babylonian clay tablet advises treating the pain of a burrowing 'tooth worm', which is thought to be the cause of caries, by plugging the hole with gum mastic and powdered henbane seeds. This is the earliest known written prescription for a painkiller.

47 BRIGHT SPARK

Roman physician Scribonius Largus prescribes electrotherapy for headaches and gout. In his medical text *Compositiones*, he recommends placing the electric ray *Torpedo marmorata* on the brow or under the feet, allowing it to discharge its electricity "until the patient's senses were benumbed".

1898 TRIAL BY ORDEAL

German surgeon August Bier proves the effectiveness of spinal anaesthesia. He administers cocaine to his assistant through a lumbar puncture, then burns and hammers the assistant's legs, finishing by twisting and squashing his testicles. The assistant feels nothing — until the anaesthetic wears off.

For thousands of years people have sought explanations for pain and ways to ease it. Despite a better understanding of the mechanisms behind the sensation, much remains baffling, and the search for better treatments continues. By **Stephanie Pain**

1899 BARK WITH BITE

German company Bayer creates aspirin. The drug has its origins in an age-old remedy for aches and pains — willow bark. The powdered bark contains the analgesic salicin, which Bayer modifies to create the less-toxic acetylsalicylic acid. Aspirin is now one of the world's most widely used drugs.

1906 ALARM SYSTEM

British neurophysiologist Charles Sherrington proposes the existence of nociceptors — specialized nerves that detect potentially harmful stimuli, such as extreme temperature. If the intensity is enough to cause injury, the nerves relay a pain signal to the brain.

1936 RIGHT JAB

Anaesthesiologist Emery Rovenstine establishes the first pain clinic at New York City's Bellevue Hospital, where he pioneers new methods for nerve blocking. Injections of anaesthetic into nerves ease the pain of angina, sciatica, neuralgia and some cancers.

2004 BRAIN DRAIN

People with chronic back pain are shown to lose as much as 11% of their brain tissue (A. V. Apkarian *et al.* *J. Neurosci.* **24**, 10410–10415; 2004). Subsequent studies find that other causes of chronic pain, such as persistent headaches and irritable bowel syndrome, also lead to shrinkage of grey matter.

2014 BACK TO THE FUTURE

An analgesic is discovered in the herb *Corydalis yanhusuo* (pictured), used for centuries in China to treat back pain. The compound, dehydrocorybulbine, binds to dopamine receptors and offers longer-term relief than opiate drugs.

1864

During the American Civil War, Silas Weir Mitchell and two fellow surgeons identify an excruciating form of chronic pain that stems from damaged peripheral nerves, a condition that Mitchell calls causalgia (now called complex regional pain syndrome). Even minor injuries cause unbearable burning pain, which soldiers liken to a “red-hot file rasping the skin”. They become hypersensitive to the slightest touch; exposure to air or heat, or even the sound of a rustling newspaper increases their pain. Some are still suffering decades later.

1965

Psychologist Ronald Melzack and neuroscientist Patrick Wall propose their gate-control theory of pain. They suggest that the spinal cord has a ‘gate’ mechanism: messages from the source, other nerves and the brain converge to determine whether the gate opens to allow pain messages to reach the brain or closes to prevent them. This suggests that the perception of pain is influenced by a combination of physiological and psychological factors, such as mood. Although the details of their mechanism later prove flawed, the theory revolutionizes the field.

1973

US researchers discover a receptor in the brain through which morphine exerts its effects. This suggests that opiate drugs work by mimicking natural painkillers made by the body. Two years later, British biologists discover enkephalins, a group of endogenous opioids — or endorphins. Endorphins form part of the body's natural mechanism for managing pain, providing analgesia by reducing the perception of pain.

1991

Neuroimaging techniques reveal that pain is processed in several areas of the brain in parallel. Positron emission tomography (the brain's pain response is pictured in red) and functional magnetic resonance imaging have since provided a deeper understanding of this phenomenon, as well as how the perception of pain is influenced by emotion, experience and expectation. Some think that these techniques may make it possible to measure pain objectively and to distinguish physical from emotional pain. Imaging could help in the search for new drugs for chronic pain (see page S8).

2015

Researchers find a fundamental difference in how male and female mice process pain, helping to explain why men and women seem to feel pain differently (R. E. Sorge *et al.* *Nature Neurosci.* **18**, 1081–1083; 2015). Women are more sensitive to pain than men, are more likely to have chronic pain and respond differently to some painkillers. Past studies showed that the immune cells microglia play a key part in pain perception, but this is now found to be true only in males. T cells serve the same function in female mice (see page S7).