

A Brief History of Microbiology

Our understanding of microbiology has evolved enormously over the last 150 years. Few institutions have witnessed our collective progress more closely than the National Collection of Type Cultures (NCTC). In fact, the collection itself is a record of the many milestones microbiologists have crossed, building on the discoveries of those who came before.

To date, 60% of NCTC's historic collection now has a closed, finished reference genome, thanks to PacBio® Single Molecule, Real-Time (SMRT®) Sequencing. We are excited to be their partner in crossing this latest milestone on their quest to improve human and animal health by understanding the microscopic world.

1886: Theodore Escherich describes a bacterium which he called "bacterium coli commune" and which was later to be called *Escherichia coli*. A strain he isolated in 1886 is added to the collection upon its founding (NCTC 86).



1887: Julius Petri invents the agar-coated glass dish for culturing bacteria; earlier attempts at culturing involved potato slices and gelatin.



1890: German scientist Robert Koch provides proof of germ theory by injecting pure cultures of the *Anthrax bacilli* into mice.



Laying the Foundation

1900: Almroth Wright isolates NCTC 160 *Salmonella enterica* subsp. *enterica* serotype Typhi from the spleen of a typhoid patient during the Boer War. His wartime experiences later lead him to persuade the armed forces to produce 10 million vaccine doses for WWI troops in northern France.



1915: Isolation of the very first bacterial strain registered in the collection. NCTC 1 is a strain of *Shigella flexneri* recovered from Private Ernst Cable, a WWI soldier who died from dysentery. It is resistant to penicillin and erythromycin even though it was isolated before the discovery of antibiotics.



1920s: Selman Waksman and Albert Schatz lead a systematic effort to screen soil bacteria for antimicrobial compounds. NCTC later acquires the *Streptomyces griseus* strain (NCTC 4523) from which they isolated streptomycin.

1920: NCTC is established to "provide a trustworthy source of authentic bacteria for use in scientific studies." Frederick William Andrews deposits the first cultures.

1928: Alexander Fleming accidentally discovers penicillin. He returns from vacation and notices that a culture plate left lying out had become overgrown with staphylococci colonies, except where mold was growing. He explores further after his former assistant Merlin Price reminds him, "That's how you discovered lysozyme." Over the next 20 years, Fleming deposits 16 samples with NCTC, including a sample of *Haemophilus influenzae* isolated from his own nose in November 1935.



1930s: NCTC introduces freeze-drying of samples to ensure longevity and streamline storage and shipment.

1930s: Fritz Kauffman and Phillip White co-develop a scheme for classifying salmonellae by serotype.

The Advent of Antibiotics

1977: Gilbert and Sanger independently develop methods to determine the exact sequence of DNA molecules.



1977: CDC researchers Joseph McDade and Charles C. Shepard isolate *Legionella pneumophila* (NCTC 11230 and 11192) as the bacterial pathogen behind the outbreak of a new pulmonary disease at a convention in Philadelphia.



1969: Don Brenner and colleagues establish DNA hybridization as a more reliable basis for classifying clinical isolates of Enterobacteriaceae. He uses the new method to replace type strains with more representative specimens and identify numerous new microbial species, including *Moellerella wisconsinensis* (NCTC 12132), *Leminorella grimontii* (NCTC 12152), *Enterobacter asburiae* (NCTC 12123), and *Citrobacter braakii* (NCTC 13630).

1961: NCTC curator Samuel Cowan and Kenneth Steel publish 'Diagnostic Tables for the Common Medical Bacteria' in the Journal of Hygiene. Demand is so great the journal reprints and distributes them in pamphlet form. The work forms the basis of Cowan & Steel's Manual for the Identification of Medical Bacteria, first published in 1965 and a bench-top staple for years to come.

1949: NCTC begins a 10-year effort to characterize every organism in the collection.

1953: Pioneering food safety microbiologist Betty Constance Hobbs publishes a study establishing *Clostridium perfringens* as the cause of many outbreaks of food poisoning. She eventually deposits more than 20 NCTC strains of bacteria associated with food-borne illness.



1947: Edward Tatum and Joshua Lederberg produce the first gene map of *E. coli* K12 (NCTC 10538). Despite being one of the most intensively studied organisms in the 20th century, no one definitively knows why it is called "K12".

1947: NCTC focus shifts from a general microbial collection to bacteria of medical or veterinary interest.

1941: Howard Florey and Ernest Chain begin mass production of penicillin with funds from the US and British governments after the bombing of Pearl Harbor. By D-Day in 1944, enough penicillin has been produced to treat all wounded Allied Forces.

1942: Florey and Chain contribute three *Bacillus* strains (NCTC 6431, 6432, and 6474) thought to produce 'antibacterial substances active against the Staphylococcus,' demonstrating the researchers were even then seeking antibiotics beyond penicillin.



Marshalling Science for Public Health

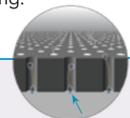
The Genomics Era

1981: The European Culture Collections' Organization, of which NCTC is a member, is established.

1987: The first automated DNA sequencing instrument, invented by Lloyd Smith, is commercialized by Applied Biosystems.



2003: Cornell University scientists led by Watt Webb and Harold Craighead publish the first report of using arrays of zero-mode waveguides for single-molecule sequencing.



1982: Future Nobel Prize winner Barry Marshall drinks a culture of the *Helicobacter pylori* (NCTC 11638 and 11639) to prove his theory that most stomach ulcers are caused by bacteria.



1995: Craig Venter, Hamilton Smith, Claire Fraser, and colleagues at TIGR elucidate the first complete genome sequence of a microorganism, *Haemophilus influenzae*, and submit the sequence to NCBI.

2011: PacBio ships its first commercial SMRT Sequencing system, introducing scientists to the long-read sequencing platform that will ultimately become the gold standard for generating complete, closed microbial genomes.

The largest recorded outbreak of foodborne hemolytic-uremic syndrome, eventually linked to German-grown sprouts, occurs in Europe. The organism responsible, a Shiga toxic *E. coli* (NCTC 13562).

2014: NCTC and Wellcome Sanger Institute (WSI) launch a five-year project to sequence 3,000 bacterial strains from the collection using PacBio sequencing technology.



Sanger scientists publish the genome of NCTC 1, generated with SMRT Sequencing, and compare it to other *S. flexneri* isolates collected in 1954, 1984, and 2002.

2018: NCTC scientists Sarah Alexander and Mohammed-Abbas Fazal complete the extraction of DNA from more than 3000 NCTC species and samples are delivered to WSI for sequencing using PacBio technology.

