John Cornforth

(1917–2013)

Nobel-prizewinning chemist who tracked how enzymes build cholesterol.

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Life depends on the geometric intricacies of enzymatic reactions. Even when molecules are exact mirror images of each other, enzymes treat the 'left-handed' and 'right-handed' versions differently. John Cornforth identified which of a series of mirror images interact with the enzymes that carry out the natural synthesis of cholesterol. This work, for which he shared the 1975 Nobel Prize in Chemistry, laid the foundations for many studies of how cells build organic compounds.

Cornforth, who died on 8 December 2013, was born in Sydney, Australia, in 1917. By the time he was ten, the first signs of his oncoming deafness had become apparent. As a boy, he built his own rudimentary laboratory at home. And, encouraged by a school teacher, he entered the University of Sydney at the age of 16 to read chemistry, a subject in which he thought his deafness would be less of a handicap. Although unable to hear the lectures, his thorough study of the scientific literature enabled him to graduate in 1937 with a first-class honours degree and a university prize.

Boyhood rambles in the bush inspired Cornforth's interest in natural products, and he began graduate studies at the University of Sydney. A number of his early papers were on the constituents of Australian plants, such as the caustic vine (*Sarcostemma australe*). His lifelong nickname, Kappa, arose from chemists' habit at the time of engraving their glassware: his initials (JC) resembled the Greek letter.

Cornforth's deafness led to an intense loneliness that was alleviated by the companionship in the laboratory. The skills he developed in his home lab, of building and repairing experimental apparatus, had many benefits. One was meeting the talented chemist, Rita Harradence, who asked him to repair a flask. In 1941, she became his wife. Throughout his career she acted both as an interpreter and a collaborator; they authored more than 40 papers together.

In 1939, Cornforth and Harradence were awarded scholarships for doctoral studies under Robert Robinson, an organic chemist at the University of Oxford, UK, who won the 1947 Nobel Prize in Chemistry. They began work on the synthesis of steroids, a biologically important class of complex, multi-ringed organic compounds that includes cortisone, estrone and testosterone. This effort eventually bore fruit in the first total synthesis of an androgenic hormone, reported in 1953 (H. M. E. Cardwell *et al. J. Chem. Soc.* 361–384; 1953).

In 1942, as part of the joint US–UK war effort, the couple joined the team working on the structure of the antibiotic penicillin. Cornforth made a number of important contributions, including identifying and synthesizing penicillamine, a key degradation product of penicillin. This work stimulated Cornforth's investigations into the class of compounds known as oxazolones, including a type of chemical rearrangement that now bears his name.

In 1946, the Cornforths moved to the Medical Research Council National Institute for Medical Research in London. Here, Cornforth continued his work on steroid and oxazolone chemistry and began a very fruitful collaboration with the medical biochemist George Popják, which continued when they became co-directors in 1962 of Shell Research's newly set up Milstead Laboratory of Chemical Enzymology in Sittingbourne, UK.

Like many chemists, Cornforth was intrigued by how natural products are formed. In the years after the Second World War, the radioisotope carbon-14 became available for basic research, providing a way to establish the biological building blocks of larger molecules. Other researchers had already begun to figure out the origin of certain carbon atoms in a side chain of the cholesterol molecule by using radioactively labelled acetate, a small organic compound containing only two carbon atoms. Cornforth took on the more demanding experimental work required to establish the origin of each of the carbon atoms in cholesterol's four conjoined molecular rings.

He identified 14 steps in the early stages of the natural formation of cholesterol. In each of these steps, the intermediate products could be transformed in one of two ways. His design for labelling experiments defined a single pathway out of the 16,384 (2^{14}) possibilities.

In another series of experiments, on acetic acid, Cornforth labelled the hydrogen atoms around a carbon, replacing the hydrogens with the isotopes deuterium and tritium such that each had a distinct position around carbon. These classic experiments opened up the possibility of exploring a wide range of enzyme reactions, including fatty-acid biosynthesis.

In 1975, the same year that he won the Nobel prize for decoding the stereochemistry of biosynthetic reactions, Cornforth accepted a Royal Society research professorship at the University of Sussex, UK. There, he began an extremely ambitious project to craft a compound that could act as an analogue for hydratase, the enzyme that adds water to another molecule.

He was knighted in 1977 and made a Companion of the Order of Australia in 1991. Kappa lectured undergraduates and supervised student projects until he was well into his 80s, often enhancing conversations with an aptly worded limerick. His kindness, generosity and humour were appreciated by all with whom he came into contact. ■

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