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SIR JOHN WARCUP CORNFORTH AC CBE

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Elected FRS 1953

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Sir John Cornforth was a pioneer in discovering the detailed chemistry used by living systems to construct the organic substances they contain. From his teenage years, he was handicapped by profound deafness yet he overcame this to reach the highest pinnacles of scientific achievement. His work was carried out in several different research centres, both academic and medical, and he was a leading figure in all.

The authors of this memoir decided at the outset that we should cover his personal biography and his scientific work in largely separate sections. We have endeavoured in this way to give a clear and full account of his life.

Personal biography (A.R.B.)

Life and career

John Warcup Cornforth, always known as Kappa to his friends, was born in Sydney, Australia, on 7 September 1917. His father, John William Warcup Cornforth, was born in Bristol of Yorkshire stock; he had read Classics at Oxford before travelling to Australia, where he met and later married Kappa’s mother Hilda (née Eipper). She was a nurse and a native Australian, the grand-daughter of Christoph Eipper, a German minister who was a pioneering missionary in Australia. Hilda’s mother came from an Irish line, and Kappa enjoyed referring to this mixture in the origins of his parents and grandparents. There were four children in the Cornforth family; he had an older sister, a younger brother and a younger sister. When Kappa was about six or seven years old (figure 1) the family moved to Armidale in the northern tablelands of New South Wales. Armidale was then a country town of about 5000 inhabitants.

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It was here that he had his primary schooling and the first year of secondary education while his father for some time taught classics in a private school, clearly of high standing as it was a member of the ‘Great Public Schools of NSW’. However, his father was also involved in several other activities, including the setting up of a mortgage company. Unfortunately, the outcome was poor and the family suffered from financial insecurity. Nevertheless, Kappa won the inaugural Dangar Scholarship in 1928 for study at Armidale High School. The family moved back to Sydney after about five years away and Kappa entered Sydney Boys High School where he received a very good education. He enjoyed this period and he studied at high school for six years. He was well ahead of his years when he entered Sydney University at the age of 16 years.

However, this was the time when his hearing loss, first noticed at the age of around 10 years as a small problem, became very serious. The cause was otosclerosis, which was passed through his mother’s line and also affected other members of the family, but less severely than Kappa. He was soon to be totally deaf. He had to decide on the direction of his future career; his father had favoured entry into law but thoughts on these lines had to be abandoned. However, he had already developed a love for chemistry, strongly encouraged by a fine young chemistry teacher at the High School, Leonard Basser. Further, this seemed to him to offer a career in which deafness might not be an insuperable handicap.

He realized that his deafness meant he would have to learn all the chemistry he needed by himself from textbooks and practical manuals and later, at the university, from the original literature. One can see his logical mind then at work in that he decided that, to do this self-learning, he must strengthen his mental powers in every way he could. So he took up astronomy and later, together with a friend at Oxford, built a telescope from a piece of steel pipe and an 8-inch parabolic mirror that they ground by hand. He became adept at chess (about
which more later) and he learned German from a dictionary. He enjoyed saying that he was not good at German grammar but that he had a huge vocabulary! He later learned French also and had a first-class command of it. As a practical part of his training process, and surely also because it was fun, he set up his own laboratory in the family laundry. He built his own weighing balance there, using the lids of two shoe-polish tins. The book he used most at this stage was *Practical organic chemistry* by J. B. Cohen, which gave instructions for both chemical and biochemical preparations. The latter awakened his interest in biochemistry to carry forward alongside his love for chemistry.

He was able to enter the University of Sydney at the remarkably young age of 16 years to study chemistry and he was strongly attracted to organic chemistry, especially to the study of natural substances and processes. The seed from which his love for this area of science came was his bush walks as a boy in the Blue Mountains, which were within reach of Sydney. There he saw the huge variety of plants and trees producing a plethora of colours, scents, gums, structural materials and so on. He became enthralled by all he saw but also intensely curious about them; thus was shaped the rest of his scientific career. To Kappa, work in science starts with curiosity, the asking of questions and then designing experiments to try to answer them. He also often said ‘You never stop learning.’

His undergraduate studies show the scale of the handicap that he had to overcome. Because he could not hear any of the lectures, he found out from the lecturers and from his fellow students what topics were being covered. He then used textbooks and also read the original literature to gain an outstandingly detailed and deep grasp of each topic. Much of the original literature at that time was in German, so his earlier decision to learn that language was well rewarded. As he read the textbooks and occasionally some of the original literature, he realized that they contained errors; that gave him a thrill because he felt he could set things right. Throughout his later career, he relied exclusively on the primary literature and he had an immense and detailed knowledge of that literature. He began to realize that science is a continuous process of discovery and correction and could see himself as a part of that process. Kappa enjoyed spotting errors, not only in science but also in any human activity, and he loved to be able to provide the correction. As a result, he was in demand from his colleagues and from editors to look at the papers that they had drafted or received, and he was amazingly good at picking out any flaws.

He graduated from Sydney in 1937 with first-class honours and was awarded a university medal; he then moved on to study for a master’s degree. One of his early original papers described work on the constituents of Australian plants such as the caustic vine (*Sarcostemma australe*). He greatly enjoyed doing practical work at the bench, such as the extraction of natural substances from the causticvine followed by their purification by skilful manipulation. At that time a researcher had to be adept at handling materials to make any progress, and being able to crystallize and recrystallize compounds was of key importance. Kappa was a master of all aspects of practical experiments. For example, he was able later in his career, when the amount of material he could obtain was minute, to crystallize and recrystallize a tiny sample in a melting-point tube. This is a ‘vessel’ holding so small a volume that one drop of liquid would more than half fill it! He carried out experiments at the bench all his life. He also found the companionship of working in the laboratory with others helped to overcome to some extent the loneliness he often felt as a result of his deafness.

Another skill he developed at this time was as a glassblower. For a chemist, this involves less ‘blowing’, more the joining together of heated glass, usually glass tubing and flasks.
Kappa used a gas blowtorch to heat the glass and, characteristically, his was home-made from an old Bunsen burner. He earned quite a reputation as a glassblower and was often asked by fellow students to repair their broken glassware; this was to have far-reaching consequences, as will be seen later.

It was during the university period of his life that he acquired the nickname ‘Kappa’, which arose because he scratched this Greek letter onto his glassware to stop fellow students from ‘borrowing’ it to add to their set. Apparently, he would have liked to have used the equivalent for the letter C but the Greek alphabet does not have one, so he used Kappa as the best near alternative. One rarely heard anyone in the chemical community speak of John Cornforth, it was always Kappa Cornforth.

It was not possible in the late 1930s in Australia to go beyond a master’s degree, so study for a doctorate required travelling abroad. Kappa’s outstanding achievements thus far led to the award of an 1851 Exhibition Scholarship for doctoral study at Oxford. Only two of these highly prized scholarships were awarded each year in Australia, and the second one was won by another organic chemist, Rita Harradence. She was one year ahead of Kappa at Sydney University and she, too, opted to study at Oxford. Their research supervisor was to be Sir Robert Robinson FRS (PRS 1945–50), who had been Professor of Organic Chemistry at the University of Sydney from 1913 to 1915. Fittingly, the laboratory in which Kappa and Rita had done their work for the master’s degree had been designed by Robinson.

During her time at the university, Rita broke the glass sidearm off her Claisen flask, then a precious item of equipment. Her friends knew of Kappa’s reputation as a glassblower and advised her to see whether he would repair her flask. By then he had been able to obtain a proper blowtorch, and he gladly made the repair. This seems to have been the first real contact between Rita and Kappa.

World War II broke out as they were travelling by boat to England and as a result they were diverted around South Africa. By the time they reached Cape Town (figure 2) they had to decide whether to continue to a Britain at war or return to Australia, far from the conflict.
They opted to continue the journey to Oxford. The diversion caused a substantial delay, so that the whole journey took eleven weeks rather than the usual five. On arrival in Oxford they were both brought into the effort, guided by Robinson, aimed at the synthesis of steroids. These are vital substances in our bodies, examples being cholesterol and the sex hormones such as testosterone. They worked in the Dyson Perrins laboratory, and figure 3 shows Kappa there with some of his colleagues. (The laboratory coats are interesting.) Their contributions to the synthetic programme were rewarded by the award to both of the DPhil degree after only two years; normally a longer period of research is needed. Rita and Kappa became engaged during the preparation of their theses and they were married in 1941 before the formal award of their doctorates.

After the research on steroids, the focus switched to various problems connected with the war effort, one being studies of antimalarial materials. But this was, in a way, a ‘starter’ as they then became members of the team working on the structure of the newly isolated antibiotic penicillin. It was clear from the properties of penicillin that it could have a massive effect on the war by saving the lives of war casualties. Initially only small quantities of penicillin were available, so great efforts were made to improve its preparation and to determine its structure. The crucially important contributions that Kappa made to the latter research are described in the scientific section of this memoir; he also helped to write *The chemistry of penicillin* (1949), which records the international effort that was focused on this antibiotic. Rita and Kappa’s first child, Brenda, was born (in 1943) during the penicillin period, and over the years the family expanded further with the arrival of John (1946) and Philippa (1948). When Brenda was born, they received strong support from Dorothy Hodgkin (FRS 1947) (who like Kappa was later awarded the Nobel Prize); they became close friends of Dorothy and remained so for life.

For recreation, Rita and Kappa joined a group of friends who made cycle rides into the countryside, not only around Oxford but also far afield, for example to Scotland. They camped under a strung-up tarpaulin just as they had in the Blue Mountains of Australia. Another Australian chemist, Arthur J. Birch (FRS 1958), was one of this group.
After the war they moved, in 1946, with the support of Robert Robinson, from Oxford to join the scientific staff at the National Institute for Medical Research, which was located first in Hampstead and later at Mill Hill. There, Kappa and Rita returned to the synthetic work on steroids, still in collaboration with Robinson. This long association of Kappa with Robert Robinson led to a close friendship that lasted until Robinson’s death in 1975. In a typical observation Kappa said, ‘The nature of our friendship was a continuous sequence of differences of opinion. Robert was an argumentative person and I have known the same thing to have been said of myself.’ In about 1950 the family bought a modest house, 22 Shakespeare Road in Mill Hill, a short bus ride from the Institute. They had no car, so everyone took a bus or walked to school or to the shops. Rita juggled with the many tasks of coping with three children, her deaf husband and her scientific work while having no extended family in the UK to give help.

Kappa and Rita worked at the National Institute for 16 years and he spoke of this period as the best years of his life. He particularly appreciated the spirit within the Institute, where there was cooperation and cross-fertilization across the various divisions. This environment led him to say that scientific advances are the product of an ambience created by many people, not just those who have the best ideas. In particular, he interacted fruitfully with several biological scientists; one such interaction, with George Popják (FRS 1961), developed into a long-running collaboration on the biosynthesis of cholesterol. This involved uncovering the detailed chemical steps used by living systems to construct this important molecule. The collaboration with Popják developed into a strong, close friendship that extended to the whole family. Kappa undoubtedly felt it keenly when Popják left (see below) for the USA.

Kappa was elected a Fellow of the Royal Society in 1953, during his time at the Institute and at the remarkably young age of 35 years.
He was approached in the early 1960s by the senior professors at the Australian National University in Canberra to consider the possibility of his joining them there. He decided to remain in the UK, probably, at least in part, because funding was provided by Shell Research Ltd to establish for him and Popják the Milstead Laboratory of Chemical Enzymology at Sittingbourne. Lord (Victor) Rothschild FRS was influential in the decision to establish this laboratory; he was strongly supported by Robert Robinson, who had professional connections with Shell. Kappa and George Popják moved to Milstead in 1962 (figure 4) to become co-directors of the laboratory, and over the years Victor Rothschild and Kappa developed a warm friendship.

The main thrust of the research of Kappa and George Popják at Milstead was the study of the stereochemistry of enzymatic reactions. Rita carried out many of the syntheses of the isotopically labelled materials that the work required. This line of research continued after Popják left Milstead in 1968 to go to the University of California, Los Angeles.

Kappa’s work at Milstead led directly to his being awarded the 1975 Nobel Prize in Chemistry (figures 5 and 6) jointly with Vladimir Prelog of the Eidgenössische Technische Hochschule, Zürich. It appealed greatly to Kappa’s sense of humour that on the Nobel citation, rather than showing two mirror-image molecules, the artist had drawn two identical ones! The award ceremony on this occasion was held in a large sports stadium because the town hall was being refurbished. Since Kappa was unable to hear a word of what was being said, he amused himself by looking around the audience, which was largely in darkness, whereas the main stage was brightly lit. Through the gloom he could see lots of flashes of light appearing all over the stadium and he finally realized they were coming from the jewels that the women were wearing. He said later that this was the thing he remembered most clearly from the award.
His short but penetrating speech should be recorded here. He spoke on behalf of both recipients:

That our work has been considered worthy of such distinction is a great satisfaction to both but I think we derive equal satisfaction from the sense of being two in the great company of those who approach the truth. In a world where it is so easy to neglect, deny, corrupt and suppress the truth, the scientist may find his discipline severe. For him, truth is so seldom the sudden light that shows new order and beauty; more often truth is the uncharted rock that sinks his ship in the dark. He respects all the more those who can accept that condition; and in returning thanks tonight we are saluting all those who make our load lighter by sharing it.

Kappa left Milstead in 1975 to take up a Royal Society Research Professorship at the University of Sussex, and he received news of the Nobel Prize shortly thereafter; later (1977) he received his knighthood (figure 7). It was in 1975 that Rita decided it was the right time to retire. They bought a lovely house in Lewes that stood high on a hillside giving a magnificent view over Sussex and, as Kappa loved to point out, of the brewery down below.

He travelled each day to the university to work experimentally at the bench (figure 8). One of his projects was to synthesize a molecule that would act as an enzyme does to catalyse a reaction; this work was unfinished. It is a sad reflection on the way in which science is supported that he had great difficulty in obtaining funds for his experiments. So he synthesized compounds that were needed by others and exchanged them for funds for his main work. He gave lectures to undergraduates until he was well into his eighties and he was always willing to discuss chemistry with them. He was particularly effective in guiding the ones who were in difficulty back onto the right track.
Kappa retained throughout his connection with Australia; he remained an Australian citizen and held both British and Australian passports. On one of his return visits to Sydney he gave an address on ‘Scientists as citizens’, one of a small number of papers not describing research results.

**Rita’s support**

This memoir has referred at several points to the support that Rita gave to Kappa (figure 9); it was immense and was the solid foundation on which he stood. She organized essentially everything for him and the family. She carried the major task of running the house, arranging maintenance and repair, the shopping and cooking, all alongside her scientific work and coping with three lively children. He made the tax returns but otherwise it was Rita who did what was needed. She was the car driver, and when they travelled abroad, Rita fixed all the flights and hotels. These trips abroad started in the 1950s and included substantial periods in Canberra and the USA; Rita’s presence was essential to him on these visits. How many women could have done what she did? He could not possibly have made his remarkable scientific achievements without her, and part of the Nobel award is rightly hers.

**Wider interests**

Kappa had many other interests, one being chess (figure 10a). He was a formidable chess player, having started at the age of 14 years; he had been given a Staunton Chess Set by his parents. In 1933 he won the New South Wales under-16 Championship and in 1937 he scored well in the Australian Championships in Perth. While there, he set an Australian record for simultaneous blind chess by taking on twelve Perth Club players, beating eight and drawing...
Figure 8. Kappa at Sussex. (Copyright © Edward Reeves Photography.)

Figure 9. Kappa and Rita at Milstead.
with two. This record stood until the 1970s. In England he played for Hampstead, Middlesex, Sittingbourne, Brighton and Sussex. Robert Robinson also enjoyed chess, so he and Kappa played ‘postal chess’ against each other; the pleasure this gave to both is clear from their correspondence.

He also greatly enjoyed tennis (figure 10b) and he had a searing serve; he played well into his eighties.

He had a deep love of poetry, which gave him both solace and huge pleasure. Poetry for Kappa was the equivalent of music for a hearing person. His knowledge of poetry was quite remarkable, matched only by his memory of it. He could accurately recite long poems, often those he had read years before. Probably his greatest love was for the poetry of W. B. Yeats, a special favourite being ‘The lake isle of Innisfree’. On one of his regular visits to see Kappa, one of us (A.R.B.) recited this poem with him; the first verse is:

I will arise and go now, and go to Innisfree
And a small cabin build there, of clay and wattles made:
Nine bean-rows will I have there, a hive for the honey-bee,
And live alone in the bee-loud glade.

Coming to the second verse, which is very moving, his eyes became moist as he recited; he was filled with emotion. Poetry was another bedrock for him.

In addition, he read prodigiously, constantly and widely and he was fond of detective fiction for relaxation. He always read the newspaper at the table, morning and evening, and this was accepted by the family because of his deafness. Initially, it was News Chronicle, but
when publication ceased, it was *The Guardian*. His choice of newspapers shows where he always stood in his political views; in addition, *New Statesman* and *New Scientist* were read regularly.

Not only an avid reader (figure 11), he also enjoyed writing and his scientific papers are models of clarity and style. So, too, were his many letters and his translations into English of, for example, German poems.

It may have been his feeling for the rhythm, balance and structure of poetry that led to his remarkable, and very amusing, ability to compose limericks after a few moments’ thought. He could do so for almost any location and on all sorts of topics. There are many, often about chemistry, but also others; the three recorded here are fine examples.

Spittoons that are made out of platinum  
Resist all your efforts to flatten ’em  
You can also use rhodium  
But never use sodium  
For then they’d explode when you spat in ’em.

The second is very much for chemists:

A mosquito was heard to complain  
That a chemist had poisoned her brain  
The cause of her sorrow  
Was para-dichloro-  
Diphenyltrichloroethane.

Finally, Kappa gave a definition of life and wrote a matching limerick: ‘A system is alive, or has life, if it resists inevitable decay by exact replication and can evolve by occasional inexact replication’;
You rot all the time you’re alive
And copy yourself to survive
A copy untrue
May work better than you
If it does, you can die; it will thrive.

His interest in walking that started when he was a boy was shared by Rita, and the photo of Rita up a tree (figure 12) shows her spirit; they had fun together! He never lost the taste for walking, and he continued almost to the end of his life to walk each day. This he could do by going up a steep track behind his house in Lewes onto rolling Sussex countryside, often returning with his collection of mushrooms. He loved the natural world and especially trees and wild flowers.

Both Rita and Kappa loved gardening, a joy that started at their house in Shakespeare Road, Mill Hill. This had a splendid garden containing a vegetable area and lots of fruit trees. Kappa taught himself how to graft tasty varieties of apple onto less tasty apple trees. Later, he took delight in showing his friends around their steeply sloping garden in Lewes. They planted a quince tree there, and he and Rita made quince jelly from the fruit; also each year when Seville oranges arrived they made their own marmalade. The recipe was their own and it appears in the Royal Society collection *But the crackling is superb* (Kurti & Kurti 1988).
The family

The family life of the Cornforths was inevitably affected by Kappa’s deafness, but it seems that everyone adjusted although it was not always easy. He never complained but he did have dark days, yet after working hard inside himself he came out of them to return to his usual equilibrium. There were frustrations; hard work on lip reading was needed and things happened that could be funny when viewed in retrospect. In all of this, Rita was his solid and patient support and she devoted herself to relaying the content of conversations to him, especially important when groups of people were talking. She maintained constant eye contact with Kappa that gave him the reassurance he needed to overcome the inevitable feeling that he had of being isolated and somewhat lonely.

He had a warm relationship with the children and would swing them over his head when they were small. They enjoyed the stories that he made up himself to tell, and he taught them how to play Scrabble and tennis although he always won at both! He introduced the children to the stars so that they could pick out the major constellations. More energetic ‘lessons’ were on swimming and the fun to be had at the seaside in rock pools. So Kappa was a ‘hands-on Dad’ who had close empathy with the children; he always gave good counsel when they had any sort of trouble or problem.

He enjoyed singing and had a lovely voice. He knew the songs from Gilbert and Sullivan and he liked those from the music hall; his favourite was ‘Two lovely black eyes’. Remarkably, these were songs he had not heard since childhood; he would sing them to the children and grandchildren. Train journeys had their interest too. At the station, Kappa thought he knew the right platform and charged rapidly off in that direction, but the rest of the family knew he was wrong. The only way to get him back was for one of the children, feeling a bit self-conscious, to run what was by now the rather long distance after him. Such events raised a family smile as they were recalled.

Obviously, talking is possible for a deaf person but listening is not, so Kappa would recite poems and tell stories and jokes at the dinner table. After a joke he would shake with huge laughter and this was totally infectious. He was very good company, knowledgeable over a wide range of topics, and both entertaining and informative. He always got to the heart of the matter under discussion at home and also at university seminars. Even without Rita present he could follow the presentation in the seminar reasonably well from the slides. It was amazing how he could then add to the discussion a penetrating question or pertinent comment even on a topic that was quite distant from his own. He loved a vigorous argument, all with good humour, although it was very difficult for anyone to win against such a brilliant mind.

The last years

Kappa continued working at the university until Rita became infirm; at that point, in 2005, he ceased his chemical work at Sussex. He cared for Rita with great devotion, and to do so he learned the skills he had previously lacked including cooking using recipes written out by Rita. She would say, ‘Chemists make good cooks’; indeed, not only was he a good cook but he also quite enjoyed it. Rita continued even at this stage to relay the conversation to Kappa when their friends visited. If ever there were a marriage of massive strength, cohesion and love, this was it. Rita’s death in November 2012 was a huge blow to Kappa, and the loneliness he had felt throughout his life because of deafness was now far worse. He was, however, fortunate to have the loving support of his family to help him cope. Inevitably, there were bleak moments,
but when his close friends visited he rallied and was always good company. Often the talk on such visits was of gardening, wine or hiking, and frequently poetry was recited. Chemistry came in as well, with Robert Robinson a favourite topic but also how the nature of research on chemistry differs so much in the twenty-first century from the earlier days. He doubted whether many chemistry students now would have the manipulative skills needed to crystallize and recrystallize a 20 mg sample of a radioactive compound until it reached constant specific radioactivity. It would have been a regular task for him.

Eventually his physical condition required the support of carers, and in his last year he accepted live-in care. All his carers enjoyed his company; they warmed to his jokes and laughter and he regularly played Scrabble with the closest of his devoted helpers. He and his helpers were together in this way during the morning of the day that he had the massive stroke from which he died on 8 December 2013.

John (Kappa) Cornforth was a wonderful human being and one of the greatest organic/bio-organic chemists in the world. His name will always live on in the history of science.

**Scientific work (D.W.Y.)**

*Early work*

Cornforth began his academic studies at the University of Sydney and published three research papers on heterocyclic chemistry during his BSc years. One of these (1)* was the first of many with Rita, his future wife. His MSc led to a further five publications on natural product chemistry, two as sole author. Given his lifelong contributions to the field of terpenes and steroids, it was somewhat prophetic that his final publication from Sydney with J. C. Earl (2) suggested a possible triterpene structure for sarcostin, the sapogenin from the Australian plant *Sarcostemma australe* R.Br. Considering this as ‘unfinished business’, Cornforth returned to the subject nearly 20 years later in a solo publication (24) that helped finally to prove the correct (steroidal) structure (Mitsuhashi & Shimizu 1963).

*Oxford and penicillin*

In 1942, having completed his doctorate at Oxford with Robert Robinson, Cornforth joined the ongoing programme of research on the isolation and structure determination of the antibiotic penicillin. E. P. Abraham had isolated the amino acid penicillamine from the acid hydrolysis of penicillin. Belatedly it was shown that it (and therefore penicillin) contained sulfur and that it formed a thiazolidine with acetone. Several structures for penicillamine were put forward in a report (Abraham et al. 1943), an addendum to which stated that Dr. J. W. Cornforth had suggested the structure 4. This had been dismissed on the basis of a low value in a Kuhn–Roth determination for C-methyl groups, but Cornforth observed that this low value might be due the presence of a *gem*-dimethyl group. Within six weeks of his suggestion, Cornforth confirmed the structure by total synthesis (4) and suggested (correctly) that it belonged to the ‘unnatural’ α-series of amino acids.

In addition to penicillamine 4, acid hydrolysis of penicillin yielded the aldehyde 3, which was also produced together with carbon dioxide and the mercaptide of penicillamine when alkali-inactivated penicillin was treated with mercuric chloride. It seemed clear that alkali

* Numbers in this form refer to the bibliography at the end of the text.
inactivation had given a thiazolidine which was then converted by mercuric chloride into 3, 4 and CO₂. Robinson deduced that the aldehyde 3 was formed by decarboxylation of the β-carboxyaldehyde 2, and so alkali treatment of penicillin had given the thiazolidine carboxylic acid 1. It followed that penicillin was a dehydration product of the acid 1, and Robinson proposed the thiazolidine-oxazolone structure 5 for the antibiotic. Abraham and Chain preferred the alternative β-lactam structure 6 as being more in keeping with the experimental results (Abraham et al., 1949), and this was finally confirmed by X-ray crystallographic analysis (Crowfoot et al., 1949).

**Oxazoles, oxazolones and related heterocyclic compounds: the Cornforth rearrangement**

The oxazolone structure 5 was an early target for penicillin synthesis, and Cornforth played a leading role in this work. Various heteromethylene-oxazolones such as the enol 7 were prepared and reacted with penicillamine in the hope of obtaining a compound of type 5, and in some cases antibacterial activity was observed.

In the course of this work it was found (5) that reaction of the acid 8 with phosphorus pentachloride gave, not the expected acid chloride, but the ester 9. In addition, Rosenmund reduction of the acid chloride 10 gave the aldehyde 11. These and other reactions were evidently examples of a hitherto unknown rearrangement of 4-carbonyl-substituted oxazoles (12→14), which has since become known as the Cornforth rearrangement. The suggested mechanism involves the intermediacy of a nitrile-ylide 13, and the likelihood of a given rearrangement occurring is dependent on the position of the equilibrium between reactant and product (Dewar & Turchi 1975).

After the lifting of the wartime publication embargo, all UK and US penicillin research appeared in 1949 as a book in which Cornforth (10) reviewed all of the oxazole chemistry.
He continued to work on these and related heterocyclic compounds on moving to the National Institute for Medical Research in 1946. He developed a new, general and convenient synthesis of oxazoles and iminazoles using imidoethers of type \( 15 \) (7). Reaction of acetimidoethyl ether with ethyl glycinate gave the product \( 15 \) (R = Me, R′ = Et), but with 2 mol of diethyl aminomalonate in moist air it gave the oxoiminazole \( 16 \) (R = Me). Formylation of \( 15 \) gave the salts \( 17 \), which reacted with HCl to give the oxazoles \( 18 \). Hydrolysis and decarboxylation then provided a synthesis of monosubstituted oxazoles \( 19 \) including the parent oxazole \( 19 \) (R = H), which had never before been prepared.

The synthesis was extended to iminazoles \( 20 \) by reacting the acid derived from ester \( 18 \) with ammonia or an amine. In an alternative method, the potassium salt \( 17 \) (R = Me, R′ = Et) reacted with ethyl glycinate hydrochloride to give the iminazole \( 20 \) (R = Me, R\(^2\) = CO\(_2\)Et, R\(^3\) = CH\(_2\)CO\(_2\)Et). Extension of the synthesis (9) gave a 4-cyano-oxazole, and an alternative synthesis of an oxazole from a thioether analogue of \( 17 \) was discovered during an attempted synthesis of penicillin (8).

The first total synthesis of ‘non-aromatic steroids’

Robinson began his synthesis of steroids shortly after the discovery of their structures in 1932 (reviewed in Fieser & Fieser 1959, pp. 53–89). His first targets were the ‘aromatic steroids’ equilenin \( 21 \) and oestrone \( 22 \), which posed less of a stereochemical challenge than did the ‘non-aromatic steroid’ cholesterol \( 23 \), which, having eight asymmetric centres, required the synthesis of one unique stereoisomer from 256 possibilities. The methods developed in this early work laid firm foundations for many future steroid syntheses. The synthesis of cholesterol \( 23 \) was begun before the discovery of its relative stereochemistry by Carlisle & Crowfoot (1945) and its absolute configuration by Cornforth in 1954 (20).

In his doctoral studies Cornforth (3) discovered a simple method of using sodium and alcohol to reduce β-methoxynaphthalenes to β-tetralones via the hydrolysis of an intermediate enol ether. The reaction was especially favourable for 1,6-dimethoxynaphthalene \( 24 \), which yielded the tetralone \( 26 \) via the enol ether \( 25 \). This finding was fundamental to the successful route to the ‘non-aromatic steroids’, which was resumed after the war both at Oxford and in Cornforth’s laboratory at the National Institute for Medical Research.
Methylation of the β-tetralone 26 and use of the Robinson annulation reaction (du Feu et al. 1937) gave the tricyclic enone 27 (6). A second asymmetric centre was now introduced by demethylation and hydrogenation. The resultant diol 28 was stereochemically homogeneous, the A/B ring junction being assumed to be cis by analogy (6, 11). Partial acetylation, and hydrogenation gave a mixture of acetoxy-alcohols, which was subjected to chromic oxidation followed by alkaline hydrolysis. The resultant ketone 29 was a separable mixture of diastereoisomers. Because these were α-decalones that had been subjected to enolization, the B/C ring junction was correctly considered to be trans (6, 11). It subsequently turned out that the desired cis-anti-trans diastereoisomer was the minor one. Later work by Cornforth (16) indicated that hydrogenation/oxidation of methyl ethers related to the cis isomer 28 and its trans counterpart gave cis-syn-trans and trans-anti-trans reduction products, respectively, so that, had the A/B junction been trans, the predominant isomer might have had the three centres retained in the synthesis in the required relative stereochemistry.

The two diastereoisomers 29 were resolved separately and each of the four stereoisomers was converted into its corresponding α-methyl ketone, which was oxidized to the corresponding diketone. One of these four diketones proved to be identical to the ‘Reich diketone’ 30, a degradation product of deoxycholic acid (Reich 1945), which could also be obtained from the cholesterol degradation product 31 known as the ‘Köster–Logemann ketone’ (Köster & Logemann 1940). Thus the absolute stereochemistry of the synthetic product was confirmed and intermediates were available in quantity to act as synthetic relays.

Conversion of the ketone 30 into the unsaturated ketone 32 (Billeter & Miescher 1950) was followed (12, 13) by conversion into the diol 33. Preferential protection of the ring A hydroxyl, oxidation and deprotection then gave the ‘Köster–Logemann ketone’ 31.

A fifth asymmetric centre was now introduced stereospecifically by carboxylation of the benzoate of 31 and esterification. Reformatsky reaction of the resultant ester 34 with methyl bromoacetate and hydrolysis gave two diastereoisomeric products 35. One of these was hydrogenated, esterified, acetylated and dehydrated to give the product 36 with trans stereochemistry at the A/B ring junction. This was hydrogenated and the acetyl group was replaced by benzoate giving 37, identical to a specimen prepared from cholesterol, thus confirming the stereochemistry at all seven asymmetric centres. All of the asymmetric centres of the ring system of natural steroids were now in place, and the synthesis of epiandrosterone 38 was completed by homologation and ring closure.

Previous work on the correlation of natural steroids by partial synthesis meant that this synthesis was sufficiently flexible to prepare all of the ‘non-aromatic’ sex hormones and many adrenal hormones. A different synthesis of ‘non-aromatic’ steroids was published (Woodward...
et al. 1951, 1952) at the same time as the preliminary report (12) of this work, and both groups completed syntheses of cholesterol 23.

**Collaborative interdisciplinary work at the National Institute for Medical Research**

When Cornforth moved to the National Institute for Medical Research in late 1946, conditions there were ideal for interdisciplinary collaboration and, in addition to carrying out steroid synthesis and heterocyclic studies, he became involved in several collaborative projects. In one of these, the discovery that the non-ionic surfactant Triton A-20 suppressed experimental tuberculosis in mice, led to a series of publications from 1951 to 1973 on the preparation and examination of analogous structures as antitubercular agents (48). He was also involved in a Medical Research Council research scheme into sources of the drug cortisone using the steroid sapogenin hecogenin, which was available in quantity as a byproduct in the manufacture of sisal fibre (19). His most fruitful collaboration was with George Popják, a medical biochemist. This lasted through Popják’s move to direct the Medical Research Council laboratories at Hammersmith and the move of both men to the Milstead Laboratories at Sittingbourne, until in 1968 Popják moved to the University of California, Los Angeles.

**Biosynthesis of cholesterol and squalene from acetate**

The hydrocarbon squalene was indicated as an intermediate in cholesterol biosynthesis by early biological experiments (Channon 1926) and, when the structures of both squalene 39 (Heilbron et al. 1926) and cholesterol 23 became known, Robinson (1934) proposed that squalene might cyclize to cholesterol 23 as shown in conformation 39a, with the loss of the three methyl groups highlighted in red. Discovery of the structure of the triterpene lanosterol 40 (Voser et al. 1952) led Woodward & Bloch (1953) to suggest that squalene might first cyclize as shown in conformation 39b with either (i) both methyl groups shown in green undergoing 1,2-shifts or (ii) one of them undergoing a 1,3-shift to give lanosterol 40. Loss of the three methyl groups in 40 shown in red would then give cholesterol 23.

In studying the biosynthesis of glycerol in foetal rats, Popják & Beeckmans (1950) noted that [1-14C]acetate was also incorporated into cholesterol, confirming Bloch’s early experiments (reviewed in (59)) showing incorporation of [2H], [14C] and [13C]acetates into both squalene and cholesterol, and incorporation of labelled squalene into cholesterol. Bloch (reviewed in (17, 59)) identified the site of each label incorporated from [1-14C] and [2-14C]acetate into the side chain of cholesterol by using degradative methods previously developed in the determination of its structure.
Cornforth’s entry to the field gave a new dimension to unravelling the biosynthetic origin of cholesterol \(23\). He began (14, 15) by examining the labelling in ring A of samples of cholesterol \(23\) derived from both \([1-^{14}\text{C}]\) and \([2-^{14}\text{C}]\) acetates by converting them into cholest-5-ene \(41\). Ozonolysis to a keto-aldehyde and aldol condensation then gave the enone \(42\). This was ozonolysed to yield a diketo-aldehyde, which, on heating, gave the aldehyde \(43\) and C6 of cholesterol as carbon dioxide. The aldehyde \(43\) underwent a retro-Michael reaction thus isolating ring A as the cyclohexanone \(44\), which could be further degraded to allow the radioactivity of each individual carbon atom to be measured. Thus the origins of C6 in ring B, all of the ring A carbons and the C19 methyl were defined.

Bloch and Dauben (reviewed in (17)) separately identified the origin of C7 in ring B of cholesterol, and Woodward & Bloch (1953) discovered the origin of the two carbons of the C-methyl moieties C18–C13 and C19–C10, showing that C13 was derived from the methyl carbon of acetate.

Cornforth and Popják (21) now turned their attention to rings C and D. The labelled samples of cholesterol were converted into samples of the olefin \(45\). Ozonolysis to the keto-aldehyde \(46\) and retro-Michael reaction gave \(47\) and \(48\). Further degradation of the ketone \(47\) revealed the origin of C12, C13 and C18 and degradation of the aldehyde \(48\) the origin of C15, C16 and C17.

In a further degradation (21), the samples of cholesterol were converted into the diene \(49\), which was ozonolysed to the lactone-acid \(50\) and a diacid, isolated as its ammonium salt \(51\). Further degradation allowed the label in atoms C9, C8 and C11 to be measured as CO\(_2\). The conclusions from the two degradations were that C8, C11, C12, C14 and C16 originate from the carboxyl group of acetate and that C9, C13, C15, C17 and C18 originate from the methyl group. Discovery of the origin of all 27 carbon atoms of cholesterol from the two atoms of acetate had now been completed.

Cornforth and Popják (18) now addressed the origin of labelling in the individual atoms of squalene \(39\) derived by incubating \([2-^{14}\text{C}]\) acetate with rat liver slices. Oxidative ozonolysis of the resultant \([^{14}\text{C}]\) squalene gave two molecules of acetone, four molecules of laevulinic acid and one molecule of succinic acid. These were separated and further degraded to identify the positions of all of the labels.
The pattern of labelling of cholesterol and squalene biosynthesized from [1-\(^{14}\)C] and [2-\(^{14}\)C] acetate 52 is summarized in 23b and 39c below. This is the result expected for the Woodward–Bloch model of squalene cyclization. The labelling pattern expected from Robinson’s model is shown in 23a and differs from that found by experiment at C7, C8, C12 and C13.

Cornforth’s general stereoselective olefin synthesis: the Cornforth model for asymmetric induction; synthesis of squalene

Interest in the synthesis of natural all-trans squalene, and the lack of a general method for the synthesis of trisubstituted olefins of predetermined geometry, led Cornforth to develop a general stereoselective synthesis of olefins.

Although the stereochemistry of nucleophilic addition to the carbonyl group of acyclic aliphatic ketones had been rationalized on the basis of Cram’s rule (Cram & Abd Elhafez 1952), it had yet to be applied to \(\alpha\)-chlorocarbonyl compounds. Cornforth (25) realized that the dipolar repulsive interaction between a carbonyl group and an \(\alpha\)-halogen might cause them to be anti as in 54, so that attack at the carbonyl group by a nucleophile from the side of the smaller \(\alpha\)-substituent would give a product 55 of defined relative stereochemistry.

To test this hypothesis, now referred to as ‘Cornforth’s rule’, 3-chlorooctan-4-ol 56 was prepared by reaction of 2-chlorobutanal with either butyl magnesium bromide or butyl lithium. Reaction with alkali with inversion at the halogen-bearing carbon gave 70% trans-3,4-epoxyoctane 57 and 30% cis isomer, whether the Grignard reagent or the lithium alkyl had been used. Reaction with ketones proved more stereoselective than with aldehydes and (i) 3-chlorobutan-2-one with ethyl magnesium bromide and (ii) 4-chloropentan-3-one with methyl magnesium bromide gave the diastereoisomeric tetrasubstituted products 58 and 59, respectively, each with 85% stereoselectivity.

Having established a new approach to epoxides from \(\alpha\)-chlorocarbonyl compounds, a general synthesis of olefins in good yield and high stereoselectivity was completed as shown for (E)-3-methylpent-2-ene 65. Synthesis of the epoxide 63 from the ketone 61 via alcohol
followed by conversion to the iodide anti-selective reductive elimination gave the olefin.

This has proved to be a general stereoselective synthesis of tetrasubstituted and trisubstituted olefins. Extension to disubstituted olefins followed when Cornforth reduced 3-chloro-octan-4-one with sodium borohydride in aqueous ethanol and completed the synthesis of the cis olefin with 85% stereoselectivity via the epoxide.

The method was now used to synthesize squalene by using 3,5-dichloropentan-2-one to supply 25 of the 30 carbon atoms of the all-trans triterpene.

**Biosynthesis of cholesterol and squalene: mevalonic acid and the methyl and hydrogen rearrangements**

Bonner & Arreguin (1949) proposed that a five-membered intermediate might be involved in the biosynthesis of terpenes from acetate, and Bloch et al. (1954) showed that 3-methylcrotonate or biosynthetically related substances were better sources of carbon than acetate for the biosynthesis of cholesterol. When the Merck group (Wolf et al. 1956) isolated the natural product mevalonic acid and incubated synthetic [2-14C]mevalonolactone with a preparation of liver enzymes, they obtained radioactive cholesterol (Tavormina & Gibbs 1956; Tavormina et al. 1956). Unlabelled cholesterol and radioactive carbon dioxide were obtained when [1-14C]mevalonolactone was used. This suggested that six units of an ‘isopentane’ structure arising from decarboxylation were incorporated into squalene and thence into cholesterol. Cornforth (22, 23) now showed that racemic [2-14C]mevalonolactone was incorporated into the six positions shown in squalene (39d) and, by implication, into the five positions shown in cholesterol (23c).

The absolute configuration of naturally occurring mevalonic acid was proved to be (R) (69a) by Eberle & Arigoni (1960), and this prompted Cornforth to ‘complete’ its synthesis from (−)-linalool, which had been assigned the stereochemistry 71 (Prelog & Watanabe 1957). This proved to be one of Prelog’s few misapplications of ‘Prelog’s rule’, because the synthesis yielded unnatural (S)-mevalonic acid. This work is the subject of the sole joint publication (28) by Cornforth and his co-recipient of the 1975 Nobel Prize in Chemistry. Synthesis of both (R)- and (S)-mevalonic acids was later accomplished with (+)- and (−)-linalool (33).
Leopold Ružička (Eschenmoser et al. 1955) put forward a detailed mechanism for the cyclization of squalene 39 to lanosterol 40, amended here because the sequence is now known to involve the 2,3-epoxide 72 (van Tamelen et al. 1966; Corey et al. 1966). Cyclization of the epoxide to the cationic intermediate 73 may be followed by a concerted sequence involving (i) migration of the C17 hydrogen to C20, (ii) migration of the C13 hydrogen to C17, (iii) two 1,2-methyl migrations from C8 and C9 and finally (iv) loss of the proton from C9 to give the $\Delta^{8,9}$-olefin in lanosterol 40.

In an approach that is now regarded as a classic, Cornforth (27) answered the question of whether the conversion of squalene 39 into lanosterol 40 involved one 1,3-shift of the methyl A in 39e or two 1,2-shifts of the methyls A and B. $[3',4-^{13}C_2]$Mevalonolactone 70a was synthesized, mixed with unlabelled material and enzymatically converted into cholesterol 23d. Oxidation allowed isolation of the CH$_3$C– groups as acetic acid. Had there been 100% $^{13}$C at the C3' and C4 of mevalonolactone, then the labelling pattern in cholesterol would have been entirely as shown in 23d whether methyl A or B had ended up as C18. However, six different molecules of mixed labelled and unlabelled mevalonolactone are incorporated into squalene, as shown by the red lines in 39e. Methyl A thus arises from a different molecule of mevalonolactone from that of the target atom C13, whereas methyl B and C13 arise from the same molecule of mevalonolactone. Careful calculation of the ratios $^{13}$C:$^{12}$C in the starting mevalonolactone and that expected of cholesterol from the two possible mechanisms showed that the double 1,2-shift mechanism would give rise to twice as much doubly labelled acetate from the oxidative degradation as would the single 1,3-shift mechanism. Mass spectrometric analysis of the recovered acetate was in accord with the former mechanism.

The question of the hydrogen shifts could now be addressed (36) by obtaining cholesterol 23e from (4R)-[2-$^{14}$C, 4-$^3$H$_1$]mevalonic acid 69b because Cornforth showed (37) that the 4-pro-R hydrogens are retained in the biosynthesis of squalene 39. By the Ružička mechanism below, on conversion to cholesterol 23e, one tritium (at C24) will have retained its original position, two will have migrated and three will be eliminated. The 5:3 $^{14}$C:$^3$H ratio found (36) in 23e was in accord with this, and treatment with a corpus luteum preparation cleaved the bond between C20 and C21 to give progesterone 74 and isocaproic acid (4-methylpentanoic acid) with the expected 3:1 and 2:1 $^{14}$C:$^3$H ratios and a loss of tritium from C20. Proof that the remaining tritium label was at C17 was obtained by Baeyer–Villiger reaction to a tetraol retaining all tritium followed by oxidation to a ketone with loss of the remaining tritium.
Cornforth and Popjak had therefore provided experimental proof for the rearrangement of hydrogen atoms and methyl groups in the biosynthesis of cholesterol.

**Biosynthesis of squalene from farnesyl pyrophosphate: 1**

Farnesyl pyrophosphate 75 is the immediate precursor of the symmetrical molecule squalene 39 (Lynen et al. 1958). Cornforth and Popjak (29, 30) used a squalene synthetase system to convert [2-14C, 5,5-2H2]mevalonolactone 70b into squalene 39f, which contained 11 deuterium atoms rather than the expected 12. They showed that the missing deuterium was replaced by hydrogen from the coenzyme NADPH rather than from the aqueous medium. Further experiments with labelled samples of farnesyl pyrophosphate and mevalonolactone and degradation of the squalene produced (31) showed that loss of the hydrogen atom occurred at one of the two central atoms of squalene. The stereospecificity of the hydrogen transfer (32) was shown to involve the hydrogen from the β-face of NADPH and NADH.

**Absolute stereochemistry of the many redox reactions involving nicotinamide adenine dinucleotide coenzymes**

The pyridine nucleotide coenzymes NAD+ and NADP+ 76 had long been known to effect a large number of enzyme-catalysed redox reactions by stereospecific hydrogen transfer to or from one or other face of the pyridinium ring at C4 (Levy et al. 1962). The reactions were classified as involving the α- or β-faces of the coenzyme, but absolute stereochemistry had not been assigned to these faces. This anomaly was removed by Cornforth and colleagues (34), who used known enzyme-catalysed reactions to prepare samples of NAD2H 77 labelled separately at each of the C4 hydrogens. These were degraded to the [2H1]succinic acids 78 (H_A = 2H) and 78 (H_B = 2H). A sample of (2R)-[2H1]succinic acid 78a was prepared from (2S, 3R)[2H1]malic acid 79 of well-defined stereochemistry, and optical rotatory dispersion (ORD) comparison of the three samples of [2H1]succinic acid showed that the absolute stereochemistry of NADH in 77 had H_A (α-face) as the pro-R hydrogen and H_B (β-face) as the pro-S hydrogen. Correlation of the stereospecificities of reactions involving NADH and NADPH had already been made (Nakamoto & Vennesland 1960), and so the assignment of absolute stereochemistry was applicable to all enzyme-catalysed reactions involving these coenzymes.
Biosynthesis of squalene from farnesyl pyrophosphate: 2

The ORD method for identifying (2R)- and (2S)-succinic acids allowed Cornforth and Popják (35) to determine the stereochemistry of the condensation of the two molecules of farnesyl pyrophosphate 75 that gives the central carbon atoms of squalene 39. Using [2,14C, 5, 5-2H2] mevalonic acid 69c (He = Hf = 2H) and ozonolysis of the squalene produced gave [2H3] succinic acid, the ORD of which was comparable to that of (2S)-[2-2H] succinic acid 78 (Hf = 2H). Its absolute configuration was therefore assigned as (S) as in 78b and so it derived from the [2H3] squalene 39g. Hence the pro-S hydrogen of NADH (β-face) is incorporated at either 11α or 12β of cholesterol depending on whether the squalene is cyclized from one or the other end of the symmetrical molecule.

Stereochemistry of the biosynthesis of cholesterol from (R)-mevalonic acid

(R)-Mevalonic acid 69a is used uniquely for terpene biosynthesis. The first two steps in the biosynthesis of terpenes and steroids involve the synthesis of (i) a monophosphate and (ii) a diphosphate (pyrophosphate) 69d. Step (ii) uses only the (R)-isomer (40) and so racemic samples of stereospecifically labelled mevalonic acid may be used to study the stereochemistry of biosynthesis. The stereochemistry of the labelled atom relative to the stereocentre C3 is the only requirement.

The first step in the biosynthesis of farnesyl pyrophosphate 75 from mevalonic acid 69c involves decarboxylation–dehydration of the pyrophosphate 69d to isopentenyl pyrophosphate 80. This is then isomerized to dimethylallyl pyrophosphate 81 with the loss of one of the hydrogen atoms originally at C4 of mevalonic acid, and protonation of the olefin. A second molecule of isopentenyl pyrophosphate 80 then loses a hydrogen atom from the same carbon in substitution at C1 of dimethylallyl pyrophosphate 81 (originally C5 of mevalonic acid). This yields geranyl pyrophosphate 82. Reaction of geranyl pyrophosphate 82 with isopentenyl pyrophosphate 80 then yields farnesyl pyrophosphate 75b.
There are many stereochemical questions to be answered here, and syntheses of samples of mevalonic acid 69c labelled stereospecifically with deuterium and/or tritium at C2, C4 and C5 were completed in their solution.

The first objective was to determine the stereochemistry of the hydrogen (H_A or H_B) lost in the isomerization of 80 to 81 and in the two carbon–carbon bond-forming reactions in the sequence. All of these involve C2 of isopentenyl pyrophosphate 80, which originates from C4 of mevalonic acid. (4R)- and (4S)-[4-2H_1]Mevalonic acids 69c (H_A = ²H) and 69c (H_B = ²H) and the corresponding tritiated compounds were prepared by stereospecific synthesis (37) and incubated with a rat liver preparation to yield farnesyl pyrophosphate 75b. Mass spectra showed that three deuterium atoms were retained when (4R)-labelled mevalonic acid had been used and no deuterium was present in the experiment using (4S)-labelled mevalonic acid. This was confirmed by using the tritiated samples and so the mevalonic acid 4-pro-S hydrogen HB was lost in all three reactions leading to farnesyl pyrophosphate 75b. Interestingly, although it is the 4-pro-S hydrogen that is lost in the synthesis of all-trans-farnesyl pyrophosphate 75 and squalene, Cornforth and colleagues (38) showed that the biosynthesis of rubber in *Hevea brasiliensis* latex involves loss of the 4-pro-R hydrogen, suggesting that the cis configuration of rubber is formed without the involvement of any trans intermediates.

To answer the question of the stereochemistry of carbon–carbon bond formation at C1 of isopentenyl pyrophosphate, a sample of (5R)-[2H_1]mevalonic acid 69c (H_E = ²H) was prepared (Donninger & Popják 1966) and incubated with a rat liver preparation (37) to give squalene 39 containing six deuterium atoms. Ozonolysis gave laevulinic acid, which was degraded to (R)-[²H_1]succinic acid, as confirmed by ORD comparison. Thus bond formation in the synthesis of farnesyl pyrophosphate 75b proceeded with inversion of stereochemistry at both centres C1 of 81 and 82 (C5 of 69c).

[2, 3-2H_2]Succinic acid obtained directly from the ozonolysis represents the central atoms of squalene 39. It was known (35) that one of these atoms has the (S) configuration and, because the isolated succinic acid had zero rotation (37), it must be the RS (meso) species. This indicated that the reaction between the two molecules of farnesyl pyrophosphate 75 involves inversion of stereochemistry at that farnesyl residue, which does not exchange hydrogen.

Cornforth and Popják (39) now examined the stereochemistry of the decarboxylative dehydration of mevalonyl pyrophosphate 69d and of the two carbon–carbon bond-forming reactions with respect to the face of the olefinic nucleophile 80 involved by synthesizing (2R)- and (2S)-[²H_1]mevalonic acid 69c (H_D = ²H) and 69c (H_C = ²H) from the two samples of [4-2H_1]mevalonic acid prepared in the previous study. Both substrates were enzymatically converted into isopentenyl pyrophosphate 80, and the (2R)-[²H_1] isomer was also converted into farnesyl pyrophosphate 75b. A chemical method was devised to determine the steric positions of the deuterium and hydrogen atoms in isopentenol and this was applied to the products of the enzyme-catalysed decarboxylation–dehydration reaction to show that trans-elimination had occurred.

The sample of farnesyl pyrophosphate 75b derived from (2R)-[2-²H_1]mevalonic acid was converted into farnesol and ozonolysed to give laevulinic acid. Further oxidation gave (2R)-[²H_1]succinic acid by ORD comparison. The coupling reactions, which had been shown to involve inversion of stereochemistry at one carbon (C1 of 81 and 82, C5 of 69c), were now also defined by the face of the double bond at the atom (C4 of 80) involved.

Cornforth and Popják had now defined the stereochemistry of all of the steps in the conversion of mevalonic acid to squalene except for the stereochemistry of protonation in the
conversion of isopentenyl pyrophosphate 80 to dimethylallyl pyrophosphate 81. The solution to this final question would await Cornforth’s development of methods for assessing chirality in methyl groups.

Although the stereochemistry of the condensation of farnesyl pyrophosphate 75 to squalene 39 was now known, there remained the question of whether it would be possible for squalene, although symmetrical, to be transferred in a spatially oriented manner from the enzyme that produces it to the enzyme that epoxidizes it. Cornforth (54) showed that this was not the case by injecting (5S)-[5-3H]mevalonic acid 69c (H_F = 3H) into living rats. They were killed after 45 minutes and cholesterol was isolated from their livers. Degradation showed equal labelling at the 11α and 12β positions so that squalene, when biosynthesized in vivo, is not transferred in a spatially oriented manner.

The chiral methyl group in enzymic reactions

There are many enzyme-catalysed reactions in which a methyl group is converted into methylene or vice versa or in which a methyl group is transferred intact from one compound to another. These reactions may be stereospecific, and Cornforth’s next challenge was to develop methods to study them. His solution to the problem required the synthesis of samples of acetic acid containing the three isotopes of hydrogen disposed in a stereochemically defined manner and the development of assays for compounds containing such ‘chiral methyl’ groups. Because it is not possible to obtain tritium undiluted with normal hydrogen, Cornforth reasoned that if compounds were made in which every molecule containing tritium also contained deuterium, and if the method of assay involved solely the measurement of tritium, then isotopic discrimination would simply be between hydrogen and deuterium.

The reaction of acetyl-CoA 84 and glyoxylate 83 catalysed by malate synthase was chosen for study (41) because there is sufficient discrimination between the isotopes, the intramolecular tritium and deuterium isotope effects being 2.7 and 1.4, respectively. If (S)-malate 79a were synthesized stereospecifically from acetyl-CoA 84 and if the isotope effect required that the C–H bond be broken in preference to the C–2H bond, then stereospecifically labelled [2H, 3H]acetate will give unequal amounts of (2S, 3R)- and (2S, 3S)-[3-2H, 3-3H]malate 79a (H_B = 2H) and 79a (H_A = 2H), respectively. Because fumarase catalyses the reversible dehydration of (S)-malate 79a to fumarate 85 by trans-elimination with loss of the 3-pro-R hydrogen, an assay of the stereochemistry of the product from the malate synthase catalysed reaction is available.

Cornforth (41) now synthesized samples of (R)- and (S)-[2H, 3H]acetate. [2H] Phenylacetylene 86 was reduced by diimide to (Z)-[2-2H]1-phenylethylene 87. Epoxidation to the epoxides 88 followed by reduction by lithium borotritide with inversion of stereochemistry gave a racemic mixture of (1R, 2R)- and (1S, 2S)-[2-3H, 2-2H]1-phenylethanol 89a and 89b. This was mixed with unlabelled material and resolved into the (1R)- and (1S)-enantiomers of known absolute configurations. These were separately oxidized with chromic oxide and peroxytrifluoroacetic acid without loss of label and hydrolysed to (R)- and (S)-[2H, 3H]acetic acids 90a and 90b, respectively.
Each specimen of acetate was incubated with ATP, acetate kinase, phosphotransferase, coenzyme A, glyoxalate and malate synthase to give \((S)\)-malate \(79a\). The samples of malate were purified with unlabelled \((S)\)-malate with and without added \([^{14}C]\)malate. Tritium retention in fumarate \(85\) from the fumarase reaction was measured, showing 67.2% retention using \((R)\)-\([^{2}H, {^3}H]\)acetate, 30.7% using \((S)\)-\([^{2}H, {^3}H]\)acetate, and 48.1% using a sample of randomly labelled \([^{3}H]\)acetate. The disparity from ideal was taken to reflect an intramolecular deuterium isotope effect of about 2.2 in malate synthase. The malate synthase reaction therefore occurs with inversion of configuration at the methyl group, and a simple method was available for determining the chirality of doubly labelled methyl groups and for studying the enzyme-catalysed reactions in which they are involved.

The preliminary report of this research (41) was published simultaneously with a report by Arigoni’s group (Luthy et al. 1969) in which the same malate synthase/fumarase assay had been developed but a different synthesis was devised for the \((R)\)- and \((S)\)-\([^{2}H, {^3}H]\)acetates.

**Chiral methyl and citric acid metabolism**

Cornforth now studied the stereochemistry of the reactions catalysed by four enzymes that synthesize or cleave citric acid (42–44): \(si\)-citrate synthase of the tricarboxylic acid cycle, \(re\)-citrate synthase from *Clostridium acidi-urici*, \(si\)-citrate lyase, and ATP citrate lyase. An improved modified synthesis of the \((R)\)- and \((S)\)-acetates above was used.

\(si\)-Citrate synthase catalyses the condensation of acetyl-CoA \(84\) at the \(si\)-face of the carbonyl group of oxaloacetic acid \(91\), incorporating acetyl-CoA as the pro-\(S\)\(CH_{2}CO_{2}H\) chain as in \(92a\), whereas the \(re\)-synthase incorporates it as the pro-\(R\)\(CH_{2}CO_{2}H\) chain as in \(92b\). Both citrate lyase and ATP citrate lyase cleave citrate, with the pro-\(S\)\(CH_{2}CO_{2}H\) group becoming acetate \(84a\) and the rest of the molecule becoming oxaloacetate \(91\).

The group in citrate \(92b\) that is cleaved to acetate \(84a\) using either of the citrate lyases originates from oxaloacetate in the \(re\)-synthase reaction, and so \((3R)\)- and \((3S)\)-\([^{3}H]\)oxaloacetate \(91\) \((H_{B} = {^3}H)\) and \(91\) \((H_{A} = {^3}H)\), respectively, were separately used as substrates for \(re\)-citrate synthase to yield samples of labelled citrate \(92b\) of well-defined stereochemistry.
These were cleaved to $[^{1}H,^{2}H]_{1}$acetate in $^{2}H_{2}O$ using si-citrate lyase. The samples of acetate were analysed using the malate synthase/fumarase assay to show that cleavage of citrate by citrate lyase proceeds with inversion of configuration at the methylene group at which replacement of the four-carbon residue by hydrogen occurs.

Knowledge of the stereochemical outcome of the reaction catalysed by si-citrate lyase now allowed the stereochemistry of si-citrate synthase to be determined. This enzyme was used to convert samples of (R)- and (S)-acetate 84 separately into citrate 92a. This was cleaved by si-citrate lyase to give samples of labelled acetate, which were analysed by the malate synthase/ fumarase assay. (R)-Acetate afforded (R)-acetate as product over the two steps, indicating that both the synthase and lyase reactions had proceeded with inversion of stereochemistry. The same results were obtained when ATP citrate lyase replaced si-citrate lyase in the sequence, and so this enzyme also catalyses cleavage with inversion of stereochemistry.

When samples of (R)- and (S)-acetyl-CoA 84 were incubated with re-citrate synthase, the citric acid 92b obtained had the labels from the starting acetates in the pro-R CH$_2$CO$_2$H group. Two methods were used to analyse the stereochemistry. In the first method, the citrates 92b were treated with aconitase, which is known to dehydrate citrate 92 with loss of the pro-R hydrogen from the pro-R CH$_2$CO$_2$H side chain, thus defining the stereochemistry of labelling in the samples of citrate. In the second method the citrates were converted to fumarate by using si-citrate lyase and malate dehydrogenase. This allowed the anti-elimination of water by fumarase to define the stereochemistry. The results from both methods indicated that the reaction catalysed by re-citrate synthase proceeded with inversion of stereochemistry.

Answering the final stereochemical question in the biosynthesis of cholesterol from mevalonic acid

Isopentenyl pyrophosphate isomerase mediates the reversible transformation of isopentenyl pyrophosphate 80 into dimethylallyl pyrophosphate 81. Cornforth and Popják (37) had shown that isomerization occurs with loss of the 2-pro-R hydrogen (4-pro-S of mevalonic acid) but the stereochemistry of protonation of the double bond had still to be elucidated. Methods for analysing chiral acetate now made this possible (46). (2R)- and (2S)-[2-3H$_1$]Mevalonic acids 69c were incubated with soluble enzymes from pig liver in $^{2}H_{2}O$, and the farnesyl pyrophosphate 75c isolated was converted into farnesol. Degradation and assay of the acetate produced showed that (R)-[3H$_1$, 2H$_1$]acetate was obtained from the sample by using (2R)-[2-3H$_1$]mevalonic acid, and (S)-[3H$_1$, 2H$_1$]acetate was obtained from the sample by using (2S)-[2-3H$_1$]mevalonic acid. Because (Z)-[3H$_1$]isopentenyl pyrophosphate 80 (H$_D$ = $^3$H) is formed from (2R)-[2-3H$_1$]mevalonic acid 69c (H$_D$ = $^3$H), and (E)-[3H$_1$]isopentenyl pyrophosphate 80 (H$_C$ = $^3$H) from (2S)-[2-3H$_1$]mevalonic acid 69e (H$_C$ = $^3$H) (37), the deuteron must have added from the 3re, 4re face of the double bond.

In his Prix Roussel lecture (47), Cornforth recognized these experiments as marking the end of a long trail for Milstead. A molecule of squalene has 50 hydrogen atoms. In their biosynthetic origin, one was a pro-4S hydrogen in a molecule of reduced nicotinamide-adenine-dinucleotide phosphate; two came from water; mevalonic acid supplied five pro-5S hydrogens,
six each of pro-5R, pro-4R, pro-2R and pro-2S; and eighteen methyl hydrogens. So far as we can ascertain, the whole process of biosynthesis is completely stereospecific.

**Biosynthesis of mevalonic acid and leucine catabolism**

3-Hydroxy-3-methylglutaryl-coenzyme-A synthase catalyses condensation of acetyl-CoA at the si-face of the 3-keto group of acetoacetyl-CoA to afford (3S)-3-hydroxy-3-methylglutaryl-CoA, which is then reduced to (3R)-mevalonic acid. Incubation with (R)- and (S)-[1H, 2H]acetyl-CoA and (H, H)acetates resulted in chemical reduction of the product to the lactone of mevalonic acid. The retention of tritium in androsta-1,4-diene-3,17-dione was indicative of the stereochemistry at C2 of the mevalonic acids derived from (R)- and (S)-acetate and so, given a normal hydrogen isotope effect, the synthase-catalysed condensation proceeds with inversion of configuration.

3-Hydroxy-3-methylglutaryl-CoA lyase and 3-methylglutaconyl-CoA hydratase are involved in the catabolism of leucine. Cornforth used chemical methods to convert [(3R, 4R)- and [(3S, 4S)-3H, 3H]mevalonic acids into samples of enzymically active (2S, 3S, 4R)- and (2R, 3S, 4S)-[2,4-3H, 3-14C]3-hydroxy-3-methylglutaryl-CoA (H = H = 3H) and (H, H)acetates to show that the carboxylation occurred with retention of configuration.

Treatment of the samples of labelled 3-hydroxy-3-methylglutaryl-CoA with the hydratase gave (E)-3-methylglutaconyl-CoA, tritium loss showing that syn-dehydration had occurred. In this respect it differed from all other dehydratases with the exception of 5-dehydroquinate dehydratase.

**Chiral methyl: a postscript**

Cornforth studied the stereochemistry of other enzyme-catalysed reactions in which methyl groups are created or reacted upon. In the oxidative decarboxylation of S-malate to pyruvate by malic enzyme it was found that hydrogen replaced the carboxyl group with retention of configuration.

Biosynthesis of fatty acids involves carboxylation of acetyl-CoA by acetyl-CoA carboxylase to give malonyl-CoA. Cornforth used (R)- and (S)-acetates to show that the carboxylation occurred with retention of configuration.

Cornforth’s groundbreaking work has stimulated others to study the stereochemistry of enzyme-catalysed reactions involving chiral methyl groups (Floss et al. 1984) and his
contribution has resulted in a step change in our understanding of the mechanism of metabolic reactions.

**Imitation of enzyme catalysis**

Cornforth now turned from studying reactions catalysed by enzymes to the design of a compound that might mimic the catalytic properties of an enzyme. As his reaction he chose olefin hydration, which is catalysed by many hydratases and dehydratases, and envisaged ways in which it might be accelerated in the manner of an enzyme. His catalyst would have a well-defined structure containing a shaped hydrophobic cavity with a precisely placed catalytic acidic group and would operate in aqueous medium. A phosphinic acid group was chosen because it would be anchored within the cavity by two bonds. Work was begun at Sittingbourne and continued at Sussex. New synthetic methods were developed and eventually two meso-atropisomers 97 and 98 and the resolved racemic atropisomers 99 were prepared (55). Stereomutation of the isomers was followed by nuclear magnetic resonance spectroscopy and the activation energy was calculated.

![Chemical structures](image)

In the final publication on imitation of enzyme catalysis (57), the phosphinic-tetraphosphonic acid 100 and phosphinic-triphosphonic acid 101 were prepared. In water at pH 2–4 these formed stable monodisperse solutions that catalysed the hydration of 2-methylpropene to tert-butyl alcohol more efficiently than did a p-toluenesulfonic acid solution of equivalent acidity. However, complexation of propene to these compounds was not comparable to that expected of an enzyme. Cornforth concluded that, to reach useful levels of catalysis, design of the cleft flanking the phosphinic acid function would need to be refined.

![Chemical structures](image)

**Other work**

Cornforth’s work covered many areas. In his stereochemical studies, he used a mixture of degradative, labelling and X-ray crystallographic methods to determine the absolute stereochemistry at the sulfonium centre of S-adenosylmethionine, the ubiquitous and versatile metabolic intermediate that is the principal metabolic donor of methyl groups (53). Over the years he published corrections to many errors in the published work of others. After his retirement he revised structures suggested erroneously in 18 different publications for a product of the Erlenmeyer–Plöchl synthesis (56) and corrected a misunderstanding on a structure thought to be 2-chloro-3H-indol-3-one that had been extant for more than 115 years.
and 40 publications (58). In a longstanding interest in the plant dormancy hormone abscisic acid he elucidated its stereochemistry and completed two different total syntheses. His research in several areas of chemistry and biochemistry has not only solved many very important questions but has greatly influenced the work of others and will continue to do so in the future.

HONOURS AND AWARDS

1939 1851 Exhibition Overseas Scholar
1953 Fellow of the Royal Society of London
Corday–Morgan Medal and Prize (Chemical Society)
1965 Ciba Medal (Biochemical Society)
1966 Flintoff Medal (Chemical Society)
1967 Hon. Member, American Society of Biological Chemists
Stouffer Prize
1968 Davy Medal (Royal Society of London)
Pedler Lecturer (Chemical Society),
1969 Ernest Guenther Award (American Chemical Society)
1970 Andrews Lecturer (University of New South Wales)
Max Tishler Lecturer (Harvard University)
1971 Robert Robinson Lecturer (Chemical Society)
1972 Commander of the Order of the British Empire (CBE)
Prix Roussel
1973 Foreign Hon. Member, American Academy of Arts and Sciences
Pacific Coast Lecturer
1975 Nobel Prize in Chemistry
Australian Man of the Year
Royal Society Research Professor, University of Sussex
Hon. DSc, Eidgenössische Technische Hochschule Zurich
1976 Royal Medal (Royal Society of London)
Hon. Fellow, St Catherine’s College Oxford
Hon. Fellow, Royal Australian Chemical Institute
Hon. DSc, University of Oxford
Hon. DSc, University of Liverpool
Hon. DSc, University of Warwick
Hon. ScD, Trinity College Dublin
1977 Knight Bachelor
1978 Chemical Society Award, Chemistry of Natural Products
Corresponding Member, Australian Academy of Science
Hon. Member, Royal Society of New South Wales
Sandin Lecturer (University of Alberta)
Hon. DSc, University of Aberdeen
Hon. DSc, University of Hull
Hon. DSc, University of Sussex
Hon. DSc, University of Sydney
John Warcup Cornforth

1978  Foreign Associate, National Academy of Sciences (USA)
      Foreign Member, Royal Netherlands Academy of Sciences
1982  Copley Medal (Royal Society of London)
1983  Trustee, Ciba Foundation
      Robert Robinson Memorial Lecturer (University of Oxford)
1986  Hon. Professor, Beijing Medical University
1991  Companion of the Order of Australia (AC)
2001  Centenary Medal of the Government of Australia

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The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2015.0016 or via http://rsbm.royalsocietypublishing.org.

Biographical Memoirs


