BIOGRAPHICAL MEMOIRS

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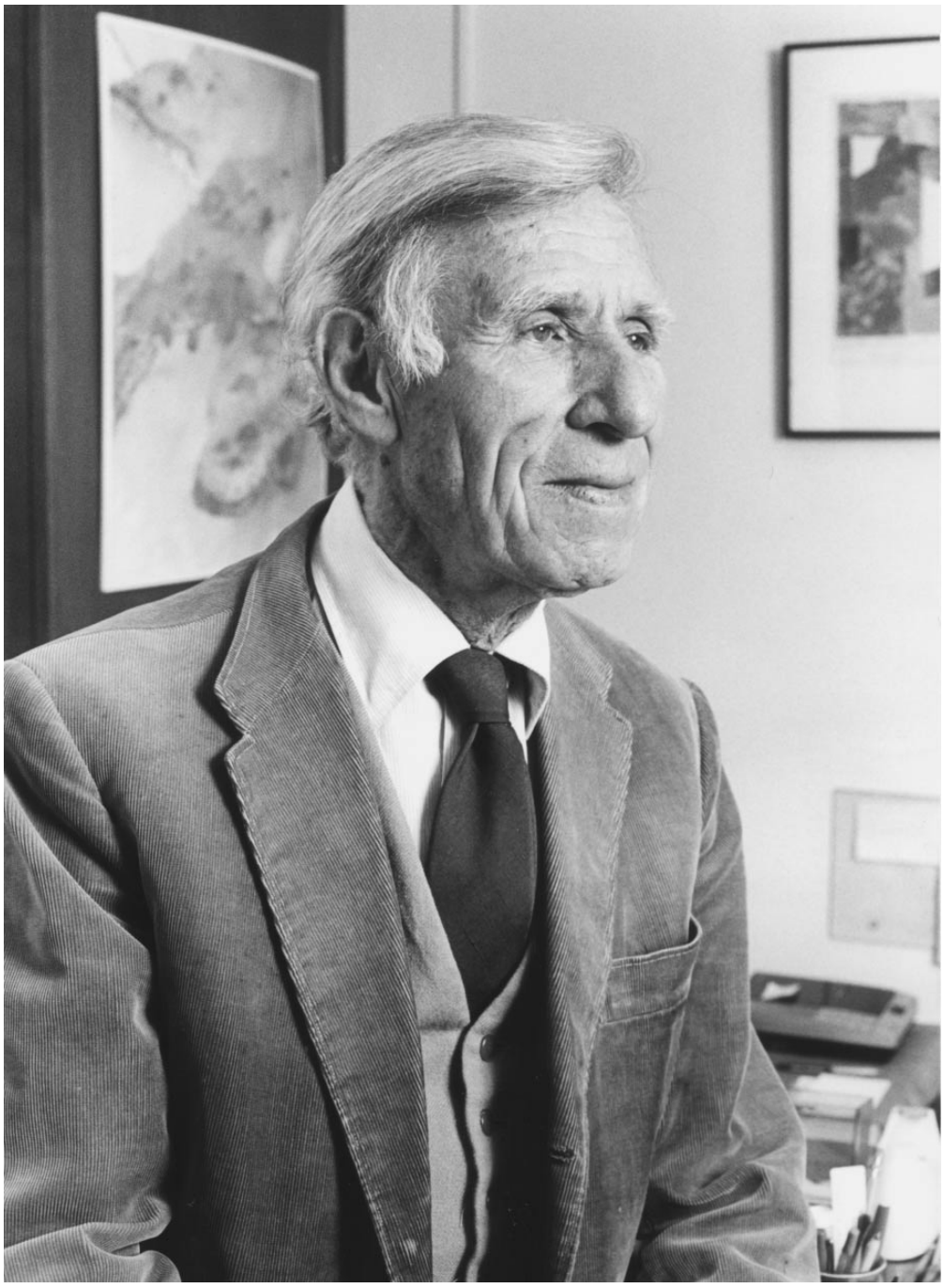

Konrad E. Bloch

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Elected For.Mem.R.S. 1985

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Konrad Bloch was one of the leaders of the small group of exceptional biochemists who unravelled the pathways of intermediary metabolism. He was born in 1912 in Niesse, Germany, into a highly cultured, prosperous Jewish family, and began his schooling at the local *gymnasium*. For his 13th birthday, a rich uncle offered Konrad his choice of a cello or a canoe. Before he had a chance to make the obvious choice of any red-blooded 13-year-old boy, his mother intervened: 'Of course Konrad would prefer the cello'. And a cello it was.

In due course, Konrad graduated from the *gymnasium* at Niesse and embarked on a career in organic chemistry in Hans Fischer's laboratory in Munich. He earned from Fischer the greatest four-word recommendation ever: 'Herr Bloch ist ausgezeichnet'. (Some critics claim that the recommendation read, 'Herr Bloch ist sehr gut'.) But spectacular recommendation or no, there was no place for Konrad in Hitler's Germany. He applied to Fritz Kögl in Utrecht but fortunately was rejected; had he been accepted he would have been trapped when the Nazis overran Holland. He managed to slip into Switzerland, where he tried to obtain a PhD This future Nobel laureate failed his doctoral examination; he had neglected to cite a publication of one of his examiners.

During his stay in Switzerland, Bloch had occasion to try to repeat some work on the fatty acids of tubercle bacilli, work that Rudolf Anderson at Yale had published. He found that Anderson's work had been faulty. With an audacity that he would never have dared towards a German *Geheimrat*, Bloch wrote to Professor Anderson to correct his experimental results. Anderson reacted as the ideal scientist is supposed to react but as not all scientists do. He checked his work again, and then wrote promptly, confirming Bloch's experiments, and thanking him for the correction.

Later, when Bloch was forced to leave Switzerland, he appealed in desperation to Anderson for help in entering the USA. Anderson again reacted as one would hope that a scientist would: he promptly sent two letters in reply, one from the Dean that Bloch could show to the US con-

sul, promising Bloch an assistantship at Yale, and a second, private letter, admitting that there was no money to support the assistantship. Bloch gratefully used the first letter to gain entry to the USA, and started his search for a PhD advisor.

Of course he talked to Anderson, who suggested, however, that he apply to Hans Clarke at Columbia, who duly interviewed him. This was long before the National Institutes of Health flooded biochemists with money; despite Bloch's obvious intelligence and qualifications, Clarke was dubious. He would be forced to scramble for funds, and was just about to dismiss Bloch when a sudden thought occurred to him, and he asked Konrad if perchance he played an instrument. He admitted to playing the cello. Clarke was an enthusiastic music lover and a classical clarinettist; his wife was the first violinist in a string quartet. Bloch had no further difficulty in joining Clarke's research group, and began his distinguished scientific career. Konrad's mother had been right all along; he preferred the cello.

After Bloch received his PhD in 1938, he remained at Columbia to perform postdoctoral research with Rudolph Schoenheimer. This was an inspired choice. Schoenheimer was a true genius, who understood and pioneered the power of isotopic labelling in working out the pathways of intermediary metabolism. Columbia was also the place to be because Harold Urey (For.Mem.R.S. 1947), who was a member of the chemistry department there, had just found out how to make heavy water (deuterium oxide) and label organic compounds with deuterium. He had also discovered how to obtain water with an excess of ^{18}O, and with Mildred Cohn he had shown how to label organic compounds with that isotope of oxygen. Most importantly, Urey was generous with his isotopes and his time in helping others to take advantage of his findings. Some years later, radiocarbon became available and its use was a normal extension of the isotopic techniques that Schoenheimer had pioneered in labelling metabolites.

In addition to Konrad, David Rittenberg and David Shemin were members of Schoenheimer's group. There has seldom, if ever, been such a collection of biochemical stars gathered in one laboratory, and of course they stimulated each other. Bloch began his epoch-making studies of the biosynthesis of cholesterol at this time, and with Rittenberg he demonstrated, using isotopically labelled acetate, that this simple molecule is a precursor of cholesterol. Bloch clung tenaciously to this project until he had solved it completely, working out most of the early steps and all of the later steps in the approximately 30 steps for the biosynthesis of cholesterol.

On the basis of his work at Columbia, Bloch was appointed to the staff in the Department of Biochemistry at the University of Chicago, where he pursued the suggestion of Sir Robert Robinson, F.R.S. (P.R.S. 1945–50), that squalene (figure 1) is an intermediate in the biosynthesis of cholesterol. Squalene is a hydrocarbon that is especially abundant in shark liver. Although sharks are somewhat inconvenient as laboratory animals, dogfish are essentially small sharks and are abundant in the water off Bermuda. Because nothing was going to stop Bloch in his search for intermediates in the biosynthesis of cholesterol, he took off for Bermuda, where the personnel at the marine laboratory enthusiastically offered to help. They caught a dogfish and put it into their aquarium. Bloch planned to feed it with labelled acetate, but it died. They caught another dogfish but it, too, died. Rats do not have nearly as much squalene in their livers as sharks do but they do have some, and they are much more manageable. Konrad returned to Chicago and, by feeding isotopically labelled acetate to rats, he proved that squalene is indeed an intermediate in the biosynthesis of cholesterol.

His next hypothesis was that lanosterol (figure 2) is also an intermediate, and again, with the use of labelled acetate, he confirmed this hypothesis. Lanosterol contains the four-ring

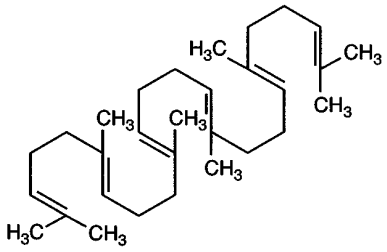

Figure 1. Squalene.

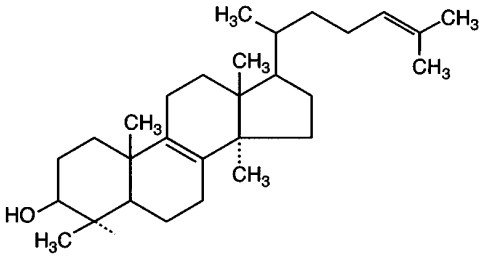

Figure 2. Lanosterol.

structure of cholesterol, but several problems remained, of which the knottiest was the exact mechanism by which the linear structure of squalene cyclized and rearranged to form lanosterol. At this time Bloch was visiting Harvard, and he and Bob Woodward (F.R.S. 1956) between them worked out a hypothesis, different from that advanced by Robinson for the cyclization, and Bloch experimentally confirmed that this new pathway was correct (1)*.

However, lanosterol contains three extra methyl groups that are not present in cholesterol (figure 3). Bloch and his students performed experiments, again using isotopic tracers, that allowed them to demonstrate that the methyl groups were removed by biochemical oxidation.

This magnificent accomplishment—the complete picture of the biosynthesis of cholesterol—earned Bloch the Nobel Prize in Physiology and Medicine in 1965 (2), an honour that he shared with Feodor Lynen (For.Mem.R.S. 1975), who had found the pathway of the biosynthesis of fatty acids.

Bloch, however, achieved one other honour for his work on cholesterol that is sufficiently unusual to warrant mention, and provides some insight into Bloch's character. The selectmen of Lexington, Massachusetts (the town where Bloch lived), called on him to ask whether there was anything they could do to honour their most famous citizen further. Konrad replied that indeed there was. He worked six days a week, and had no opportunity to take his trash to the town dump, which was open only on weekdays. He hoped that the town dump could be opened for several hours on Sunday. And, to honour Konrad, the selectmen agreed.

After his work on the biosynthesis of cholesterol, Bloch embarked on a study of some unsaturated fatty acids, stimulated, perhaps, by Lynen's work and by his success in correcting Anderson's contribution to the chemistry of the fatty acids of tubercle bacilli. In particular, he investigated the conversion of $\beta\gamma$ to $\alpha\beta$ unsaturated fatty acids, or to be more precise the inter-

* Numbers in this form refer to the bibliography at the end of the text.

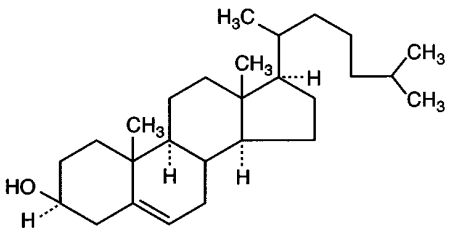

Figure 3. Cholesterol.

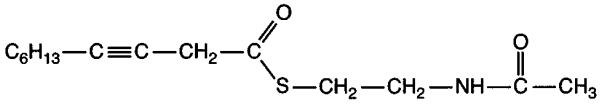

Figure 4. Cysteamine thioester of 3-decynoiic acid.

conversion of their *N*-acetylcysteamine (NAC) thioesters. This interconversion consists of the shift of a double bond from a remote position to one that is conjugated with the carboxyl group.

Conveniently, this caused a large change in the ultraviolet spectrum of the acid and its thioester. The spectroscopic change provides an easy way of following the progress of the enzymatic reaction. One sample of the starting material, however, behaved badly. It did not undergo the expected spectroscopic change but somehow killed the enzyme. Never one to ignore inconvenient experimental findings, Bloch reacted in accordance with an aphorism attributed to Enrico Fermi, For.Mem.R.S.: 'If you carry out an experiment and get the result you expected, you have made a measurement; if you get a result you had not expected, you have made a discovery'. Bloch set about to find out what it was that he had discovered.

The sample of the NAC thioester of the decenoic acid that behaved badly turned out to be impure; it contained about 5% of the NAC thioester of the acetylenic acid from which it had been synthesized. The NAC thioester (figure 4) of the pure acetylenic acid promptly inactivated the enzyme (3). But why? An acetylic bond can be regarded as two double bonds, one piled on top of the other. If the enzyme catalysed a change parallel to that with the NAC thioester of the olefinic acid, it would move one of these bonds into conjugation with the carboxyl group, and leave the other alone. The resulting compound would have two double bonds side by side. Such a structure is called an allene, and is highly reactive. Bloch and his co-workers showed that an allene was indeed formed and had reacted with a histidine residue of the enzyme at its active site (4); the new structure prevented the enzyme from functioning. The 5% of the NAC thioester of the acetylenic acid present as an impurity in the critical sample was plenty to kill all of the enzyme, because substrates are present in huge excess (often a million times that of the enzyme) so that a small percentage of an impurity in the substrate still overwhelms the enzyme.

This explained what had happened when an impure sample of substrate killed the enzyme, but more significantly it suggested a general method of killing enzymes: find a substrate that, when the enzyme performs its function, produces a compound that reacts irreversibly with the enzyme. Because the destruction of specific enzymes is the key to the control of many diseases, the general method is potentially valuable in pharmaceutical research. The method was promptly christened that of suicide inhibitors (5) because the inhibitor itself is harmless but is

converted to a deadly reactant by the enzyme itself. Shortly after this discovery, Konrad received the National Medal of Science, presumably for this accomplishment.

After he moved from the University of Chicago to Harvard and took up residence in Lexington, Konrad delighted in tennis and swimming as well as in science. Jointly with Paul Bartlett he bought a summer house in Vermont, and more significantly, bought and beautifully restored a wreck in northern Italy. In his later years he vacationed in both of these houses. In the process of using the latter one, he found it convenient to learn Italian and add that language to the three that he already knew.

For many years Konrad taught the course in general biochemistry at Harvard and introduced a large number of students to that subject. After he retired, he wrote a series of entertaining stories about biochemistry that he incorporated into a book entitled *Blondes in Venetian paintings, the nine-banded armadillo, and other essays in biochemistry* (6). One of the stories concerned 'The importance of being contaminated', and allowed him to tell the story of suicide inhibitors and point out that he would never had made the discovery had he worked with pure materials. There are many other examples, too, of the importance of impurities in scientific discovery. This should not be construed as an argument in favour of sloppy research but an argument in favour of tracking down any unusual experimental result.

In 1941 he married Lore Teutsch. He is survived by her, by a son, Peter, and by a daughter, Susan. And by a horde of admiring friends.

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A full bibliography appears on the accompanying microfiche, a photocopy of which is available from The Royal Society's Library at cost.

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