Herbert Hauptman

(1917–2011)

Mathematician whose theories reveal the shapes of molecules from scattered X-rays.

The intricate molecular structures that regularly grace the covers of scientific journals — including this one — are all monuments to Herbert Hauptman. Fifty years ago, he pioneered mathematical tools for deducing the configurations of molecules as recorded in the patterns of X-rays scattered by crystals. With the architectures of hundreds of thousands of molecules, including numerous drugs — from vitamins to hormones to antibiotics — now established, his efforts have transformed chemistry and biology. In 1985, he shared the Nobel Prize in Chemistry with Jerome Karle. Hauptman died on 23 October, aged 94.

Born in the Bronx in New York City, Hauptman was interested in mathematics from a young age. He earned a bachelor's degree in the subject from the City College of New York in 1937 and a master's degree from Columbia University in 1939. After serving in the US Navy during the Second World War as a weather forecaster in the South Pacific, he moved in 1947 to the Naval Research Laboratory in Washington DC. Here his fruitful collaboration with Karle began. Both were enrolled in the graduate programme at the University of Maryland in College Park, where Hauptman earned his doctorate in 1955.

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The combination of Hauptman's mathematical skill and Karle's physical-chemistry background proved powerful in the emerging field of X-ray crystallography. Some researchers — including James Watson, Francis Crick, John Kendrew and Max Perutz — were deducing the shapes of macromolecules, such as DNA and the proteins myoglobin and haemoglobin, through complementary crystallographic techniques. Hauptman, Karle and others sought ways to automatically convert the scattered X-ray patterns from small molecules into structural information.

At the time the only way to do so was to apply the Patterson methods — rules that worked well for some materials, such as organometallic compounds (containing heavy atoms), but were inadequate for others, notably organic molecules. Molecules larger than about 50 atoms remained a challenge, and many drugs, antibiotics and materials of technological interest were beyond reach altogether.

Hauptman and Karle developed mathematical tools — known as direct methods — to convert X-ray crystallography data to molecular forms. In 1953, they introduced two ideas: the most general approach for the solution of the loss of phase information during measurement in crystallography; and the concept of 'structure invariants', which shows the combination of phases that can be estimated from experiments.

In the mid-1960s, Hauptman and Karle's mathematical ideas met the applied skills of Michael Woolfson, another father of direct methods. He combined computer algorithms and direct-methods techniques so that many different trial solutions could be explored to find the correct one. Within a few decades, the development of powerful computers and contributions from younger scientists solved the phase problem for molecules of up to 250 atoms. Today, most crystal structures can be computed within minutes.

In 1970, Hauptman moved to the Medical Foundation of Buffalo in New York (renamed in 1994 the Hauptman–Woodward Medical Research Institute), becoming its research director two years later and president in 1988. He turned his mathematical skill to large molecules. Hauptman extended his direct-methods framework to unravel more complex structures by incorporating extra experimental data from complementary crystallographic techniques. Today these methods can be applied to macromolecules with thousands of atoms.

The impact of Hauptman's work goes beyond pinpointing atoms. By establishing bond distances and angles, the chemical activity of a molecule can also be understood — and so, in a biological context, can its function: for example, DNA's double-helical structure is essential to its ability to replicate. This information, now stored for hundreds of thousands of molecules in data banks, is invaluable for chemists, physicists and biologists, whether for designing high-temperature semiconductors, inventing pharmaceuticals or studying biologically active molecules.

Hauptman had a warm personality and was continuously active in teaching direct methods to students of all nationalities in summer schools. He was patient and diligent in his presentation: he spoke quietly, with long pauses so that students could follow his detailed descriptions more easily. To students he was simply 'Herb', always available for a personal tutorial after the official lectures, both before and after having received the Nobel prize.

I first met Hauptman at such a school in 1970, in Parma, Italy. It was there that I decided to dedicate my scientific activity to this field. In the decades since, Hauptman always encouraged my efforts, even recognizing our similar yet independent approaches in his Nobel lecture. We are all in debt to his great generosity. ■

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