Reminiscences

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It is not easy to write of what happened fifty years ago because the things remembered are so rarely what we now imagine as most important. In my case crystals were objects of early fascination but in memory this interest was aesthetic and not at all alloyed with what might underlie their beauty of form. Though such childhood concerns undoubtedly colour what we do later in life, my choice of crystal structure as a doctoral thesis was purely accidental. I had been proposing to see how J. J. Thomson's investigations of positive rays could be turned to chemical advantage. But it happened that S. Nishikawa, one of the first to follow the Braggs in determining atomic positions, was spending a couple of war years in the physics department at Cornell; and the chairman of my graduate committee thought I should take advantage of his presence to learn something about the then-new methods of X-ray diffraction and their chemical potentialities. Nishikawa and I became friends and he agreed to guide me in working through a couple of structures—of sodium nitrate (I have forgotten why) and of cesium dichloroiodide (chosen because of current interest in the chemistry of cesium and because this compound had a mystery which it has since lost). It was from Nishikawa that I learned how to prepare X-ray spectra and Laue photographs and to use their data to select between possible atomic arrangements. He also brought a knowledge of the theory of space groups, acquired from a Japanese professor who had been one of the few to work in Germany during the 1890's when the theory was being created. In looking back one expects to remember some details of the inevitable discussions through which these things became clear; but in fact what remain vivid are a laboratory consisting of a decrepit medical X-ray machine and homemade instruments in lead-covered wooden boxes, and trips together over the countryside in a still more decrepit Ford—or lasting insights into the very different ways an easterner and a westerner looks at life's basic problems.

Contents

On getting my degree in 1919 I went to the Geophysical Laboratory to begin there an application of X-ray diffraction to minerals. Much of the first two years was spent in getting together the Analytical Expression of the Theory of Space Groups and in trying to have it published. It has always been a matter of gratitude to remember how, in the end, it was Dr. Woodward, not as President of the Carnegie Institution but as a mathematician, who intervened to authorize its publication. About then Ellis, who with Burdick had published the first structure to be obtained in the United States, stopped on his way to California. He arranged for Dickinson, then transferring to the California Institute of Technology, to spend a short time in Washington familiarizing himself with the use of Laue photographs and space-group results; and out of Dickinson's visit came the year I spent in Pasadena in 1922. During that time Bozorth, working on his thesis, Dickinson and I turned out a number of structures. In those days one could find excitement in success with the simplest of crystals but more vivid than these excitements is the memory of the still-unspoiled beauty of California's mountains.

With the completion of my *Structure of Crystals* in 1924 came the freedom to spend summers in Europe. At this time recovery from the war was fostering contacts across the ocean and the costs of travel were low enough to permit two or three months abroad each year, spent partly in visiting laboratories and partly on vacation. I had been corresponding with Professor Schoenflies since shortly after the war ended and these trips gave the chance for visits to him in Frankfurt and in Austria. It was also during one of these summers that Ewald organized what must have been X-ray diffraction's first international conference in his mother's studio on the Ammersee. Meetings were not then the almost daily occurrences that they have now become and this one had all the advantages given by its small size and informal character. A snapshot taken at it shows von Laue, Darwin and W. L. Bragg, Mark and H. Ott, Waller, Fokker, Debye and one or two others I no longer recognize.

There must be few of us who do not find their interest shifting as their work develops. I found that, as the power of X-ray methods grew, the possibility of their ultimate application to biological systems became increasingly alluring. When, after eight years at the Geophysical Laboratory, the opportunity unexpectedly arose to go to the Rockefeller Institute to start X-ray work on such substances, it therefore seemed the obvious thing to do. Studies there began with aliphatic-substituted ammonium salts and gradually extended to amino com-

pounds. During most of the ten years in New York Corey worked with me and when the work was halted in 1937 he took with him to Pasadena a partly finished study of glycine; the structures of this and other amino acids he has since published are an essential part of the understanding of proteins that is now emerging. During the last years at the Rockefeller Institute we were developing air-driven ultracentrifuges to purify and crystallize the proteins and other biologically significant substances from which we were beginning to get X-ray patterns; and I found that with these ultracentrifuges animal and plant viruses too unstable for chemical treatment could be isolated. From one of the viruses thus purified Beard and I prepared an effective vaccine against the sleeping sickness of horses which was at that time epidemic in the United States. When I had to stop work at the Rockefeller Institute, the job that presented itself was in industry and involved the attempt to prepare large amounts of such a vaccine. It turned out that a satisfactory vaccine could be made without costly ultracentrifugation and the next two years were spent in devising large scale methods and making it in million-dose quantities. The work was exciting because of the dramatic way in which widespread use of our vaccine effectively ended a disease which the year before had killed more than 170 000 horses and was beginning to take a considerable toll of human victims. It was scientifically important in providing the first successful 'killed' vaccine against a virus disease and the first vaccine of this sort to be manufactured in chicken embryos. By the time this job was finished the war was imminent and we turned our experience of embryos to the making of a rickettsial vaccine against epidemic typhus fever. After preparing several million doses for the U. S. Army, my laboratory undertook the large scale freeze-drying of human blood plasma that the Red Cross was beginning to collect for the armed forces. A new apparatus was developed for doing this and two plants incorporating it and each processing individually more than a thousand bacterially sterile bleedings per day were built and operated. When this was over I returned to academic life and during a brief stay at the University of Michigan began using the electron microscope to visualize the virus and other protein molecules earlier investigated by ultracentrifugation. It was here that Robley Williams and I discovered the advantages of metal shadowing for this purpose. From that time till I retired two years ago (with the exception of two years spent in the Foreign Service as Science Attaché in London) my work at the National Institutes of Health, with frequent visits to the virus laboratory of P. Lépine at the Pasteur Institute in Paris, has been largely devoted to the electron

microscopy of virus and other macromolecular particles and to observing how some of these are produced in living matter.

Throughout the 25 years since leaving the Rockefeller Institute I had no facilities for continuing the determinations of crystal structure which were a primary concern of early years. It was in order not to lose complete touch with the subject that I started, in odd moments during the war, the compilation of data that has since been appearing as *Crystal Structures*.

As our electron microscopic methods have grown more powerful it has become increasingly possible to employ them as a new way to examine the molecular and atomic order in crystals. With this in view I showed a number of years ago how the individual molecules could be seen in crystals of virus and other proteins. The molecular marshaling proved to be substantially what one would expect, but there was a deep satisfaction in actually seeing what X-rays predict and in effecting a meeting at the molecular level between direct observation and the elaborate deductions that relate these data to the order in nature producing them. It is unlikely that photographs such as these will greatly aid in our determinations of crystal structure but they can give a new insight into the anatomy of crystal faces and a direct picture of crystalline perfection. With microscopes that now attain resolutions of almost atomic dimensions such studies are being made of crystals with small molecules and of metallic crystals where effects due to individual atoms are sometimes seen. At this level direct visualization and diffraction commingle to furnish a technique whose evidence about individual atoms and molecules can complement the statistical information of X-ray diffraction.

This high resolution electron microscopy is, however, only for those whose eyes are still young and with my retirement from the National Institutes of Health personal research in this field has, like the determination of crystal structures, become an affair of the past. There are, however, applications of X-rays still to be made which do not require either the instrumental and computational elaborateness of modern structure determinations or the sensory acuteness of electron microscopy. Soft X-rays seem to offer such possibilities and I am now occupied in their reinvestigation using the various modern experimental procedures that have so greatly furthered what can be done in the ordinary X-ray region.

Next Section