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The Bragg legacy: early days in macromolecular crystallography

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W. H. Bragg arrived in Australia in 1886 as Head of the Mathematics and Physics Departments at the University of Adelaide. His son, W. L. Bragg, grew up in Adelaide and graduated from the Physics Department. Many years later I graduated from the same department and had the opportunity to share Lawrence Bragg's recollections of life in Adelaide. As well as touching on the 'Adelaide' connection, this report briefly reviews Bragg's critical role in encouraging, supporting and establishing the field of large-molecule crystallography.

1. The Adelaide connection

The personal connection with Sir Lawrence Bragg that I am proud to make is that we grew up within 20 miles of each other. Bragg was born on 31 March 1890, in the South Australian city of Adelaide (named for Adelaide, Queen Consort of William IV). My birth, 48 years later, was in Mount Barker, then a nearby country town, now virtually a suburb of the city.

As is well known, Bragg's father, W. H. Bragg, at age 23, had sailed to Australia in 1885 to become Professor of Mathematics and Physics at the University of Adelaide (Phillips, 1990; Jenkin, 2008). W. H. Bragg's degree was in mathematics but his exposure to physics was limited. In offering him the position the selection committee presumably assumed that it was a long voyage to South Australia and that Bragg could accumulate a sufficient knowledge of physics to acquit himself honorably amongst the colonials. His ship arrived on 27 February 1886 and he disembarked at Glenelg (Fig. 1). His first child, W. Lawrence Bragg, was born on 31 March 1890.

I had the great good fortune to meet Lawrence Bragg during the time when I was a postdoctoral associate in the MRC Laboratory in Cambridge. My undergraduate and doctoral training had been at the University of Adelaide in the same department of which W. H. Bragg had been head and Lawrence Bragg an undergraduate. At the MRC I had joined David Blow's group working on structural studies of α-chymotrypsin. David, together with Max Perutz, generously suggested that Bragg might be interested in work I was doing to combine information from isomorphous replacement and anomalous scattering. Of course they also knew that I was from Bragg's 'home town'.

There are three things I remember from that conversation.

First, Bragg could not have been more kind and generous in his comments.

Second, he wanted to make sure he understood the basic, underlying, physical principles of the work, but was unconcerned about the details.

Third, Bragg was more than happy to reminisce about his memories of growing up as a small boy in Adelaide. The city is built on a coastal plain and at the time was serviced by a network of horse-drawn trams. Because of the flat terrain, each tram could be pulled by a single horse. There was one exception, however, where the tram left the center of the city and went up a short hill to the suburb of North Adelaide.

Figure 1
View of the beach at Glenelg where W. H. Bragg first set foot on Australian soil. In 1886 ships frequently anchored offshore and passengers and luggage were ferried ashore in tenders (Jenkin, 2008). The trees in the foreground are Norfolk Island Pines, not native to Australia, and not planted at the time of Bragg's arrival. Photograph taken from the condominium of the author and his wife, Helen (seated, right).

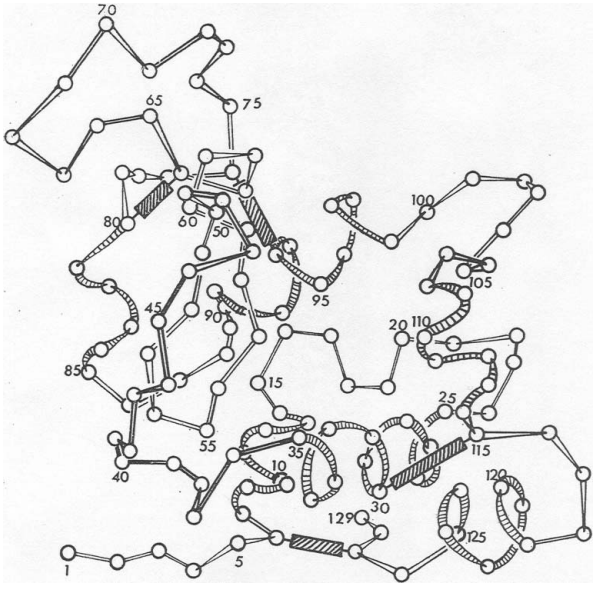

Figure 2
Sketch of the three-dimensional fold of hen egg-white lysozyme, drawn by Lawrence Bragg at the time that the structure was first determined. Reprinted by permission from Macmillan Publishers Ltd: *Nature* (Blake *et al.*, 1965), copyright (1965).

Bragg lived close to the city center but attended a preparatory school in North Adelaide. He said that he particularly remembered watching the driver add a second horse for the uphill segment. It resonated very much with me because my grandfather had been a tram driver and I wondered if he and Bragg might have met.

2. From single atoms to proteins

It goes without saying that Lawrence Bragg was intimately involved in X-ray crystal structure determination from its inception (Phillips, 1990). He introduced the method of X-ray crystal structure analysis and pioneered its use *via* the determination of simple 'atomic' structures such as sodium chloride. Toward the end of his career he could appreciate and enjoy the triumphs of Perutz and Kendrew in their structural studies of myoglobin and hemoglobin. He could also enjoy Phillips' determination of the atomic structure of lysozyme (Blake *et al.*, 1965) and demonstrate his considerable artistic skills through an elegant sketch (Fig. 2) which stripped away the clutter and made clear the key elements of the structure.

Although Bragg was not so much involved in the eventual determination of a protein structure at atomic resolution, his support, his enthusiasm, his leadership and his example were all essential. Also, in the earlier stages he was personally involved. His 1939 Letter to the Editor in *Nature* discussed the problem of using Patterson functions to obtain information for proteins (Bragg, 1939) and was accompanied by another letter from J. M. Robertson suggesting that the structure of insulin might be pursued by replacing the naturally occurring zinc ions with mercury (Robertson, 1939). Bernal also participated in that correspondence and in the same year gave a Friday Evening Discourse to the Royal Society (Bernal, 1939) where he made remarkably prescient assertions regarding protein structure and stability.

'Direct analysis of (X-ray) photographs is rendered impossible by the fact that we can never know the phases of the reflections corresponding to the different spots. The ambiguity introduced in this way can only be removed by some physical artifice, such as the introduction of a heavy atom . . . '.

'The behavior of the hydrophobe groups of the protein must be such as to hold it together . . . . In this way a force of association is provided which is not so much that of attraction between hydrophobe groups, which is always weak, but that of repulsion of the groups out of the water medium'. Not only does Bernal foresee the use of isomorphous replacement in protein structure determination but he also understands that the hydrophobic effect is the basis for protein folding and stability.

Bragg summarizes his involvement in the early years of macromolecular crystallography in his article 'First Stages in the X-ray Analysis of Proteins' (Bragg, 1965). According to Perutz (1970), Bragg's preferred title was 'How Proteins Were Not Solved'.

3. Enthusiastic support

The way in which Bragg first met Perutz (in 1938) and found support for his pioneering studies of hemoglobin is well known. As recalled by Perutz (1970), 'I waited from day to day, hoping for Bragg to come round the Crystallography Laboratory to find out what was going on there. After about six weeks of this I plucked up the courage and called on him in Rutherford's Victorian office in Free School Lane. When I showed him my X-ray pictures of hemoglobin his face lit up. He realized at once the challenge of extending X-ray analysis to the giant molecules of the living cell. Within less than three months he obtained a grant from the Rockefeller Foundation and appointed me his research assistant. Bragg's action saved my scientific career . . . '.

Notwithstanding skepticism on many fronts, Bragg's support for Perutz's studies of proteins was unwavering. As Kendrew put it (Kendrew, 1990), 'As far as I could determine, Bragg was the *only* crystallographer in Cambridge – apart from Max Perutz – who did not believe we were wasting our time on a project more complicated than had been attempted by the methods of X-ray crystallography. But we were carried along by his continuous enthusiasm – a most valuable characteristic that he displayed in all his research activities – and together with David Keilin (Professor of Parasitology and a very distinguished biochemist) he persuaded the Medical Research Council to support a research program which produced no results, except wrong ones, for the following ten years.'

4. Leadership and example

Perutz refers to Bragg as his 'scientific father' (Perutz, 1990). At the same time, Bragg came from the 'old school' and his relationships with his subordinates seem to have been somewhat stiff. As Kendrew (1990) recalled, '(Bragg) combined enthusiasm with a certain formality; I remember one day, hearing me talking to Max, his saying to me that he felt simply unable to refer to us except as Perutz and Kendrew; for him Christian names just could not be used outside the family. Very occasionally the formality verged on pomposity . . . . But as one came to know him better one realized that the occasional pomposity was simply a cover for shyness'. But it might also be noted that Uli Arndt (1990), who worked under Bragg at the Royal Institution, recalls, 'In the more intimate surroundings of the small groups at the Royal Institution we got to know Sir Lawrence – he was never 'the professor' at the R.I. – and his family well. We were all treated as family . . . . Bragg continued to address everyone by surname in the old style for many years, long after Lady Bragg had discovered and used our first names'.

It was his approach to science, and his example, that impressed his peers. That he was a superb crystallographer was a given. As explained by Dorothy Hodgkin (1990), ''So all the structures that seemed particularly difficult to W. H. Bragg were sent to W. L. Bragg for his assistance. He was the structure solver 'par excellence' of the world . . . ''.

Separate from Bragg's unmatched technical expertise, however, was his way of doing science. Francis Crick, who would hardly need help in tackling scientific problems, outlines his debt to Bragg (Crick, 1990).

First, says Crick, he learned from Bragg not to get bogged down in details. Rather, look for other evidence and not be too persnickety about the exact fit with the experimental data. He quotes the attempt of Bragg, Kendrew and Perutz to determine the structure of the α-helix which was abortive because it relied on X-ray data alone and ignored chemical information which was second nature to Pauling.

Second, Crick explains how he learned from Bragg how to give a lecture, 'or, rather, how not to give a lecture'. Make a few simple points that set out the main aspect of the work. Be clear and straightforward. Minimize the technical details. The lecture was to be judged a success if, the following morning, the listener could remember one item. I'd like to believe that this appeal for simplicity, and abhorrence of embellishment, bespeaks Bragg's Australian roots.

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