

Figure 2 Structural models of insulin based on electron density maps at 4Å (left) (1970) and 1.8Å (right) (1974) resolutions, respectively.

Initiation of the project with a pioneering spirit of courage and dedication

Chinese scientists had a long-standing interest in proteins, particularly the insulin molecule, because of its feasibility for research due to its known sequence and its importance in medical applications. Crystal structure analysis of the insulin molecule was a natural follow-up to their successful synthesis of beef insulin in 1965. Encouraged by that remarkable achievement, both the government and scientists knew that they would never be able to better understand the hormone's biological activity without unraveling the three dimensional arrangement of its atoms in space. Together, they made serious attempts to launch this project in 1966.

Despite the inevitable grave interferences and postponements caused by the political situation of the time, this desire or lofty ideal drove a group of enthusiastic young scientists to pave their way for such a formidable task. Formidable was not a word of exaggeration for this group consisting of members mainly in their thirties and trained inside China, with only a few who had solved small molecule structures of a dozen atoms. To them, it was a formidable task scientifically, because they were inexperienced with the multidisciplinary state-of-art technologies involved, and politically, because at that time science and education had otherwise come to a complete halt in China.

Under fragile and inconsistent support from the government, the move flourished into a national collaboration. In 1969, young men and women from Peking University and

various institutes under the Academy of Sciences (including the Physical Institute, the Biophysics Institute, the Shanghai Biochemistry Institute, the Computer Science Institute, the Fujian Structure of Matter Institute, etc.), all with different training back- grounds and work experiences in a variety of scientific disciplines, gathered together under the one roof of the Physics Institute, fascinated by and dedicated to the simple burning desire and lofty ideal to do something new and significant in science. They were confident in themselves as a united entity that they would eventually achieve



Figure 3 Professor Hodgkin (at right middle) was comparing the electron density maps from Oxford Group to that of Peking Insulin Structure Research Group one-by-one, together with the scientists of PISRG (left) in the laboratory at Beijing.

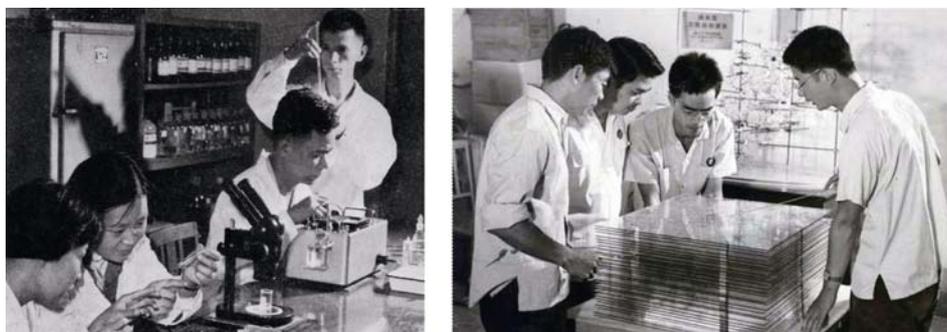


Figure 4 Scientists were preparing insulin derivatives (left) and examining electron density map (right).

that goal. There were a handful of institutions involved and the size of the group fluctuated a bit during the course of the five years before the 1.80 Å resolution structure was com-

pleted. But the majority of the core members stayed on with great dedication, faithful to their simple desire with selfless unity and integrity.

Battling the hurdles to achieve the goal

From a burgeoning army of volunteers and special invited members, a core was elected to organize a steering committee to oversee subgroups formed according to the needs of the research: crystallization, heavy atom derivative preparation, diffraction data collection and data processing, phasing, modeling and structure analysis, etc. Leaders and their groups were not based on age or social hierarchy as before but on expertise and creativity. Timely and free discussions, often heated, were held when necessary, and most of the time the members came to a wise consensus of what to do next and how to do it. This system proved to be a truly efficient leadership structure for pushing the job forward.

Undaunted by the overwhelming challenges the group was forced to realize and face after the true launch of the project, the scientists set forth to tackle the hurdles one after another, with cool wisdom, relentless patience and dogged hard-work. Beautiful large crystals were produced by growth in the basement on cement tables to maintain temperature stability and minimize vibration. During the early

stages of data collection, intensity measurements and data processing were all carried out manually with the diffraction camera, the naked eye and slide rules. Eventually, a linear diffractometer was secured and a giant general computer became available from a government center. The computer, however, could be used only in the evenings when nobody else was working on it. Heavy atom derivative preparation was preceded first by preparation of the necessary chemical reagents; these efforts turned out to be painful and mostly sad nightmares until, finally, three excellent derivatives for phasing were obtained. All necessary programs were also developed for the first time by young Chinese programmers to carry out the calculations. Eventually, stacks of electron density maps drawn on glass plates started to yield the course of the polypeptide chains. The group rejoiced at every step of progress when finer details of the side chains and aromatic rings became better delineated as the resolution was slowly improved.

Epilogue

The group slowly reorganized itself as they watched the flow of international visitors coming in to look at their insulin model under the Richard's half-silvered mirror. Most of the members went back to the institutions from where they came, each one of them carrying back the unique experience and evidence of integrated research in different disciplines by members from different labs. They remembered their own unflinching courage and dedication, collective wisdom, and selfless unity all motivated by that simple burning desire of doing something new and significant in science. The final resolution achieved at the Institute of Biophysics was 1.20 Å and productive inter-institutional collaboration in structure-function relationship studies and protein engineering studies of the insulin molecule went on well into the nineties of the last century. Recollections of that sweet-and-bitter ordeal remain vivid in their minds to this day, with all the unforgettable moments of mad exhilaration and profound disappointment which went hand in hand with the ups and downs of the experiments in the lab through all the years.

As two of the members of that group and as editors of *Science in China*, we feel that the year 2009 is an appropri-

ate time to look back, in respect for all our colleagues and comrades-in-arms and in gratitude to *Science in China*, which first ventured to break the news to the outside world.



Figure 5 Contracting the insulin structure model.