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August 9, 1974

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Dear Francis:

I have taken your letter rather seriously. Because it has taken me time to collect full documentation, there has been some delay in my reply. However, I am replying in a detailed fashion and this accounts for the length of the enclosed document.

The bulk of your charges have no substance. I say this with confidence, especially in view of the fact that Sung-Hou Kim gave several public lectures in which he substantially revealed prior to the Steenbock Meeting most of the detailed interactions in our Science paper.

There are two types of documentation which I can present to you. One deals with internal materials: several notebooks and eight three-dimensional Fouriers accumulated by Sung-Hou and Joel Sussman at Duke over a time span of eight months or so. However, let me defer discussion of the internal documentation and develop first a chronological description of what I call "external" documentation. This refers to interactions with other people who have known of the gradual progress of the solution of the tertiary structure problem and have made notes or have other materials available which you can check directly.

When we obtained our first 3Å Fourier in the late fall of last year, we studied it for a while and came to three general conclusions. First of all, the map was good enough so that we could see segments of polynucleotide

were large numbers of complex interactions in the loop areas which would take time to unravel and thirdly, we believed our phasing was not very good and that there were areas in the map especially in the anticodon region where we knew we would have to obtain more data in order to make an unambiguous tracing of the chain. The article which appeared in Nature in March of this year was designed as a preliminary statement of the fact that the general shape of the molecule is similar to that which we had seen at 4Å resolution, but the details would have to await further study. Unfortunately, in the course of drafting this paper, we made an important error. At that time, Sung-Hou was at Duke University. We both had copies of the three-dimensional map and independently built models. The models were similar in general, but had a major difference in the D stem and minor differences in other areas including the position of the Y base. The differences in the D stem were related to which riboses were paired together. When Sung-Hou came to M. I. T. to draft the paper, he pointed this out; nonetheless, the overall decision was made to describe the M. I. T. model. However, the degree of our tentativeness in interpreting the map is shown in the text where we clearly indicated that further work will have to be done in interpreting the loop regions. This paper was sent off rather hurriedly since I was about to go to China and would be away from the laboratory for over a month and a half and we wanted to have something in press concerning the 3Å map.

no mention made of an alternative model in Nature paper

At that time, we decided to press ahead in two different directions. Since we were set up for data collection and heavy atom testing at M. I. T., we concentrated on searching for new derivatives and extending the data collection to higher resolution. Our high resolution phases in the 3Å map are determined largely by the normal and anonomalous samarium components and we felt that things would improve considerably with another derivative. To avoid duplicate data collection, at Duke Sung-Hou concentrated on developing methods for interpreting the map.

In carrying out this work, Sung-Hou together with Joel Sussman developed a group scattering approach to interpreting the map, basically a partial structure method. I enclose in Appendix I a Xerox copy of the abstract which Sung-Hou and Joel submitted to the American Crystallographic Association meeting held in Berkley. The abstract was submitted prior to January 25, 1974, and the paper was actually delivered in Berkeley on March 26. Paul Sigler attended the Berkeley Symposium and said that he was rather favorably impressed by the trial structure studies that were presented with tRNA, as the method clearly was useful in increasing the signal to noise ratio. (In Appendix II, I have listed the names, addresses, and telephone numbers of people with whom I have been in contact during this past week. I have explained the situation to all of these people, and they have indicated a willingness to write or talk with you or other members of the MRC concerning the validity of the comments which I enclose here.)

The next readily verifiable date is April 9, 1974, when David Kearns of the University of California received a letter and diagram from Sung-Hou showing the backbone and secondary structure of the molecule. This diagram was made from a photograph and a computer printout of the group coordinates with round bars indicating the secondary structure connecting the backbone. David Kearns says it is the same diagram as in Figure 3 of our recent August Science paper except it does not include the bars which describe the tertiary interactions. The diagram clearly shows the correct assignment of bases which are paired in the D stem. This is absolutely essential in order to complete the interpretation of the map. Sung-Hou's letter to David states "I am enclosing a drawing which I made a few months ago." This interpretation was the one which Sung-Hou had made initially several months earlier. He used this diagram in talks, and Paul Sigler who saw this diagram at a later talk received a copy of it some time after David Kearns. As is the case of Figure 3 of our recent Science paper, the molecule was plotted perpendicular to the plane determined by the CCA and anti-codon stems. A similar diagram of the model in the March Nature paper would have quite a different appearance.

During April, Sung-Hou went to a number of meetings and gave seminars in which he talked of tertiary interactions. At that time, he felt confident of 5 or 6 tertiary interactions and described them. Unfortunately most of the records are incomplete, but some notes are available. On April 15, he spoke on tRNA structure at the University of Iowa at Arthur Arnone's department. Arthur distinctly remembers Sung-Hou's discussion of several detailed tertiary interactions, but did not make notes. He was impressed, however, that the net result provided a good explanation for the photoreactivity and chemical modification data. The chemical modification data is not understandable based on the model in the March Nature paper.

On April 18, he spoke at Stony Brook in Bernard Dudock's department. Dudock asserts that Sung-Hou presented 5 or 6 tertiary interactions and remembered explicitly the description of the U8-A14 reversed Hoogsteen interaction, because he asked Sung-Hou to draw it on the blackboard since the nomenclature was new to him. In the reversed Hoogsteen pairing, the uracil O2 and N3 are involved; normal Hoogsteen pairing involves O4 and N3. Dudock sees no conflict with his memory of Sung-Hou's description of the structure and the material presented in the recent Science paper, but he does not have notes on other explicit interactions.

A meeting of the East Coast protein crystallographers was held at Jung End in Massachusetts on April 21-25 of this year. At that meeting, Sung-Hou made brief comments on the tertiary interactions in the tRNA model following a talk by Sussman on the use of the group scattering method. At that time he mentioned the interaction between the U8 and A14 as a reversed Hoogsteen, the interaction between G15 and C48 as a reversed or trans Watson-Crick pairing and he spoke about the manner in which the m^7 G46 interacted with the D stem. Many people have a clear recollection of his having made comments about tertiary interactions. Paul Sigler who attended this meeting wrote down notes which describe the relationship U8-A14. His

notes indicate Hoogsteen, but he says it could also be reversed Hoogsteen. He also has a note mentioning the interaction of the charged m^7 G46 with the D stem.

On June 3, Sung-Hou delivered an invited lecture to an Ameri can Chemical Society Great Lakes Regional Meeting at Purdue University. It was a Symposium on Biological Stnucture and he described in detail many interactions in the model. Fortunately, the audience contained Struther Arnott together with a number of people from his laboratory. They were keenly interested in the details of the talk and were familiar with nucleic acid terminology. I have spoken with Struther and he has collected his group to pool their information on Sung-Hou's talk. Struther indicates the following relations were discussed: U8-A14 (reversed Hoogsteen); G15-C48 (reversed Watson-Crick); G19-C56 (Watson-Crick); T54-A58 (reversed Hoogsteen); m^7 G46 paired to G22 (a drawing on the board to show this explicitly); A21 near the phosphate of A9; m_2^2 G26 linked to A44 with a twist between the bases and some interaction between A9 and A23. Struther and his group state that the interactions are identical to those described in our recent Science paper. In fact, every interaction was discussed except the G18-pseudo U55 which we are still uncertain of as it may only have a single hydrogen bond. He also described several conversations with Sung-Hou about unusual aspects of the interactions which he was especially interested in because of his extensive and detailed work on base pairing in triple stranded polynucleotides.

In view of this, it is reasonable for you to ask why we had not written up the paper at an earlier date. Unfortunately, the two laboratories are separated and communication was made difficult. However, in early June we started to rebuild our wire model at M. I. T. to bring it into complete accord with the Duke model and we started to assemble the manuscript. Sung-Hou visited M. I. T. prior to the Steenbock Meeting and we had discussions about various aspects of the interactions. At that stage my familiarity with some of the details of the structure was much less than his,

and it is possible that some misunderstanding at the Steenbock Meeting may have derived from that source, but I do not know. We spent a great deal of time discussing various aspects of the tertiary interactions which puzzled us (and still puzzle us) in that we could not tell whether one or two hydrogen bonds were involved. However, a rough draft manuscript was in hand then together with a number of figures.

During the Steenbock Meeting (June 17-19) we were prepared to speak fully with the MRC people who were going to be there and to fully describe our status. I recall having mentioned to Aaron during my visit to Cambridge in the spring that we would look forward to talking in Madison as he was planning to attend the meeting. When we arrived at Madison, we learned that the MRC group had sent in a paper, and we further learned that both John Robertus and Brian Clark were unwilling to talk about tertiary interactions. We learned this in conversation with John Robertus in which we volunteered a few tertiary interactions which he acknowledged but then he stated rather clearly that he had been instructed not to talk about this, and this terminated our substantive interactions.

which?

Alex, John, Ernst, the Kim

This response surprised and distressed me very much. David Blow apologized to me for this attitude and said that he personally thought it was wrong. Sung-Hou and I got together to confer about what our course of action should be. We did not understand the reasons for the secrecy. Unfortunately, secrecy breeds secrecy. I feel I made a fundamental error of judgment at that time in deciding not to reveal all of the interactions such as those which Sung-Hou had talked about two weeks earlier at Purdue. In retrospect this was an unfortunate decision since it clearly is the root cause of all of the misunderstanding. I cannot defend the decision since I do not enjoy this kind of secrecy in science; however, we took it in a competitive spirit. We surmised that perhaps we should not reveal all of our interactions as the MRC may not have them all. We surmised that perhaps the MRC were being closed mouthed because they think we do not know the whole structure. In any

because we didn't trust Alex

case, what we decided on was a rather limited exposure. In my formal presentation, I commented on chemical modification data and its relevance for understanding the structure. I presented a brief discussion of the molecule as it looks at 4Å and at 3Å resolution as we had described in the earlier Nature paper. Unfortunately, Sung-Hou had forgotten to bring along the slide showing the Duke wire molecular model, consequently, I was forced to use a slide with the Nature model. However, in doing so I pointed out rather clearly that the D stem interactions were incorrect in this model and that the loop areas were not defined properly. I then brought on a cloverleaf diagram and described some tertiary interactions.

Since there has been some doubt concerning exactly what I said, I have contacted a number of people who have given me their notes. Paul Sigler's notes indicate that I said U8-A14, G15-C48, G19-C56 and T54-A58. He said that he did not write down the types of hydrogen bonding, but just the numbers involved. For Robertus' talk he has U8-A14, G15-C48 and A9 involved with the 12-23 pair. David Kearns has in his notes of my talk: U8-A14 (reversed Hoogsteen); G15-C48 (rev. Watson-Crick); G19-C56 (Watson-Crick) and T55-m'A58 (reversed Hoogsteen). For John Robertus he has listed U8-A14 (Hoogsteen) and the ternary A9 interacting with the 12-22 pair. Philip Bolton of the University of California has listed for me: U8-A14; G15-C48; G19-C56; and T54-A58. For Robertus he has U8-A14; G15-C48 and no ternary interactions.

Bob Shulman of Bell Labs has notes of a conversation with Sung-Hou which took place after my talk. His notes have the interactions U8-A14 (rev. Hoogsteen); G19-C56 (Watson-Crick); m_2^2 G26-A44 (may have 1 hydrogen bond); G15-C48 (rev. Watson-Crick) and T54-m'A58 (rev. Hoogsteen). Bob states that Sung-Hou told him there were several additional interactions which would be found in our forthcoming publication.

In checking the notes of several different people I learned that although they were all similar, they were not all identical. I suspect that what is actually written down is in part a function of the familiarity which a person has with the rather specialized nomenclature as well as random events such as whether one can hear or see well. In any case, I am attempting to get a copy of a tape recording which was made at the meeting which would clear up any residual uncertainties.

I found the atmosphere at the Steenbock Meeting very disturbing. Although I will not try to defend my response to the situation, I will try to explain it to you. In particular, I was rather offended by the continued statements and implications made publicly by Brian Clark to the effect that our interpretation had not progressed from that which we published a few months earlier in Nature. He seemed unwilling to recognize that we were working on the problem. Michael Rossmann made a comment to me on how badly he thought Brian was misbehaving at the meeting. I am afriad that I was irritated by this attitude and by the fact that the whole project was treated in a hush-hush manner.

Let me comment briefly on the question of the exact number of tertiary interactions which were discussed at different places and at different times. If you look at the map and the structure in detail, you will see that the important decision about the D loop starts with the correct pairing in the D stem and the U8-A14 arrangement (which we have clear documentation for in mid April). If a few other contacts are recognized, such as G19-C56, G15-C48 and the fact that the TΨC loop is internally hydrogen bonded to itself, as through T54 and A58, the tertiary structure is largely determined. The number of additional possibilities are quite constrained. In your letters you made much of the fact that Robertus pointed out the A9 triple interaction. It is true he mentioned it, but as it was one of the published Levitt interactions, it would be unreasonable to imagine that we had not been considering it. Furthermore, since U8 and m^2G10 were already fixed as of the April documentation, the possibilities for placing A9 are quite limited.

Let me urge you to look at the map and the model and you will see that although the overall course of the chain is fixed, there is still room for alternative decisions with a 3A° map. We debated these among ourselves for a considerable period, and it is clear from comparing our manuscript with the MRC manuscript that several different decisions were made using different numbers of interactions. (John Robertus mailed a preprint of his paper to Sung Hou which was received on August 5th).

After the Steenbock Meeting, we went back to the task of completing our manuscript. It took a while to process the figures and much time was spent on deciding how we should describe various interactions, such as single bonded or doubled bonded ones. This uncertainty in interpretation is reflected in the paper itself. However, there is nothing in the paper which is not present in our coordinates prior to the Steenbock Meeting. I do regret very much, however, that I failed to append a note in the paper referring to the Steenbock Meeting and rather explicitely to the MRC contributions. This was not a conscious decision on my part, but I suspect one which was facilitated by the annoyance of the moment. I apologize for this to the MRC workers and I will be happy to make amends for this discourtesy by sending a letter to Science describing what was discussed at the Steenbock Meeting with an explicit reference to the MRC work.

OK no!

When we wrote this paper, we prepared it for PNAS since I wanted to be certain that the paper came out on a predictable publication schedule. The manuscript was sent to the PNAS and Miss Carolyn Noel of the Proceedings office has a letter from me dated June 27, 1974, formally submitting the paper for publication in the Proceedings with a receipt date of July 1, 1974. With that submission date it would have been published in the September issue. However, at the Proceedings office they measured the text together with the six figures and I learned by telephone that the paper was 5.4 pages in length and it would have to be shortened in order to

be published in the Proceedings. Since the paper was already rather tersely written and could not be shortened easily, I decided to withdraw the paper and submit it to Science instead. The original manuscript was returned to me from the Proceedings office in Washington; however, the second copy of the manuscript remains in their files together with my letter of submission. I have asked them to retain that letter and manuscript in their files and, as you see in Appendix III, I have asked them to send you a copy if you request it. I do this in view of the comments made by you and David concerning the events at the Gordon Conference, July 1-5, 1974.

I have talked to John Robertus about the sequence of events during the Gordon Conference and he agrees that he did not provide Sung-Hou with information during that meeting but that Sung Hou presented data first. In any case, the manuscript at the Academy office would resolve any doubts you may have on this point.

The major detailed documentation for the development of our interpretation of the map lies in several notebooks at Duke that Sung-Hou and Joel have covering more than eight months of work and a set of eight three-dimensional Fourier maps which were used in gradually making decisions regarding the interpretation of the data. Both Sung Hou and I feel very strongly about the charges raised in your letters and we are willing to bring this mass of data to Cambridge so that you can inspect it and go over it in detail in order to remove any doubts you may have concerning the complete independence of our work. The material all antedates the Steenbock Meeting. We feel this documentation is of central importance. We may have been guilty of bad judgment in responding to the unusual situation presented by the attitudes at the Steenbock Meeting, but the central issue is not a question of judgment but rather one of fundamental honesty. We do not know, of course, the pace at which the MRC work evolved since the only communication we had occurred at the Steenbock Meeting. In April I learned they were wrestling with the interpretation of the 3A° map, but nothing more. At that same

time, Sung-Hou had already made substantial inroads in interpreting the map and these are documented in detail.

We are rather anxious to have this issue resolved and I would appreciate hearing from you. All of the people whom I have spoken to during this past week have indicated a willingness to confirm with you the material which I have set forth either by telephone or in writing. I believe that the present account responds in detail to all of the various charges outlined in your letter and in David Blow's letter. There may be other questions that you or David may have and I will be happy to respond either by telephone or in writing.

Most of the principals involved in this matter are old and close friends and I hope the enclosed will resolve this unfortunate misunderstanding. I am sending copies of this letter to David Blow and Max Perutz and look forward to hearing from you.

With best regards.

Yours sincerely,

Alexander Rich