# THE SALK INSTITUTE

April 27, 1977

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Dear Aaron,

I'm sorry for the delay in replying to your many interesting
letters but I had a cold last week which made me rather thick-headed.
Also I feel baffled by what you have told me.  Naturally it would be
easier seeing the e/m pictures but I think there is little point in
sending me these as one really needs to brood over so many of them.

My main reaction is that you are trying to extract too much
information from a very confusing mass of soft evidence.  I feel the
potential advantage of the x-ray single crystal approach is that it
can lead to hard conclusions.  Let me give an example.  It seems to
me very reasonable, from all the lines of evidence, to believe that
the packing in the xy plane is the hexagonal packing of roughly
"circular" objects.  This leads naturally to the question, what is
the "size" of the object in the z direction.  Now if your density
measurement, giving 12 nucleosomes per cell, is correct, then this
distance must be of the order of 340/6 ≒ 57 Å if the object is fairly
compact.  What one wants to know is whether this value for the clipped
core particle fits the x-ray scattering and neutron scattering in
solution and also the sedimentation value (the Stokes radius).  Have
all these measurements been made on the core particle, clipped or
otherwise, and what are the results?  From your letters and enclosures
I gather that some of these have been done.  Let me say that I don't
think the work on either the tetramer or octamer without DNA helps
a lot because of the problem of the "tails".  So, as I see it, what
one wants is a hard value for the density of the crystals and without
this the arguments are only suggestive.  However such a model does
support the strong 006 and the general appearance of the b projection
though one could easily argue that this could be deceptive.

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I agree that it may be possible, with luck, to guess the arrange-
ment of the DNA in the nucleosome but how will one prove it?  Every-
body is now having a guess.  If the x-ray phases were determined,
however, the guessing would have to stop.  Do I gather that you
dispair of ever getting a rough idea of the phases by isomorphous
replacement?  I can see that the e/m plus the x-rays may perhaps
suggest the broad arrangement of the nucleosomes in the cell but I
doubt very much if you could find how the DNA folds this way.  This
is mainly because we lack any strong theoretical assumption to decide
between alternatives (one such might be:  DNA doesn't kink, it only
bends).

However, there is one general argument you may be able to use.
I am assuming that with 200 base-pairs per nucleosome there are
about two turns of DNA, not one.  (But see the enclosed correspondence
with Walter Keller.)  Then if you are going to make any sort of
250-300 Å solenoid you must have close DNA packing (say 25-30 Å)
on the inner surface of the solenoid.  There simply isn't space for
wide (i.e. 40 to 50 Å) packing there.  Thus the nucleosome must be
fairly thin on one side.  Whether, starting from this, you can de-
duce the rest of the shape, I rather doubt, though your wedge shape
is a very plausible one.

I think I won't make any further detailed comments at this stage,
as I need time to brood on the problem.  Let me just deal with others
points in your letters.  About the four-stranded DNA.  I have just
written to the authors asking if they have a preprint.  I don't think
our efforts at four-stranded structure were worth anything and I've
quite forgotten the argument about C's on one chain.  The point of
Morgan and Johnson's structure is that while one base-pair of the
quadruple is standard, the other one is very non-standard and that
not at all like McGavin's or Chen's.

I have now had an Mss from Abe Worcel.  The idea is clear enough
in a broad way but hopelessly badly expressed from our point of view.
I assume you also have some sort of manuscript from him.  If not, send
me a telex and I will post you a xerox copy.  I shall have to write to
him about it shortly.

About the New Zealand SBS model.  It looks too ugly to be true
and your comments on their x-ray methods are very much to the point.
If it were really side-by-side it would be easy to disprove but they've
given it a small rotation of 36° or so per 10 base-pairs which makes it
a little more difficult to refute.  I doubt if it can be ignored com-
pletely.  I have plans in my head to write a short note about it, per-
haps for PNAS.  If I do find the time to write a draft before I leave
here on May 22 I'll show it you at Cold Spring Harbor.

I don't share your enthusiasm for the H4 fibers but perhaps
I'm being too stuffy.

Incidentally I do feel, quite strongly, that there is a good case
for preparing "Zachau" (DNA + the 4 histones) material and looking at
fibers of that.  He reports a repeat about 150 bp but my belief is that
if they were made very carefully you might get a repeat nearer 140 bp
and that micrococcal DNase might hardly touch it.  (Remember Len's
resistant dimers.)  Moreover, as with Len's material, you should get
very long 10 base ladders with DNase I.  Perhaps fungal DNA has such
material naturally -- I believe some was quite resistant to the enzyme --
in reasonable quantities.

Such fibers might give a very revealing x-ray pattern, especially
if you get a good fiber diagram.  I feel such an effort would be more
worthwhile than much of the other non-crystal x-ray work.  It really
might decide how the DNA folds on the core nucleosome.  This is because
adjacent nucleosomes must have their DNA continuous with the next one,
which is not necessarily true for the DNA in the core particles in the
crystals.

While I remember it, exactly how much protein do you need to clip
off a core particle to get the clipped particles which form 3-D crystals?

I have read the papers by Zachau and Chambon and have the general
gist of them but I must reread them carefully.  If I have any comments
I'll send them to you.  But first I must write to Joel about his paper,
which I plan to do in the next couple of days.  I also have a long
explanatory letter from Michael Levitt which I will also reply to
shortly.  It's nice to have all these letters but I'm afraid they're
not nearly as good as continual face-to-face discussion.

You ask if I am going to Spetsai.  Sadly, I feel I ought not to do
this as I have already cut my three month visit to Aarhus to six weeks,
and that period includes a week at the FEBS meeting at Copenhagen and
two or three days in Helsinki.  However we shall at least be able to
meet at CSH and at Copenhagen.  Of course in the summer of 1978 I plan
to spend 2 to 3 months at Cambridge but that seems a very long time away.

Apologies for this rather damp letter,

Yours ever,

Francis

F. H. C. Crick
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