from SIR and AS information and this should be compared with figure 2a in (*2*).These maps are "before" and "after" solvent flattening respectively, and clearly demonstrate that our noise filtering procedure did not introduce artifacts into the map.

4) Klug *et al.*, seem to have overlooked the information presented (*2*, p. 547) and concluded that we have incorrectly chosen the protein boundaries. On the contrary, 95 percent of the boundaries of the octamer are unambiguously delineated by large solvent regions between molecules [Fig. 1 and figure 2 in (*2*)] and the constraints imposed by the crystallographic symmetry elements (*2*, p. 547). Five helices, not two, were mentioned in our paper (*2*), and these plus several smaller helices make up about 50 percent of the protein mass, consistent with circular dichroism and Raman spectroscopy (*16*). Furthermore, we have reported that the chains of H2A and H2B have been traced nearly from end to end, and sufficient segments of characteristic amino acid sequences have been identified in the map to allow the assignment of the polypeptides. The quality of the map itself proves the validity of our procedures. The accompanying stereo pair (Fig. 2) is a replot of the alpha-helical region we showed before [figure 1 in (*2*)], contoured at a lower level and thus illustrating some side chains.

We believe that the resolution of the causes for the differences between the two structures will come about through further experimentation rather than rhetoric and argumentation. The results of our ongoing efforts in fitting the amino acids to the electron density map should shed some light on the resolution of the differences between the two structures.

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We have solved the crystallographic structure of the nucleosome core particle (histone octamer with 146-bp DNA) (*1*). We are having considerable difficulty in rationalizing the interpretation of the histone octamer of Burlingame *et al.* (*2*) with the nucleosome structure we have solved (*1*), with those of Richmond *et al.* (*3*) and Bentley *et al.* (*4*), and with many other biophysical studies. We see no problem with the electron density of the octamer presented by Burlingame *et al.* It appears to be of very high quality. It is the interpretation of the structure that we think should be reexamined. Burlingame *et al.* seem predisposed to assume that the DNA will lie in the grooves of the histone octamer. Our own nucleosome structure, along with those of Richmond *et al.* and Bentley *et al.*, indicated that in many locations rather than lying in the grooves of the histone octamer, the DNA actually rides on the ridges or "high points" of the proteins. The "helical ramp" is therefore somewhat discontinuous and complex. It appears to us, from statements in their article, that Burlingame *et al.* have ignored all but the most obvious (to them) possibilities for placing the model DNA on the octamer.

It seems quite possible to us to place superhelical DNA onto their histone core in a way that is consistent with our own and the other nucleosome structures, and which has a superhelical radius (~43 Å), superhelical pitch (~28 Å), and number of superhelical turns (~1.85 for 146 bp DNA) to be consistent with the bulk of previous experimental evidence about the nucleosome (Fig. 1).

Also, in this orientation, the octamer seems to have a size and extent, and occupy a volume which is not much different from what is seen in the crystallographic studies of nucleosome core particles. Some of our early modeling studies, which tested model nucleosomes with ellipsoidal histone octamers against diffraction data, showed us that the best ellipsoidal representation for the octamer has its long axis *not on the superhelical axis*, but about 45° from it and points in the direction of the DNA ends (Fig. 1). If at 0.15*M* ionic strength, in the presence of the DNA, the H2A region in the octamer of Burlingame *et al.*, (that is, the protein region shaded dark) moves in ~20 Å to fill the apparent solvent channel, the resulting structure (with the DNA bound as we propose) bears a very good resemblance to the crystallographic structures of the whole nucleosome core particle. The maximum thickness of the octamer in the superheli-

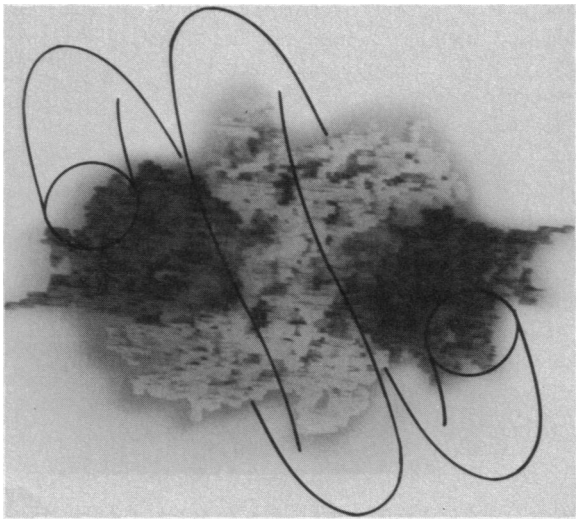

Fig. 1. Diagram of the nucleosome core particle showing proposed placement of superhelical DNA on the histone octamer model of Burlingame *et al.*, which is consistent with the nucleosome crystal structures and other biophysical studies.

cal axis direction would then be approximately 75 Å, which is very close to what is seen in the nucleosome structures. Furthermore, the octamer of Burlingame then forms ramp and groove-like regions precisely where they are seen in our own nucleosome structure. We suggest that Burlingame *et al.* seriously reconsider the model DNA placement on a condensed histone octamer structure.

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Instead of using a heavy atom derivative to phase their 15 Å data set, Uberbacher and Bunick (*1*) used molecular replacement and model building to obtain a structure for the nucleosome core particle. In this process they used the structure of Richmond *et al.* (*2*) as their starting point. Their structure is dominated by the features of their starting model, since this is the expected result of the molecular replacement operation. Continuing their model building, they have now drawn lines representing DNA on our photographs (*3*), thus developing an additional model for the structure of the core particle. They appear to have generated this model in order to compact our octamer structure and force it to resemble the model of Richmond *et al.* We do not feel the need to do so and our reasons are presented in our reply to Klug *et al.* (*4*).

The model proposed by Uberbacher and Bunick requires that the length of the histone octamer be condensed to 75 Å. The so-compacted structure, which represents an averaging of the length of the structure of Richmond *et al.* with ours, does not fit parameters imposed by diffraction data. It is well known that the diffraction pattern of chromatin consists of the first- and higher orders from a Bragg spacing of 110 Å, that is, 1/110, 1/55, 1/37, 1/27 (*5*). Our model-built nucleosome is roughly spherical and is 110 Å in diameter. The pitch of the DNA is about 37 Å, and the tripartite protein core is roughly divided into three 37-Å long pieces. Thus the first-order reflections from the DNA superhelix and from the internal arrangement of the protein would superimpose on the third-order from the whole particle. Both our model and that of Richmond *et al.* are consistent with the above criteria, but the model presented by Uberbacher and Bunick would give additional reflections, which are not observed. Averaging two differing structures does not yield the correct one.

In the modeling studies of Uberbacher and Bunick, the value initially assumed for the length of the octamer was 50 Å, and no new value was reported as a result of their procedures [reference 1 in (*1*)]. The dimensions that they cite now for the structure in Fig. 1 (*1*) differ from those that can be obtained by measuring directly the model shown there, when the dimensions of our balsa wood model are used as a scale. The superhelical radius is 48 Å (not 43 Å), the superhelical pitch is 37 Å (not 28 Å), and the length of the particle parallel to the superhelical axis and measured only to the outermost edges of the DNA is 94 Å (not 75 Å). Furthermore, direct inspection of our three-dimensional octamer structure reveals that there is some room for *small-scale* closure of the dimer-tetramer channels at the *front* if the dimer is allowed to pivot about the dimer-tetramer contact point at the back. However, there is no space available to permit the dimer to shift inward along the entire channel, and there is no evidence suggesting that the dimensions of the octamer change drastically when it associates with DNA (*4*).

We have already stated that we have attempted several alternate placements of the DNA around the histone octamer (*3*, p. 551). We have published our preferred orientation in which the DNA "follows the path dictated by these grooves and ridges" (*3*, p. 550), not just the grooves. We found two other interesting orientations. In one (left-tilt), the DNA path is tilted 30 to 45 degrees to the left (similar to theirs) of the path it occupies in our preferred orientation, while in the other (right-tilt) the DNA path is tilted about 45 degrees to the right. In the right-tilt model the DNA rides on the front of the long "propeller" of the H3. The histone octamer remains 110 Å long in all three models, each of which has its own probability of existing in vivo. However, in the absence of direct information on the DNA location, we did not present these models to avoid contributing to excessive speculations.

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Crystallographic Structure of the Octamer Histone Core of the Nucleosome

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