Hepatic Fibrosis in Ahr<sup>−/−</sup> Mice

In their recent report, Pedro Fernandez-Salgueiro et al. state that mice deficient in the aryl hydrocarbon receptor have decreased peripheral lymphocytes, small livers, and pronounced fibrosis in the hepatic portal tract (1). However, the photomicrographs offered in the report (figure 2, p. 724) appear to show, at best, only mild portal fibrosis. Also, the specimens shown are stained with hematoxylin and eosin (H&E) and not Masson’s trichrome, the usual stain for showing fibrosis.

A potential confusing aspect of the data presented may lie in the comparison of Ahr<sup>−/−</sup> liver sections with large bile ducts with control liver sections that show small portal tracts. Sections from larger, more central portions of the biliary system normally contain more connective tissue than smaller, peripheral bile ductules, which makes comparison of these different regions of the liver difficult. Fernandez-Salgueiro et al. state in the legend of figure 2 that the fibrosis shown in these photomicrographs was moderate at this stage, which seems to imply that more severe fibrosis did occur.

A Research News article “Dioxin receptor knocked out” by Richard Stone in the same issue (5 May, p. 638) shows a photomicrograph (provided by Fernandez-Salgueiro et al.) of a portal tract from an Ahr<sup>−/−</sup> mouse liver stained with Masson’s trichrome that exhibits significantly more collagen in the portal tract than the accompanying normal portal tract. However, the portal triads pictured also appear to come from different regions of the biliary tree, with a much larger bile duct in the Ahr<sup>−/−</sup> liver section.

To demonstrate differences in connective tissue from different sized portal tracts in normal liver, we took photomicrographs of CBA mice tissue at about the same magnification as those taken by Fernandez-Salgueiro et al. The smaller, distal bile duct we present (Fig. 1A) is about the same size as

Response: Belotserkovskii and Johnston suggest that the phenomenon which we described in our report is catalyzed by the surface of polypropylene tubes. This is an interesting observation, which we have also seen, independently, since the publication of our report, and with which we agree entirely. We plan to describe our results on this point (1).

Belotserkovskii and Johnston also suggest that the interaction of DNA with polypropylene induces a denaturation, and that this denaturation is responsible for the formation of multistranded complexes. Their results seem to be in agreement with this suggestion, but do not prove it unambiguously. It seems likely that the interaction with polypropylene induces a change of conformation of DNA (1), but is this a denaturation in the classical sense? We have performed denaturation-reassociation experiments similar to theirs, but we did not obtain the same result: Under conditions where interaction of DNA with polypropylene was inhibited, the formation of multistranded complexes was hardly detectable in our hands.

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the control liver section shown in figure 2A in the report (1), and the larger proximal bile duct we show (Fig. 1B) is about the same size as the Ahr-/— liver section shown in figure 2D of the report. The amount of connective tissue in the larger CBD mouse portal tract (Fig. 1B) is about the same as that in the Ahr-/— portal tract in figure 2, C and D, of the report. We also performed Masson’s trichrome stains of different sized portal tracts of normal mice (Fig. 1, C and D) that are similar to the portal tracts presented in the Research News article (page 638). Thus, the striking difference in collagen in the figures in the report and Research News represents differences in portal tract size, not differences between control and Ahr-/— livers. Finally, we show a mouse liver infected with schistosomiasis that does demonstrate significant hepatic fibrosis (Fig. 2).

Increases in hepatic fibrosis can be quantitatively and not just qualitatively analyzed. This can be done morphometrically by measuring an area of collagen deposition in defined regions such as portal zones (2). Several computer programs are available that digitize microscopic images captured by video camera. Alternatively, hydroxyproline content of liver sections can be measured.

Fernandez-Salguero et al. have been kind enough to allow us to review the hepatic tissue sections from Ahr-/— mice and controls. We cannot agree there is any fibrosis present. There was a vague suggestion of aberrant vascular formations in association with bile ducts, the significance of which requires independent evaluation. In summary, on the basis of the data presented by Fernandez-Salguero et al., hepatic portal fibrosis in Ahr-/— livers is not convincingly different from the amount of connective tissue seen in normal portal tracts of similar size. This does not, however, diminish our interest in other aspects of the report by Fernandez-Salguero et al., particularly the finding that livers are significantly smaller in these knockout mice.

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Response: We understand the criticism of McDonnell et al. but respectfully disagree with their conclusion that hepatic portal fibrosis in Ahr-/— mice is not convincingly different than the amount of connective tissue found in normal animal’s portal tracts of similar size. We agree that the degree of fibrosis is not severe, as suggested by our use of the term “pronounced” in our report. Pronounced, which also means distinct, does not infer severe fibrosis. The portal areas of these mice, whether of large or small size, had increased amounts of collagen present as compared with portal tracts in our wild-type mice. This was determined on the basis of H&E stain and the use of Masson’s trichrome stain. We observed increased amounts of collagen in portal areas and adjacent parenchyma of our Ahr-/— mice as compared with normal mice of the same age (Fig. 1). We agree with McDonnell et al. that morphometric and other analyses would confirm our subjective description of the changes. However, we stand by our conclusion that the Ahr-/— mice have distinct portal tract lesions not described previously in other mice or results from other experimental treatments.

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