differences exist between the hepatotoxicity seen in Wilms' tumours (WT) treated with actinomycin D (AD) and that following bone marrow transplantation. Therefore, we feel that the criteria defined by McDonald [6] for veno-occlusive disease (VOD) in transplanted patients might not be applied strictly to VOD patients treated with AD for WT. For example, in the latter patients, a marked increase of liver enzymes has been frequently reported and this feature might well be included among the criteria for 'VOD' in WT patients. In any case, in Raine's series [7] there were only three right-sided WT out of a total of 5 VOD patients.

Bisogno and colleagues also state that tumours originated on the right side in less than 50% of their patients, but the overall evaluation of their series should also *include* the 7 cases, all with right-sided tumours, observed by the German Pediatric Oncology Group enrolled in the SIOP-9 nephroblastoma protocol [1]. Furthermore, whereas histopathological data in WT-VOD are rare and the WT-VOD diagnosis is ordinarily based on clinical findings, in 5 of the above 7 cases, liver biopsies were performed and confirmed clinical VOD [1]. With the addition of the 21 cases of WT-VOD now mentioned in the letter by Bisogno and colleagues to the 33 cases reported in the literature, children with right-sided WT still appear to develop 'VOD' more than twice as often as children with left-sided tumours.

In regard to the mechanisms leading to VOD in WT, mentioned by G. Bisogno and colleagues, we should like to further clarify our speculation. The venular endothelium appears to be the first site of injury when VOD occurs after radiation or when produced experimentally by pyrrolizine alkaloids [2–5]. The end result of the venular damage is the obstruction of sinusoidal blood flow, leading to ascites and hepatocellular necrosis. A similar type of injury may occur following only a few courses of AD, but with no clinical consequences, unless the venular endothelium is already somewhat damaged by a chronic partial blockade of the blood drainage of the liver, as caused by a right-sided WT. Thus, the shrinkage of the tumour and the resolution of the vascular compression within a few months would probably not be enough to prevent AD from causing VOD.

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Response from A. Davidson

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BISOGNO AND COLLEAGUES have reviewed their series of Wilms' tumours treated according to SIOP 9 protocol, originally published in 1997 [1], and found that there was no predominance of right-sided tumours in their patients who developed actinomycin-D related hepatopathy. This is in contrast to the findings of Tournesello and associates who found a marked excess of patients with right-sided renal tumours amongst those who developed actinomycin-D related hepatopathy, although these patients had been treated on a number of different protocols [2]. In the series reported by Bisogno and colleagues, only those patients with hepatoxicity who fulfilled the criteria of hepatic veno-occlusive disease (H-VOD) as defined by McDonald and associates were considered. However, there would not seem to be any logical explanation why this should alter the relative incidence of right versus left tumours developing the complication. Nor does it offer any alternative explanation of why patients receiving actinomycin-D for treatment of Wilms' tumours are so much more likely to develop hepatotoxicity than those receiving treatment for sarcomas.

Bisogno and colleagues also noted that actinomycin-D dose reduction did not influence the incidence of liver toxicity in their series. However, the experience from several other groups does suggest an increased risk when doses of more than 1.5 mg/m^2 or 45 μg/kg are used [3–5].

We are left with the following observations. Actinomycin-D hepatopathy is clearly more common in children treated with the drug for renal tumours; young infants are an increased risk; there is a probable dose effect and a possible laterality effect. One way of improving our understanding would be to improve our knowledge of actinomycin-D pharmacokinetics, especially in young infants. Limited pharmacokinetic studies in adults show a slow phase of plasma disappearance and a half-life of approximately 36 h, suggesting that there is likely to be accumulation after repeated administration. The drug is minimally metabolised, and probably around 10% of the drug is excreted via the biliary tree [6]. Although these observations were based on studies performed on only 3 adult patients, they lend weight to the suggestion that hepatic compression leads to delayed excretion after the first dose of actinomycin-D, and subsequent courses lead to progressive

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accumulation with a peak after the second and third courses of treatment. It has been suggested that young infants have a smaller pool of circulating bile acids compared with older children [7], possibly partly explaining the relative susceptibility of young infants to actinomycin-D related hepatotoxicity.

Pharmacokinetic studies in infants and children receiving actinomycin-D, with right- and left-sided Wilms' and in those with non-renal tumours such as rhabdomyosarcomas would, therefore, be a useful adjunct to further clinical studies investigating this problem.

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