Administration of Triton WR 1339 Aggravates Chronic Aminonucleoside Nephrosis

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obtained before the initial AN administration and on days 10, 24, 42, 54, 66, 78 and 90. TC and TG levels were also assayed before and 1, 2 and 4 days after the initial TR injection. Renal tissues were removed for histology on day 90. Coronal sections were stained with periodic acid-Schiff, and more than 150 glomeruli from each specimen were examined.

Dear Sir,

It has recently been suggested that abnormalities in lipid metabolism may play an important role in the pathogenesis of focal glomerulosclerosis (FGS) [1]. Previous studies [2[†]] have shown that diet-induced hyperlipidemia aggravates various experimental FGS. On the other hand, it is known that Triton WR 1339 (TR), a nonionic detergent, produces hyperlipidemia when injected intravenously into experimental animals [5]. Therefore, we have examined by using the chronic aminonucleoside model whether TR-induced hyperlipidemia also aggravates FGS.

Ten-week-old male Sprague-Dawley rats were first uninephrectomized and then injected with puromycin aminonucleoside (AN; 10 mg/day/kg body weight s.c.) for 4 days, and after a 10-day interval, again with AN (now 5 mg) for 4 days. Twelve days after the last AN injection, TR at a dose of 250 mg/kg body weight dissolved in 0.9% saline or saline alone was intravenously injected, and the injection was subsequently repeated every 4 days for 2 months (fig. 1). Urine was collected over a 24-hour period. During the urine collection, rats were deprived of food, but had free access to water. Blood was obtained from the tail veins of rats subjected to light ether anesthesia at the end of the 24-hour period. Urinary protein and fasting serum total cholesterol (TC) and triglyceride (TG) levels were

0 10 24 42 54 66 78
Experimental days

Fig. 1. Urinary total protein on various experimental days in TR-injected (•) and saline-injected (O) animals. The time course curves show a significant difference between the TR-injected and saline-injected animals ($p < 0.01$; two-way ANOVA). The mean values and standard error are indicated by points and bars.

Ethanol-fixed and paraffin-embedded sections were stained using a specific monoclonal antibody, EDI, for rat monocytes/macrophages by the immunoperoxidase technique as previously reported [6].

At the time of the initial TR injection, serum TC and TG levels were markedly elevated and subsequently fell to basal levels:

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Table 1. Serum lipids and light-microscopic findings of the glomeruli on day 90

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before and 1, 2 and 4 days after the TR injection, TC levels (mean $\pm$ SE) were 191 ± 28 , 579 ± 35 , 459 ± 39 and 154 ± 13 mg/dl; TG levels were 189 ± 22 , $3,150 \pm 469$, 755 ± 172 and 117 ± 13 mg/dl. Serial values for urinary protein excretions throughout the study are shown in figure 1. Urinary protein excretions, which had declined toward normal levels after the acute nephrotic phase induced by AN injections, rose progressively in TR-treated rats. Histologically, the TR-injected group showed a significant increase in the percentage of glomeruli with segmental sclerosis and foam cells (table 1). The foam cells in TR-injected rats were seen more frequently in sclerotic glomeruli than in nonsclerotic glomeruli (glomeruli with foam cells: $76 \pm 5\%$ vs. $24 \pm 5\%$; $p < 0.01$). Moreover, most of these foam cells showed positive staining for EDI (fig. 2).

The mechanisms by which repeated TR injections can enhance FGS in chronic aminonucleoside nephrosis remains unclear. It may be a direct toxic effect of TR on glomerular cells, or alternatively, be secondary to TR-induced lipid abnormalities. Lipid-laden macrophages, or foam cells, are frequently found in early atherosclerotic lesions [7] and in the glomeruli of human FGS [8]. Most foam cells participating in atherosclerosis are transformed from macrophages when the uptake of modified LDL through the scavenger receptors was accelerated in hyperlipidemic conditions [7]. It is conceivable that a similar process may be an important step in the progression of FGS analogous to atherosclerosis, as Diamond and Karnovsky [9] have proposed. Accordingly, a close association between increased foam cells and sclerotic lesions in the glomeruli of TR-injected rats suggests that lipid abnormalities induced by TR may contribute to the development of glomerular sclerosis. Further studies need to be conducted to elucidate how TR-induced abnormalities in lipid metabolism produce many foam cells in the glomeruli and aggravate FGS.

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Fig. 2. Glomerular foam cells in TR-injected rats. Foam cells show positive staining for ED1 (counterstained with hematoxylin). x 300.

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