Acute Miliary Necrosis Resembling Peliosis Hepatis Produced by the Combination of Glucocorticoid and Gadolinium Chloride (36259)

HANS SELYE, SANDOR SZABO, BEATRIZ TUCHWEBER, AND FRANCINE LEFEBVRE

Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal 101, Canada

In man, peliosis hepatis was first described by Wagner in 1861 (1) and named by Schönlank in 1916 (2). Macroscopically, it is characterized by multiple dark red or livid ("pelios" = livid) small areas 1 or 2 mm in diameter, corresponding to cyst-like, blood-filled cavities (3, 4). Often these blood spaces do not appear to possess an endothelium, being lined only by remarkably compressed, flat hepatocytes (5, 6).

According to Trites (7), it is an unusual pathologic entity without clinical significance. The various theories concerning its etiology have been summarized as follows: "1. congenital malformation, 2. vascular varicosities with or without preceding angiitis, 3. ruptured vessels with or without inflammation, 4. primary focal hepatic necrosis followed by local hemorrhages, or 5. a combination of local hepatic necrosis and angiitis with bulging of the vessels into the softened parenchyme" (8).

Here we should like to describe the experimental production (in rats) of a lesion resembling peliosis hepatis.

Materials and Methods. Female ARS/Sprague-Dawley rats (60) (Madison, WI), with a mean initial body weight of 100 g (range 90–110 g), were divided into four equal groups and maintained on Purina Laboratory Chow (Ralston Purina Co. of Canada) *ad libitum*. The animals of all groups received gadolinium chloride ($GdCl_3$) at the dose of 12 mg/100 g of body weight in 1 ml of water iv once. Group 1 was not otherwise treated. The remaining groups were pretreated, respectively, with 3β-hydroxy-20-oxo-5-pregnene-16α-carbonitrile or "PCN" (Upjohn), prednisolone acetate (Roussel) or triamcinolone (Lederle) at the dose of 10 mg in 1 ml water, twice daily by stomach tube, beginning 4 days before the injection of the $GdCl_3$. All survivors were killed with chloroform on day 7 following $GdCl_3$ injection.

PCN was employed because of its particularly strong catatoxic activity against many toxicants (9). The other two steroids were selected because of their considerable glucocorticoid potency. $GdCl_3$ is known to be a strong calcergic agent (10), which causes intense calcification of the spleen and sometimes focal calcification of the liver, within 1 week after iv administration. In earlier experiments, we failed to protect the rat against these gadolinium-induced organ calcifications by any steroid. In fact, glucocorticoids greatly increased the immediate lethal effect of $GdCl_3$.

The present experiments were designed to examine the organ lesions associated with death occurring 1 to 2 days after $GdCl_3$ injection.

Results. Both in the controls given $GdCl_3$ alone and in those pretreated with PCN, mortality was only 15% whereas all but one rat per group died among those pretreated with either prednisolone or triamcinolone. Furthermore, in groups 1 and 2, death occurred only 1–3 min after the iv injection and all surviving animals showed intense splenic calcinosis, sometimes associated with small calcified foci in the liver. On the other hand, the rats of groups 3 and 4 died 24 to 48 hr after the $GdCl_3$ injection and showed macro- and microscopic manifestations of peliosis hepatis. The two survivors in these last two groups likewise had peliosis but, in this case, the hemorrhagic lesions were combined with calcification.

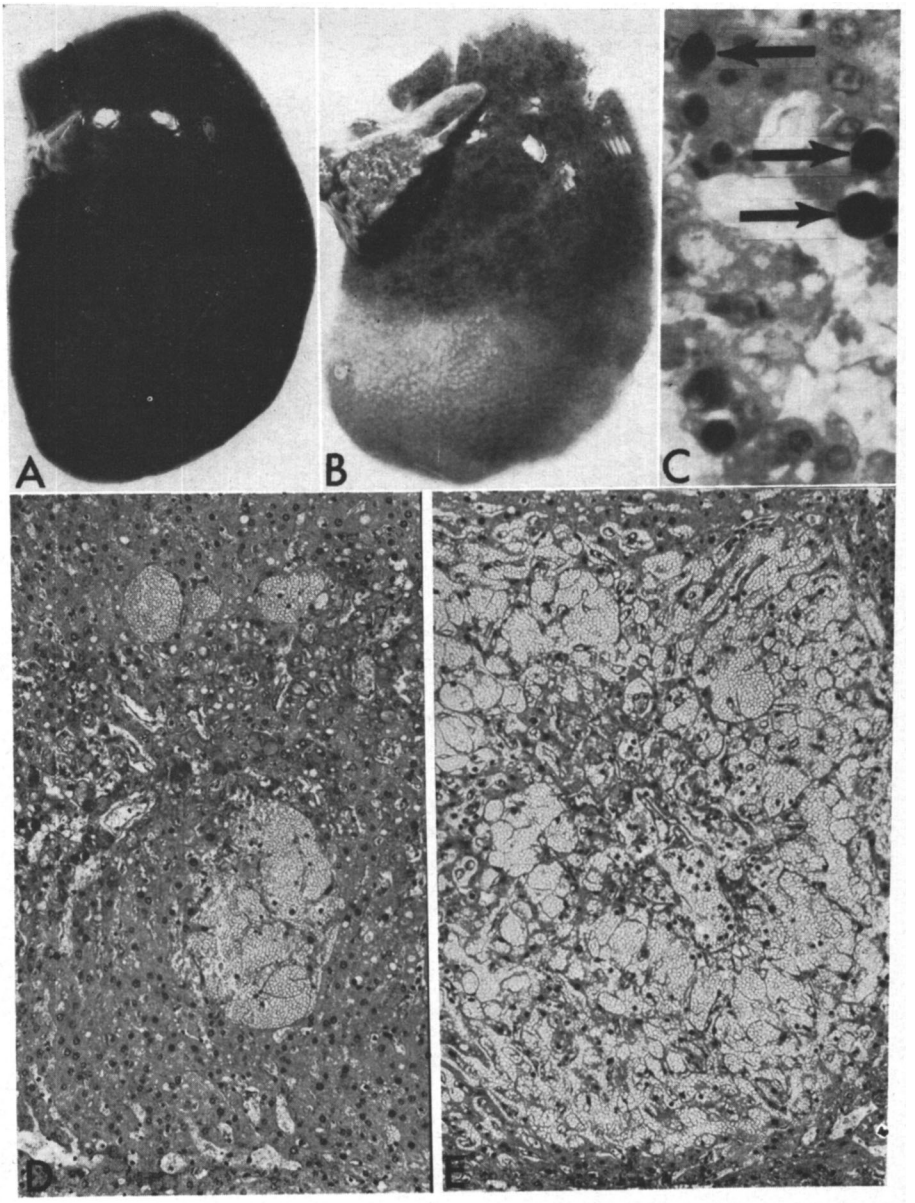

FIG. 1. Production of lesions resembling peliosis hepatis: (A) macroscopic appearance of the left lateral hepatic lobe in a normal control animal; (B) corresponding photograph of the liver showing typical hemorrhagic patches of "peliosis hepatis" in the upper part and palor with pronounced lobular pattern in the lower part of the lobe; (C) early lesions with dilated sinusoids (light central channel) and numerous hepatocytes containing bright red PAS-positive granules (here black and marked by arrows) (×368); (D) small early focus of peliosis with greatly dilated sinusoids separated by flattened almost endothelium-like hepatocytes (×96); (E) another region of the liver shown in (D) where the sinusoidal dilatation is much more advanced and many sinusoids have perforated into each other (×96); sections stained with PAS.

The highly potent catatoxic steroid, PCN, gave only doubtful protection against splenic calcinosis and none against immediate mortality; prednisolone and triamcinolone considerably increased mortality in conjunction with hepatic morphologic changes which resemble peliosis hepatis. These lesions (Fig. 1) are characterized macroscopically by small, but eventually confluent, red patches, often selectively localized in certain regions of the hepatic lobes. In such instances, the remainder of the lobe is usually pale, showing the individual hepatic lobules with particular clarity. Histologically, the hepatic sinusoids prove to be greatly dilated and the surrounding hepatocytes often contain strongly PAS-positive round droplets. In subsequent stages, the sinusoids become even wider, compressing the septa of hepatocytes between them. Eventually, between the sinusoids the partitions rupture creating the macroscopically visible large blood lakes.

Discussion. The experimental lesions observed here show all the characteristics of peliosis hepatis as described in the literature yet, obviously, their etiology must differ from the corresponding changes seen in man. In the rat, we are undoubtedly dealing with a "pluricausal disease" (11, 12), one that is due to the simultaneous agency of two or more potential pathogens, none of which is, in itself, capable of producing the characteristic lesions. In the clinical literature on peliosis hepatis, it is often mentioned that the lesion tends to develop in patients treated with anabolic steroids or suffering from tuberculosis, cancer, or other wasting diseases. In rats, changes resembling peliosis hepatis have been observed following infection with 9H virus (13) or following injection of high doses of lasiocarpine (14).

Summary. In the rat, pretreatment with prednisolone or triamcinolone sensitizes the liver for the production of hepatic peliosis by a single subsequent injection of gadolinium chloride. The morbid changes thus produced develop constantly and within a very short period.

This work was supported in part by the Ministère des Affaires Sociales, Quebec, the Medical Research Council of Canada (Block Term Grant MT-1829), and Succession J. A. DeSève.

The authors also thank the Companies listed in the section on "Materials and Methods," for kindly supplying the compounds used in these experiments.

1. Wagner, E., Arch. Heilk. **2**, 369 (1861).

2. Schönlank, W., Virchows Arch. Pathol. Anat. **222**, 358 (1916).

3. Hanser, R., *in* "Handbuch der speziellen pathologischen Anatomie und Histologie" (F. Henke and O. Lubarsch, eds.), Vol. 5, p. 132. Springer-Verlag, Berlin (1930).

4. Grätzer, G., Frankfurt. Z. Pathol. **36**, 134 (1928).

5. Hamilton, F. T., and Lubitz, J. M., A.M.A. Arch. Pathol. **54**, 564 (1952).

6. Zak, F. G., Amer. J. Pathol. **26**, 1 (1950).

7. Trites, A. E., A.M.A. Arch. Pathol. **63**, 183 (1950).

8. Saphir, O., *in* "A Text on Systemic Pathology" (O. Saphir, ed.), Vol. 2, p. 1280. Grune & Stratton, New York (1959).

9. Selye, H., "Hormones and Resistance," 1140 pp. Springer-Verlag, Berlin (1971).

10. Selye, H., "Calciphylaxis," 552 pp. Univ. of Chicago Press, Chicago (1962).

11. Selye, H., "Thrombohemorrhagic Phenomena," 337 pp. Thomas, Springfield, IL (1966).

12. Selye, H., Exp. Med. Sur. **24**, 191 (1966).

13. Bergs, V., and Scotti, T., Science **158**, 377 (1967).

14. Ruebner, B. H., Watanabe, K., and Wand, J. S., Amer. J. Pathol. **60**, 247 (1970).

Received Sept. 1, 1971. P.S.E.B.M., 1972, Vol. 139.