⅓ of rats, in the light of above observations, authors believe it is premature to identify luteotropic action with lactogen.

It may be pointed out, also, that 1 μg EB used in present experiment stimulated increase in lactogen in 5 days equal to peak level observed on day 16 of pregnancy(8), yet EB had no effect on placentoma formation. If lactogen is luteotropic hormone, it is strange that its concentration is low in early pregnancy when its need for maintenance and secretory activity of corpora is great.

Summary. Sprague - Dawley - Rolfsmeyer rats showing full estrous smears were administered 1 mg/day of ovine lactogen containing 15 IU/mg for 5 days. On day 6, one uterine horn was traumatized and 1 μg EB and 1 and 2 mg lactogen (LGH) were administered on days 6 to 9. On day 10, horns of uteri were separated and processed for DNA. EB had no influence on placentoma formation; whereas, both levels of LGH stimulated placentoma in ⅓ of rats with graded reaction as measured by DNA. EB, .5 μg or 1 μg, with 1 mg LGH improved neither % response nor total DNA in comparison with LGH alone. While lactogenic preparation stimulated placentoma formation, reasons are advanced why it is premature to identify luteotropic action with lactogen.

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Plasma Cholesterol Concentrations in Cockerels and Dogs Treated with Bile Acid Binding Polymer and Cholesterol Synthesis Inhibitors. (26895)

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Plasma cholesterol concentrations in animals and men can be lowered by feeding the bile acid binding polymer, cholestyramine resin (MK-135)†(1,2), or the hepatic cholesterol synthesis inhibitors, benzmalecene† (3,4,5,6), and triparanol (MER-29)†(7,8). In men the average maximum blood cholesterol lowering achieved with practical doses of these compounds is about 20%. Larger doses are either inconvenient, or produce no greater effect. Bile acid binders and synthesis inhibitors presumably lower cholesterol levels by different mechanisms, and thus combinations of the 2 might produce greater cholesterol lowering than can be attained with either alone. The present work is a study of the action of combinations of cholestyramine resin with benzmalecene and with triparanol in normocholesterolemic cockerels and dogs.

Methods. Cholesterol was determined by the method of Abell *et al.*(9) in plasma prepared by mixing 2.0 ml of whole blood with 0.35 ml of citrate-dextrose (ACD) solution. (Serum cholesterol concentrations may be

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† Cholestyramine resin is the generic name for a bile acid binding quaternary ammonium anion exchange resin with styrene-divinylbenzene skeleton. Benzmalecene is the generic name for N-(1-methyl-2,3-di-p-chlorophenylpropyl)-maleamic acid (α-isomer). Both are experimental developments of Merck Sharp & Dohme Research Laboratories, Rahway, N. J., and West Point, Pa. Triparanol is the generic name for 1- [(4-diethylaminoethoxy)phenyl] -1-(p-tolyl)-2-(p-chlorophenyl)ethanol, a product of Wm. S. Merrell Co. Cincinnati, Ohio.

approximated by multiplying the plasma levels by 1.3.) White Leghorn cockerels, 9-11 weeks old, raised in the laboratory, and fed a mixed natural diet(10), were used for experiments which lasted for 4 days. Treatment was started on Mondays, and blood was drawn for analysis on Fridays. Dogs used were male Beagles, fed a mixture of canned meat and commercial dog meal. Weights and cholesterol concentrations were determined once a week.

Results. Benzmalecene was given to cockerels by intramuscular injection, either as free acid or as sodium salt, at 100 mg/bird/day in 3 experiments. Cholestyramine resin was fed as 1%, dry weight, of the diet. Average plasma cholesterol concentration, ± standard error of the mean, of 60 controls was 69 ± 1.1 mg %; of 26 birds given benzmalecene, 60 ± 1.6 mg %; of 30 birds fed cholestyramine resin, 53 ± 1.5 mg %; and of 28 birds given benzmalecene plus resin, 49 ± 1.5 mg %. Both substances lowered plasma cholesterol concentrations ($P<.001$) when given alone. Further lowering occurred when they were given in combination. In the same experiments benzmalecene was also given as 0.125% of the diet (about 100 mg/bird/day). Average plasma cholesterol of 30 benzmalecene-fed birds was 71 mg %; and of 30 birds fed benzmalecene plus resin, 56 mg %. Thus, the feeding of benzmalecene did not lower plasma cholesterol, but also did not interfere with the cholesterol-lowering effect of the resin. Increasing the dose of benzmalecene to 1% of the diet, in 3 other experiments, caused decreased food consumption, and loss of weight. Plasma cholesterol levels rose. The increase was comparable to that seen here and elsewhere(11,12) during inanition.

Inasmuch as cholestyramine resin lowered plasma cholesterol of cockerels when fed in the diet, and benzmalecene lowered it only when given by injection, the two substances must exert their effect by different modes of action.

In 4 dogs we have studied the effect on plasma cholesterol of feeding cholestyramine resin (25 g/day, dry weight), sodium benzmalecene (25 mg/kg/day), and triparanol (MER-29) (15 mg/kg/day), alone and in combination. Results with one dog are presented in Fig. 1. Dosing periods generally lasted for 4 to 8 weeks. The order of the different treatments was varied from one dog to another, but this did not influence the results. For all dogs, average cholesterol level during control periods was 101 mg %; with cholestyramine resin, 74 mg %; with benzmalecene, 66 mg %; with benzmalecene plus resin, 41 mg %; with triparanol 42 mg %; and with triparanol plus resin, 15 mg %. All 3 substances lowered plasma cholesterol concentrations ($P<.001$), and further lowering occurred when they were given in combination. On 3 occasions with triparanol plus resin, determined sterol levels were 12, 10, and 9 mg %. Frantz *et al.*(13) and Avigan *et al.*(14) have found desmosterol in the blood of triparanol-treated animals. By our analytical technic pure desmosterol is half as chromogenic as cholesterol. Thus if, during triparanol treatment, all of the plasma sterol were desmosterol, the true concentrations would be twice those reported.

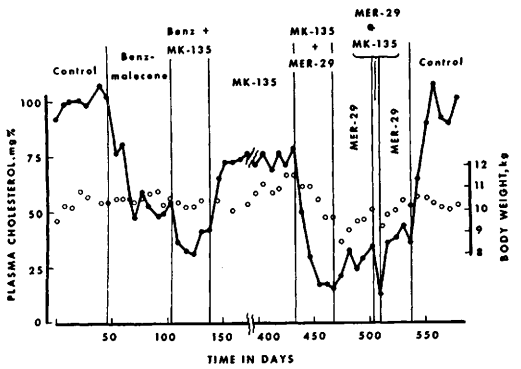

FIG. 1. Plasma cholesterol concentrations (———) and body weights (○) in a dog fed cholestyramine resin (MK-135) (25 g/day), benzmalecene (25 mg/kg/day), and triparanol (MER-29) (15 mg/kg/day).

Toxic signs were detected in dogs with very low blood sterol concentrations. The feeding of resin plus triparanol produced debility, reddened conjunctiva, diarrhea, and anorexia in a dog (Fig. 1) in which plasma cholesterol had already been continuously depressed for 11 months by feeding of resin alone. This dog, and another treated with resin plus triparanol, lost hair at very low

blood sterol levels. Their coats improved when treatment was stopped.

Summary. In normocholesterolemic cockerels the bile acid binding polymer, cholestyramine resin (MK-135), lowered plasma cholesterol concentrations when fed in the diet; the hepatic cholesterol synthesis inhibitor, benzmalecene, lowered cholesterol levels when given by injection, but not when fed in the diet. In combination, their effect was additive. In dogs, feeding of cholestyramine resin plus benzmalecene or triparanol (MER-29) had additive cholesterol-lowering effect.

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Phagocytosis of Colloidal Carbon by the Reticuloendothelial System During Hepatocarcinogenesis in Rats. (26896)

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Evidence that the reticuloendothelial system (RES) may be involved in the carcinogenic process has been reviewed by a number of investigators(1,2,3). Several different types of colloids which act directly on the RES have been implicated in the development of tumors(4,5,6). There is also evidence that procedures which stimulate or block the RES will affect the carcinogenic process in animals being fed azo dyes(7,8,9).

It was of interest, therefore, to determine the functional capacity of the RES during the carcinogenic process by measuring the rate of phagocytosis of colloidal carbon. Rates of phagocytosis were determined in rats fed the carcinogens 3'-methyl-4-dimethylaminozobenzene (3'-Me-DAB) or DL-ethionine as well as the basal diets and a weakly carcinogenic azo dye 4'-methyl-4-dimethylaminozobenzene (4'-Me-DAB). A combination of DL-methionine with DL-ethionine was also employed since methionine has been shown to eliminate the liver damage and tumors caused by ethionine(10). Studies with hypophysectomized rats on a 3'-Me-DAB diet were included, since removal of the pituitary gland has been shown to suppress tumor formation in rats fed azo dyes (11). Administration of ACTH or growth hormone will partially restore tumor forma-

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