# Effects of Dextran on Cortisone-Induced Hyperlipemia in Rabbits.* (25879)

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Following administration of cortisone, rabbits commonly develop marked hyperlipemia (1,2), associated primarily with increase in plasma triglycerides(2). However, as an incidental observation we noted that hyperlipemia failed to develop in cortisone-treated rabbits maintained on high doses of dextran given intravenously prior to and concurrently with cortisone administration. Further investigation is the subject of the present report.

*Methods.* Female rabbits weighing from 3-5 kg were kept in metabolism cages and fed standard rabbit ration *ad lib.* Dextran (Laros Lot H. average molecular weight of 188,000) was prepared as 6% solution in saline and sterilized by passage through bacterial filter. Daily doses of 1.0-1.5 g of dextran were administered intravenously and cortisone acetate (3 mg/kg body weight/day) was administered subcutaneously. All animals on cortisone therapy received 75,000 units of procaine penicillin and 0.25 g of streptomycin intramuscularly every 3rd day as well as 5 meq of potassium chloride in drinking water. Blood samples were obtained after fasting 12-16 hours. Intravenous glucose tolerance tests (400 mg of glucose/kg body weight) were performed in 12 control rabbits, 12 rabbits receiving cortisone 2-3 weeks, 4 rabbits receiving dextran 2 weeks and 3 rabbits receiving both dextran and cortisone 3 weeks. Intravenous glucagon† tolerance tests (2-3 $\mu$g glucagon/kg body weight) were performed in 7 rabbits as controls, in 4 rabbits after dextran and cortisone and in 3 after cortisone alone. Blood glucose was determined by Somogyi method(3). Total plasma lipids were determined gravimetrically(4). Plasma dextran levels were determined by method of Roe(5).

*Results.* Plasma lipid concentrations were determined in animals treated for various periods with cortisone or cortisone plus dextran with results shown in Fig. 1. When 5 normal rabbits were given dextran 10-15 days, their total plasma lipid was 104 $\pm$ 16 mg/100 ml compared to control levels in same animals of 116 $\pm$ 9 mg/100 ml. Differences between groups given cortisone alone and those given cortisone plus dextran at 10, 20 and 30 days (Fig. 1) are significant ($P<0.01$) for each period.

Six animals were started on cortisone treatment and subsequently given dextran while cortisone was continued for varying periods. There was no immediate effect on lipemia, but after 1 week a definite lowering of plasma lipids was obtained in 4 of 6 animals, numbers 10, 11, 3a, 5a (Fig. 2). Following withdrawal of dextran but continuance of cortisone treatment for another 10 days, rabbits 9, 10, and 11 showed increasing plasma lipid levels.

Intravenous glucose tolerance tests failed to reveal any significant differences between control and dextran groups or between cortisone and cortisone, dextran groups. Glucagon tolerance curves in 5 animals on cortisone therapy and 2 animals on cortisone-dextran therapy were not significantly different. Plasma dextran levels ranged between 1.3 and 2.2 g%. When added *in vitro,* dextran had no clearing effect on lipemic plasma.

*Discussion.* Non-sulfated mucopolysaccharides have been reported to effect a rapid reduction of elevated fat levels produced by intravenous injection of plasma from hyperlipemic patients into rats(6). Furthermore, administration of dextran to nephrotic rats (7) and to humans(8) has been associated with a decrease in plasma cholesterol and total lipids. It has been suggested that blockage of the reticuloendothelial system by dextran may have caused reduction in serum cholesterol(8). However, although accumulation of dextran has been demonstrated in re-

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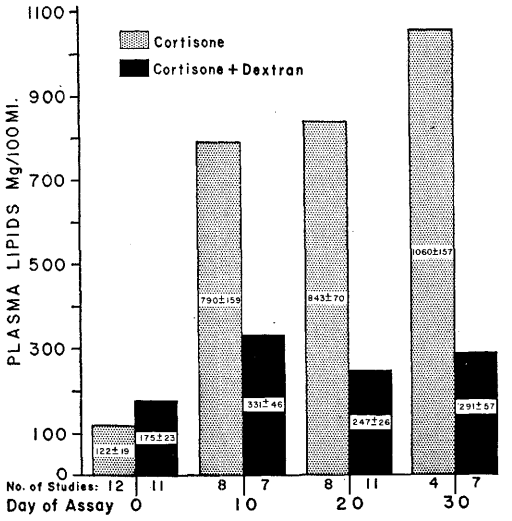


FIG. 1. Total plasma lipids (mg/100 ml ± S.E.) in rabbits on cortisone (3 mg/kg/day), and cortisone and dextran (1.0-1.5 g/day) after 0, 10, 20, and 30 days of therapy (see text).

ticuloendothelial cells(9), known reticuloendothelial blocking agents produce a rise in serum lipid levels(10) and a decreased clearance of cholesterol(11). In addition, dextran has been shown to increase rate of phagocytosis of carbon particles in the rat and mouse (12) and in the rabbit. Thus it is interesting to speculate that dextran effects its lipid clearing action by stimulation of the reticuloendothelial system. Cortisone administration on the other hand is associated with a depression of reticuloendothelial cell function(13) and dextran may have antagonized this action.

In addition to effects on fat metabolism, adrenal cortical hormones exert a significant influence on carbohydrate metabolism(14). However, our results failed to correlate inhibition of cortisone induced hyperlipemia with changes in glucose tolerance or glycogen stores.

Sulfated polysaccharides, such as dextran sulfate(15) and heparin(2) also exert an anti-hyperlipemic action and heparin increases clearance of cholesterol(11). The possibility exists that the lipemic clearing action of dextran may be due to conversion of dextran to a sulfated ester *in vivo*. However, it is doubtful that this is the basis for the clearing action of dextran since cortisone hyperlipemia is insensitive to heparin(16). Lipemic sera from cortisone-treated animals appears to contain some substance which inhibits the lipemic clearing factor(2).

In the present studies dextran not only inhibited development of lipemia but also

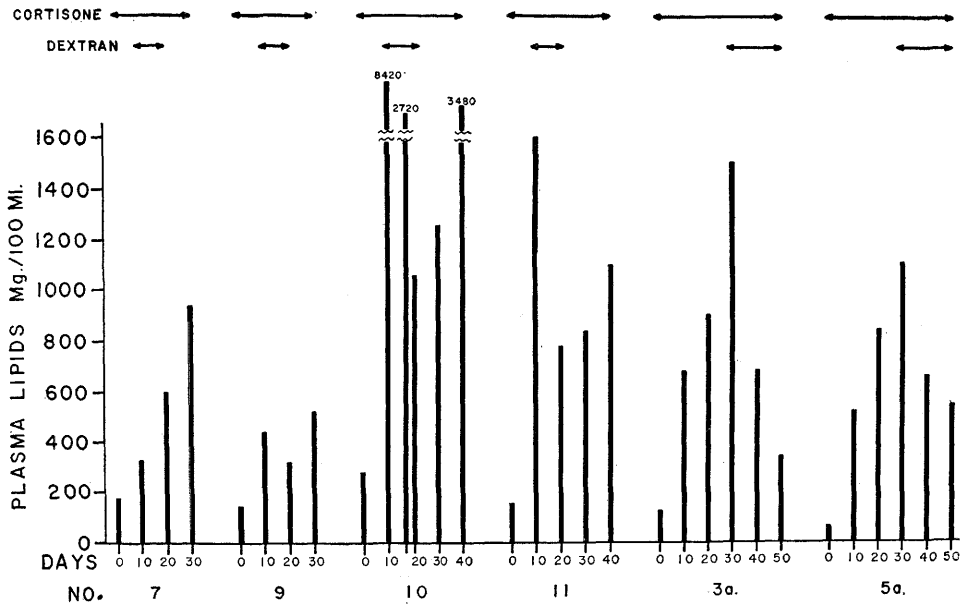


FIG. 2. Total plasma lipids (mg/100 ml) in 6 rabbits. Cortisone (3 mg/kg/day) was administered throughout the study in all the rabbits. Dextran (1.0-1.5 g/day) was administered from day 10 to 20 in rabbits 7, 9, 10, and 11, and from day 30 to 50 in 3a and 5a (see text).

partially reversed lipemia which had already appeared. This action could have resulted by blocking production of a clearing factor inhibitor or from stimulation of the lipid transporting system.

*Summary.* Dextran in doses of 1 to 1.5 g/day inhibited production of cortisone hyperlipemia in rabbits and partially reversed the hyperlipemia produced by cortisone. Alterations in fat transport, fat mobilization or in clearing factor action are considered as the basis for antagonism between dextran and hyperlipemic action of cortisone.

1. Rich, A., Cochran, T. H., McGoon, S. C., *Bull. Johns Hopkins Hosp.,* 1951, v88, 101.

2. Dury, A., *Ann. N. Y. Acad. Sci.,* 1959, v72, 870.

3. Somogyi, M., *J. Biol. Chem.,* 1952, v195, 19.

4. Natelson, S., *Microtechniques of Clin. Chem.,* Charles C. Thomas, Springfield, 1957, pp256.

5. Roe, J. H., *J. Biol. Chem.,* 1954, v208, 889.

6. Seifter, J., Baeder, R. H., Zarafonetis, C. I. D., Kalas, J., *Ann. N. Y. Acad. Sci.,* 1959, v72, 1031.

7. Heyman, W., Nash, G., Gilkey, C., Lewis, M., *J. Clin. Invest.,* 1959, v37, 809.

8. Morrison, A. B., *Quart. J. Exp. Physiol.,* 1951, v41, 51.

9. Perrson, B. H., *Nature,* 1952, v170, 716.

10. Feigenbaum, L., Byers, S. O., Freedman, M., PROC. SOC. EXP. BIOL. AND MED., 1954, v85, 530.

11. Neveu, T., Biozzi, G., Benacerraf, B., Stiffel, C., Halpern, B. N., *Am. J. Physiol.,* 1956, v187, 269.

12. Biozzi, G., Halpern, B. N., Benacerraf, B., Stiffel, C., Mouton, D., *Compt. Rend. des Seances de la Soc. de Biol.,* 1956, v150, 317.

13. Thomas, L., *Ann. N. Y. Acad. Sci.,* 1953, v56, 799.

14. Long, C. N. H., *Ciba Colloquia on Endocrinology,* Little, Brown and Co., Boston, 1953, v6, 136.

15. Cohen, H., Tudhope, G. R., *Brit. Med. J.,* 1956, v2, 1023.

16. Constantinides, P., Szasz, G., Dannach, M., 19th International Physiol. Cong. 1953, abs. 277.

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## Some Pharmacological Actions of Amphenidone* A New Psychotherapeutic Drug. (25880)

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A new chemical structure, 1-m-Aminophenyl-2-pyridone (amphenidone), is of interest in that it induces emotional stability without depression of psychic or motor functions(1). Because of promise shown in clinical trials, some of its pharmacological actions are described below.

*Methods.* Potentiation of a subhypnotic dose of hexobarbital (50 mg/kg) by amphenidone and other drugs was measured as reported(2). Inhibition of the effects of LSD in the mouse (CF #1) was investigated using Haley's method(3). Anticonvulsant activity was determined in the mouse, using maximal electroshock (MES) and Metrazol (Met) seizures(4) and in the cat, in which clonic convulsions were evoked by injecting 50 mg/kg Metrazol, subcutaneously. Analgesic activity was assayed according to Eddy and Leimbach(5), using a 40-second exposure to the hot plate at 54-55°C. Cardiovascular and respiratory effects in the anesthetized (pentobarbital) dog were recorded kymographically using a Hg manometer and an Anderson inspirometer. Studies of isolated cat and rabbit hearts were conducted according to Langendorff(6). Effects on the nictitating membrane were studied using the method of Plummer *et al.*(7). Whenever linearity of dose-response relationships permitted, $ED_{50}$'s with 95% fiducial limits were computed graphically(8) and, in general, 10 or more animals were used at each of 3 or more doses.

*Results.* Loss of the righting reflex was noted only in response to toxic doses of the drug, *e.g.,* 500 mg/kg i.v. and 1000 mg/kg

* Amphenidone manufactured under trade-name Dornwal by Maltbie Labs., Wallace & Tiernan.

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