indicate that the water shift following estradiol may be due to the action of the hormone on the electrolytes. Present experimentation is now being concluded on the action of relaxin on the electrolytes of the uterus.

It is of further interest that this effect of relaxin on uterine water content is produced without previous sensitization by estrogen. In all actions which have been previously demonstrated, it has been necessary to pretreat the animal with estrogen to obtain an effect. This necessity for estrogen priming is observed in the separation of the guinea pig pubic symphysis, the dilatation of the sow uterine cervix, and inhibition of uterine contractions in the rat.

*Conclusions.* Relaxin causes an increased concentration of water in the uterine tissue of the immature rat. Maximum hydration was obtained at 6 hours following administration of the hormone. The minimum effective dose of relaxin is 1 G.P.U. and the maximum response occurs following 10 G.P.U. relaxin. Contrary to the effect seen following estradiol administration, no secondary rise in uterine water content and no increase in dry weight is observed. Pretreatment with estrogen is not necessary for this action of relaxin on the water content of the uterine tissue.

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## Role of Liver on Consequences of Lipid Mobilization.* (23352)

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We have reported the isolation of a lipid mobilizer (LM) from the plasma of animals administered cortisone(1-4) and from the posterior pituitary of hogs(5). The greatest sensitivity to the hyperlipemic action of LM occurred in animals which had been inadvertently exposed to minute amounts of potential hepatotoxic agents. This suggested that the liver may play an important role in determining lipid concentrations in the peripheral blood following mobilization of fat from the depots.

*Materials and methods.* Male and female Wistar strain rats weighing 125-250 g were obtained from the same source as those used in our previous studies(1-5). They were maintained from weaning on Wayne Chow Checkers supplemented with K penicillin G (4 g/ton) and 0.005% butylated p-hydroxyanisole. Desensitization to the hyperlipemic action of LM was accomplished by changing the diet to Warner Dog Chow which did not contain added antibiotics or antioxidants. Sensitivity was reestablished by restoring the Wayne diet. LM was either from the same batch used previously(1-4) or from a new batch. Bleeding and chemical analysis of the blood samples were by the methods previously described(1-4). Determination of liver cholesterol and fatty acids was by a modification of the Baruch and Chaikoff method(6) as furnished by Kaplan and Cohn. Lipid P in the liver was determined by the method of Zilverschmidt *et al.*(7). Liver glycogen was determined by the method of Seifter *et al.*(8). Hepatectomy was performed in one stage under sodium thiopental anesthesia (20 mg/kg). The hilus of the liver was exposed by a midline incision, ligated with No. 1 braided

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TABLE I. Effect of LM on Lipids in Liver (%) and Plasma (mg %) 2 Hr after 5 mg/kg IV. 10 rats/series.

| | | Liver fasted, LM | | Plasma fasted, LM | | Liver fasted, no LM | | Plasma fasted, no LM | |
|---|---|---|---|---|---|---|---|---|---|
| Week | Diet | CH | FA | CH | FA | CH | FA | CH | FA |
| 0 | Wayne | 1.9 | 3.4 | 202 | 400 | | | | |
| 1 | Warner | 3.4 | 3.4 | 143 | 174 | | | | |
| 2 | | 4.6 | 4.9 | 82 | 102 | | | | |
| 3 | | 4.8 | 4.9 | 64 | 96 | | | | |
| 4 | | 4.4 | 4.2 | 62 | 84 | .6 | 1.2 | 56 | 80 |
| 5 | Wayne | 4.3 | 4.1 | 60 | 85 | .9 | 1.8 | 64 | 86 |
| 6 | | 2.2 | 3.9 | 74 | 90 | 1.8 | 2.6 | 60 | 87 |
| 7 | | 1.2 | 3.7 | 200 | 374 | 3.0 | 3.2 | 62 | 86 |

CH = Cholesterol. FA = Total fatty acids.

silk and excised leaving a small stump. This procedure left the vena cava and hepatic portal vein intact. Closure was with continuous silk sutures and 2 hours later the surviving rats were injected intravenously with test material. Only 10 to 20% of rats survived the 4 hours necessary for the experiment. These survivors presumably represent animals with sufficient anastamoses to systemic circulation.

*Results.* The data in Table I demonstrate the effect of LM on concentration of lipids in liver and plasma of fasted rats during desensitization and resensitization. The largest accumulation of lipids in liver as a result of fasting occurred in rats exposed longest to the Wayne diet. Two hours after intravenous injection of 5 mg LM/kg sensitized, fasted rats had an elevation of total cholesterol and total fatty acids in plasma and a decrease of cholesterol in liver. As desensitization proceeded LM produced a progressive decline in plasma cholesterol and fatty acids and an increase in accumulation of cholesterol and total fatty acids in liver. Resensitization resulted in reappearance of the hyperlipemia and decrease in liver cholesterol.

The data in Table II demonstrate the effect of LM on concentration of lipids in liver and plasma of sensitized and desensitized rats. Fasted, sensitized rats had significant hyperlipemia following injection of LM. Fasted, desensitized rats had questionable elevation of plasma cholesterol and total fatty acids. The lowest concentration of liver lipids occurred in desensitized rats not receiving LM. Fasting caused questionable increase of liver lipids in desensitized rats but a significant increase in sensitized ones. Injection of LM caused elevations of liver lipids which were greater in fasted, desensitized rats. Liver cholesterol in fasted, sensitized rats was considerably less following injection of LM than in the group receiving no LM.

The data in Fig. 1 demonstrate the effect of LM on concentration of lipids in the liver and plasma of sensitized rats at various intervals following intravenous injection of 5 mg/kg. Each point is the mean of 10 rats. The liver values are in % and the plasma values in mg %. Except for the immediate increase in total fatty acids of liver the injection of LM caused a decrease in the concentration of all lipid components in the liver. Restitution towards normal values began in the 4th hour

TABLE II. Effect of LM on Liver and Plasma Lipids in Sensitized and Desensitized Rats. (2 hr after 5 mg/kg IV.)

| | | Liver (%) | | Plasma (mg %) | |
|---|---|---|---|---|---|
| Condition | No. | CH | FA | CH | FA |
| Fasted sensitized, LM | 10 | 1.8 | 3.6 | 324 | 668 |
| Fasted desensitized, LM | 10 | 4.6 | 4.9 | 82 | 102 |
| Nonfasted sensitized, LM | 10 | 2.8 | 3.4 | 62 | 86 |
| Nonfasted desensitized, LM | 10 | 1.2 | 3.1 | 61 | 90 |
| Fasted sensitized, no LM | 20 | 3.1 | 3.8 | 58 | 84 |
| Fasted desensitized, no LM | 10 | .6 | 1.2 | 56 | 80 |
| Nonfasted sensitized, no LM | 10 | 1.9 | 2.7 | 56 | 82 |
| Nonfasted desensitized, no LM | 10 | .4 | 1.0 | 52 | 78 |

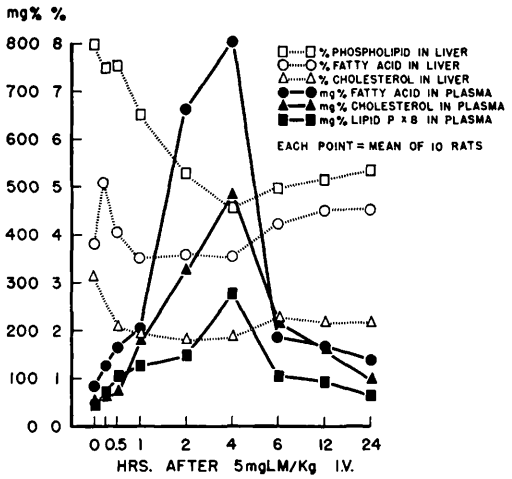


FIG. 1. Effect of LM on lipids in liver and plasma of sensitized rats.

after injection. Coincidental with the fall in liver lipid values there was a marked increase in all plasma lipids which reached their peak concentration in the 4th hour after injection and then fell to almost normal values within the next 2 hours. The data in Table III demonstrate the effect of hepatectomy on response of sensitized and desensitized rats to intravenous injection of 5 mg LM/kg. The operative procedures had no significant effect on the plasma lipid values. Injection of LM into either sensitized or desensitized rats resulted in a marked elevation of the total fatty acids in the plasma but had no effect on either the cholesterol or lipid P. In contrast, injection of LM into sensitized intact rats caused an elevation in the three plasma lipids.

*Discussion.* The most significant observation was that LM elevated plasma fatty acids in hepatectomized rats whether fasted, nonfasted, sensitized or desensitized, and that hypertriglyceridemia was not associated with corresponding elevations in cholesterol and lipid P. These findings demonstrate that LM mobilized triglycerides from the fat depots and that the liver determined the subsequent concentration of lipids in the blood. In the absence of liver there was hypertriglyceridemia. Liver containing adequate glycogen (4%) either retained or metabolized mobilized lipid in sensitized or desensitized rats. Liver depleted of glycogen (0.09%) handled the fat load adequately in nonsensitized rats but not in sensitized ones and hyperlipemia resulted. The liver was the source of the excess cholesterol and lipid P in the hyperlipemia as indicated by the data in Fig. 1. The gradual restoration of liver lipids may reflect redeposition from the circulation after the peak effect of LM had passed. The data in Tables I and II suggest that sensitization by administration of potential hepatotoxic agents consisted of producing "subclinical" fatty liver. Sensitized rats had high lipid content in liver and greater accumulation of lipids in response to fasting indicating that they did not metabolize a fat load as well as those desensitized. LM caused elevation of total fatty acids in liver of sensitized, desensitized, fasted or nonfasted rats indicating that it mobilized fat from the depots.

*Summary.* (1) The role of the liver on the consequences of lipid mobilization from the depots by LM was investigated in sensitized and desensitized rats. (2) Sensitization to the hyperlipemic action of LM involved administration of minute amounts of potential hepatotoxic agents which produced "subclinical" fatty liver as determined by chemical analysis. (3) Desensitization to the hyperlipemic action of LM occurred when the potential hepatotoxic agents were removed from the diet. (4) The liver in desensitized or fed sensitized rats was capable of handling the mobilized lipid without consequent hyperlipemia. (5)

TABLE III. Effect of Hepatectomy on Plasma Lipid (mg %) Response to LM. (2 hr after 5 mg/kg IV.)

| Treatment | No. of rats | CH | FA | LP |
|---|---|---|---|---|
| S + IV NaCl | 20 | 58 | 86 | 5.2 |
| S + LM (fasted) | 20 | 398 | 402 | 12.6 |
| S + sham hepatectomy + IV NaCl | 20 | 71 | 98 | 6.9 |
| S + ligated vena cava + IV NaCl | 20 | 68 | 94 | 5.8 |
| S + hepatectomy + IV NaCl | 20 | 70 | 92 | 5.0 |
| S + hepatectomy + LM (nonfasted) | 20 | 68 | 430 | 5.1 |
| DS + hepatectomy + LM (nonfasted) | 6 | 64 | 306 | 5.2 |

CH = Cholesterol. FA = Total fatty acid. LP = Lipid phosphorus. S = Sensitized. DS = Desensitized.

Fasted, sensitized rats were not capable of handling the fat load and hyperlipemia resulted. (6) The source of the cholesterol and lipid P in the hyperlipemic rats was the liver. (7) LM actively and immediately mobilized triglycerides from the depots and this action did not depend upon sensitization or fasting.

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## Effect of Specific Activity on Distribution of Radiolutecium ($Lu^{177}$).* (23353)

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In previous studies on effectiveness of radiolutecium ($Lu^{177}$) for irradiating lymph nodes in the dog, the possibilities of this rare earth were demonstrated(1,2). Certain difficulties, however, greatly limited the effectiveness of the isotope. With both tracer and therapeutic amounts, irradiation was selectively delivered to the regional lymph nodes draining the mammary gland of the dog. The tissues at the site of local injection tolerated large amounts of the isotope and general body distribution was well below a dangerous level for the animal. The major problem in previous experiments was that often there was not homogeneous distribution of the particles within the lymph node, hence irradiation effects were patchy and often large areas of the nodes remained undamaged. This difficulty was also encountered when $Au^{198}$ was similarly studied(6).

It seemed to us that the amount of rare-earth carrier might influence homogeneity of particle distribution and therefore distribution of irradiation effect. Two factors might be expected to play a role in such a study. The first is that high carrier doses (low specific activity) of radioactive rare-earths tend to remain at site of injection, whereas low carrier or carrier-free doses (high specific activity) show a greater tendency to be mobilized away from site of injection(3). If we desire to damage the regional lymph nodes of a given area, and to prevent local irradiation damage at site of injection, the material with high specific activity would seem to be advantageous. The other problem concerns the total mass of rare-earth particles available to saturate a lymph node. In previous studies we had injected up to 131 mc of $Lu^{177}$ into the mammary gland of a dog without producing consistent homogeneous radiation effect. In any given node considerably more total concentration of radioactivity was present than was necessary to produce the desired effect; on the other hand, the nodes contained "cold" spots. Dilution of the radioactive particles by additional nonradioactive material would therefore be a possible approach to even dispersion in lymph nodes and their more nearly complete destruction with much lower curiage. This study was undertaken to determine the over-all effect of the specific activity of $Lu^{177}$ on its intranodal pattern. A mixed carrier of stable lutecium and stable yttrium was used in the preparations of low specific activity. The heterogeneous

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