Mohme-Lundholm(16). Carbohydrate metabolism may be involved.

Summary. 1) Protective effects of various types of adrenergic inhibition have been tested against lethal action of injected bacterial endotoxin in mice. 2) Preliminary experiments substantiated abilities of phenoxybenzamine to block lethal effect of injected epinephrine and of cocaine to augment its toxicity. 3,4-Dichloroisoproterenol also increased lethal effect of epinephrine. TM 10, or 2,6-xylyloxyethyltrimethylammonium bromide had no effect acutely but offered low order of protection when given 24 hours before epinephrine. Reserpine also protected when given 24 hours in advance. Iproniazid was without effect. 3) Against bacterial endotoxin from *E. coli* the only compound to give significant protection was 3,4-dichloroisoproterenol. This substance has been shown by previous workers to block inhibitor and vasodilator effects of epinephrine and related catechol amines. Such effects are probably metabolic in nature and may concern carbohydrate metabolism.

1 Boquet, P., Izard, Y., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 254.

2. Thomas, L., *J. Exp. Med.,* 1956, v104, 865.

3. Zweifach, B. W., Nagler, A. L., Thomas, L., *ibid.,* 1956, v104, 881.

4. Loew, E. R., Micetich, A., *J. Pharm. Exp. Therap.,* 1948, v93, 434.

5. Litchfield, J. T., Jr., Wilcoxon, F., *ibid.,* 1949, v96, 99.

6. Wilcoxon, F., *Some Rapid Approximate Statistical Procedures,* Am. Cyanamid Co., N. Y., 1949.

7. Powell, C. E., Slater, I. H., *J. Pharm. Exp. Therap.,* 1958, v122, 480.

8. Moran, N. C., Perkins, M. E., *ibid.,* 1958, v124, 223.

9. Exley, K. A., *Brit. J. Pharmacol.,* 1957, v12, 297.

10. Luduena, F. P., O'Malley, E., Oyen, I. H., *Arch. Internat. Pharm. Ther.,* 1959, v122, 111.

11. Gillis, C. N., Lewis, J. J., *J. Pharm. Pharmacol.,* 1956, v8, 606.

12. Borowitz, J. L., North, W. C., *Science,* 1959, v130, 710.

13. Burn, J. H., Rand, M. J., *Brit. Med. J.,* 1958, v1, 903.

14. Shimamoto, T., Incue, M., Konishi, T., Iwahara, S., *Arch. Internat. Pharm. Ther.,* 1959, v121, 342.

15. Pletscher, A., *Experientia,* 1958, v14, 73.

16. Mohme-Lundholm, E., *Acta Physiol. Scand.,* 1953, v29, Suppl. 108.

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Placental Transfer and Fetal Tissue Uptake of Mg^{28} in the Rabbit.* (26020)

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The factors regulating the metabolism of magnesium are obscure and very little is known about the placental transfer of this ion or its uptake in the fetal tissues. The purpose of the present study in rabbits was to investigate, by use of a radioactive isotope of magnesium (Mg^{28}), the maternal-to-fetal transfer of magnesium and uptake of the isotope by various maternal and fetal tissues.

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Material and methods. Pregnant domestic albino rabbits, between 28 and 30 days of gestation, were anesthetized with sodium pentobarbital given intravenously in a dosage of 40 mg/kg of body weight. After a tracheotomy had been performed, the carotid artery was cannulated and an indwelling polyethylene catheter, connected to a reservoir of heparin, was inserted.

Mg^{28} was then injected into the marginal vein of the ear as a solution of magnesium sulfate, prepared according to a method previ-

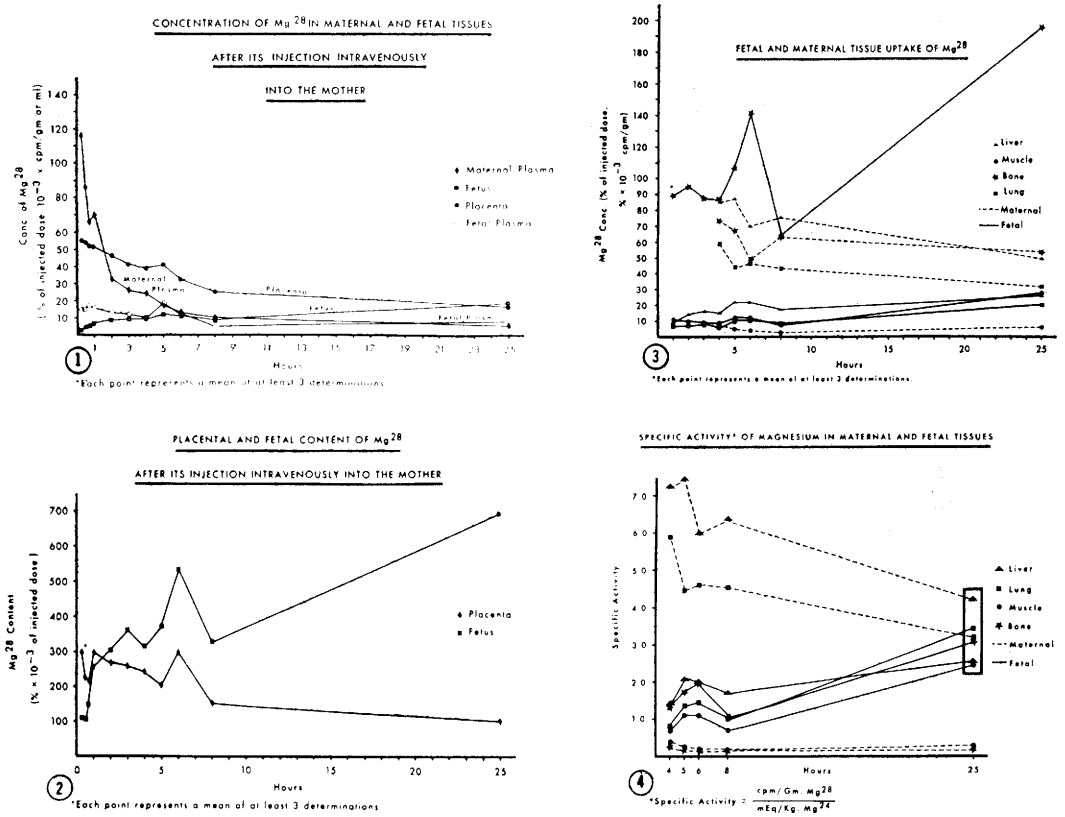

FIG. 1-4.

ously described(1); 20 μc of Mg^{28} was contained in 2 meq of stable magnesium.

Abdominal cavity was exposed by a midline incision. At intervals varying from 7 minutes to 26 hours after injection of Mg^{28}, a fetus and its placenta were removed from the uterus. A wide V-shaped incision was made over the thorax of the fetus and blood was obtained by cardiac puncture with a 20-gauge hypodermic needle attached to a heparinized syringe. Simultaneously, with withdrawal of fetal blood, a maternal blood specimen was obtained from the carotid artery. At termination of each experiment, the mother was killed by air embolism and samples of tissues were obtained for assays of radioactivity and magnesium content.

Serum and tissue magnesium determinations were performed by the molybdivanadate method for phosphate(2).

Radioactivity assay. Samples of plasma and tissues were assayed for gamma ray activity in a well-type scintillation counter. Total Mg^{28} content of each fetus and placenta was determined; samples of liver, kidney, skeletal muscle, tibia and femur, and skull were then removed from each fetus and their concentrations of radioactivity determined separately. All results are expressed as percentages of total administered dose of radioactivity.

Results. A total of 86 fetuses and their respective placentas were obtained from 11 pregnant rabbits. Clearance of Mg^{28} from the maternal circulation, its concentration in placenta and fetus, and appearance of Mg^{28} in fetal circulation are summarized in Fig. 1.

Changes in concentration of Mg^{28}. Concentration of Mg^{28} in maternal plasma decreased rapidly during the first 2 hours; thereafter, the decline was slower, but progressive. Concentration of Mg^{28} was initially lower in the placenta than in the maternal plasma, but within 2 hours, placental concentration became higher and remained higher thereafter.

The progressive decrease of Mg^{28} in the placenta paralleled that in the maternal plasma. Concentration of Mg^{28} in the fetus was initially lower than that in maternal plasma or placenta; it increased gradually, however, and at 24 hours exceeded both maternal and placental concentration of the isotope.

Changes in Mg^{28} content. Average fetal content of Mg^{28} increased progressively (Fig. 2). Between the first and second hour it surpassed the placental content and remained higher thereafter. As fetal content of Mg^{28} increased, that in the placenta decreased progressively.

Tissue distribution of Mg^{28} (Fig. 3). Of all the *maternal* tissues studied, uptake of Mg^{28} was lowest in the muscle. Successively higher concentrations of Mg^{28} were found in lung, long bone, liver and kidney. Concentration of Mg^{28} in all maternal tissues tended to decrease progressively with time as concentration in the fetal tissues increased.

Relative concentrations of Mg^{28} in *fetal* tissues remained consistently in the following order: (1) lung (lowest), (2) muscle, liver and kidney (intermediate) and (3) bone (highest). Comparison of tissue concentrations of Mg^{28} in mother and fetus at various time intervals revealed that concentrations of Mg^{28} in the kidney, lung and liver were higher in the mother than in the fetus. Mg^{28} concentrations in fetal muscle and bone, however, were much higher than maternal concentrations.

The maternal and fetal *tissue contents* of magnesium are summarized in Table I. Magnesium content of all the tissues studied was lower in the fetus than in the mother, the most notable difference being bone.

Specific activities of maternal and fetal liver, lung, muscle and bone are summarized in Fig. 4. By 26 hours, all values, except those for maternal bone and muscle, appeared to reach a constant level.

TABLE I. Fetal and Maternal Tissue Content of Magnesium.

Tissue	Muscle	Kidney	Liver	Lung	Bone
Mother	19.8*	18.5	11.7	10.0	298.1
Fetus	10.8	11.2	10.4	7.9	62.9

* meq/kg (wet wt) of tissue.

Comment. When Mg^{28} was injected intravenously into pregnant rabbits, its clearance from the blood stream was similar to that previously observed in healthy young adult rabbits(3). Its distribution in tissues of the mothers was also similar to that in nonpregnant animals, except for slower uptake in bone and muscle of pregnant rabbits. Previous studies have shown that, in pregnancy, magnesium is mobilized from maternal tissues (4). In addition, bone uptake of Mg^{28} tends to decrease with age. Both of these factors probably contributed to the low uptake of Mg^{28} by maternal bone and muscle.

The observation that placental concentration of Mg^{28} at 2 hours was higher than concentration in maternal plasma suggests that the placenta actively concentrates magnesium. Because of the low specific activity of the Mg^{28} available for this study, the mother was subjected to a slight magnesium load. This maternal loading may have affected the placental concentration of Mg^{28}.

Comparison of tissue magnesium content in mother and fetus shows a higher concentration of untagged magnesium in all maternal tissues studied. In spite of the lower magnesium concentration of fetal tissues, Mg^{28} uptake was rapid and increased progressively. The fact that the specific activities of all fetal tissues and of maternal liver, kidney and lung approached a constant value at 24 hours suggests that Mg^{28} was at equilibrium with the untagged element in these tissues by this time. It is of interest that the specific activity of fetal muscle and bone was considerably higher than that of the respective maternal tissues. Previous studies support the interpretation that rabbit fetuses at this stage of development are rapidly increasing in bone and muscle mass and, hence, turnover of magnesium in these tissues is more rapid than that in the respective maternal tissues.

Our results show that Mg^{28}, injected intravenously into the mother near term, rapidly crosses the placenta and, because of the more rapid growth of the fetus, is concentrated in the fetal tissues. These results further suggest that rate of uptake of magnesium by various tissues is related to anabolic activities of the cells involved. In comparison with the

cellular exchange of potassium, for instance, transport of magnesium across the cell membrane is a relatively slow process.

Summary. Mg^{28} was injected intravenously into 11 pregnant rabbits between 28 and 30 days of gestation. Fetuses and placentas were removed at intervals ranging from 7 minutes to 26 hours. Maternal tissue uptake of Mg^{28} resembled that previously found in nonpregnant young adult rabbits, except that uptake in bone and muscle was slower. Concentration of Mg^{28} in the placenta rapidly rose above the maternal plasma level. Specific activity of magnesium in all fetal tissues studied reached a fairly constant value by 26 hours. Magnesium turnover in tissues of the fetus *in utero,* especially in bone and muscle, is considerably more rapid than that in the respective tissues of the mother.

Mg^{28} was supplied by Brookhaven Laboratory on allocation from U. S. Atomic Energy Comm.

1. Aikawa, J. K., PROC. SOC. EXP. BIOL. AND MED., 1959, v100, 293.

2. Aikawa, J. K., Rhoades, E. L., *Am. J. Clin. Path.,* 1959, v31, 314.

3. Aikawa, J. K., Harms, D. R., Reardon, J. Z., *Am. J. Physiol.,* 1959, v197, 99.

4. Guercio, F., *Fol. Gynaec.,* 1935, v32, 59.

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Systemic and Coronary Hemodynamic Effects of 2 Amino-4-Methyl Pyridine.* (26021)

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2 amino 4 methyl pyridine, also known as RA 1226, W 45, and Ascensil® is a sympathomimetic agent which has been reported to have a marked pressor effect in the experimental animal(1,2). At higher dosage levels (1-3 mg/kg) a moderate positive inotropic effect is reported(3). Furthermore the agent is reported to have a long period of action and no tachyphylaxis(2). The present study concerns the acute systemic and coronary hemodynamic effects of this agent.

Material and methods. The study was done in 10 mongrel dogs weighing between 19 and 26 kg. Anesthesia was secured by administration of 3 mg/kg of morphine sulphate subcutaneously followed one hour later by 0.25 ml/kg of a 50/50 mixture of Veterinary pentobarbital and Dial-Urethane.† During the ensuing 1 hour after administration of the anesthetic cardiac catheters were maneuvered fluoroscopically into the pulmonary artery, coronary sinus and the right atrium and Cournand needles were placed in the femoral arteries. Pressures were recorded by Statham Strain gages on the Gilson Macro-polygraph with means determined by electrical integration. PH was determined on whole blood with the Cambridge model R pH meter. Cardiac outputs were determined by the Fick principle simultaneously with the Hamilton indicator dilution method. Coronary blood flow was measured by the N_2O method. Blood gas analyses were done by the method of Van Slyke and Neill whereas expired air was analyzed by the method of Scholander. Formulae used for calculations are those used traditionally in measurements of coronary blood flow(4), ventricular work and vascular resistance were calculated by the usual formulae(5) without subtracting atrial pressure

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† Veterinary nembutal contains 60 mg pentobarbital /ml. Dial-Urethane was supplied by CIBA Pharm. Products, Summit, N. J., and contains Dial 100 mg/ml, Monoethylurea 400 mg/ml, and Urethane 400 mg/ml.