tained at the lower level for the duration of ventricular standstill. This drop in pressure, while moderate in amount, occurred in all experiments.

Fig. 2 shows pre-fibrillation pressure in the left atrium plotted against pressure after onset of atrial fibrillation for 23 observations in 4 dogs. The data indicate that intracardiac pressure decreased with atrial fibrillation in the order of 1 mm Hg over the entire range of pressure tested. These findings were confirmed in an additional animal where duplicate injections were made over a range of volumes. The first injection of each pair was made into the non-fibrillating atria and the second after atrial fibrillation was produced. In each case the pressure was lower after second injection.

Volume-pressure plots were made for each heart before and after onset of atrial fibrillation by plotting change in pressure against change in volume. All pre-injection pressures agreed within ± 0.5 mm Hg. Fig. 3 shows a typical plot of the data from one animal.†

The shift of the curve toward the volume axis with atrial fibrillation occurred in all experiments. This was an unexpected finding as *a priori* reasoning might suggest that atrial pressure would rise with atrial fibrillation. Displacement of the curve is apparently not due to a change in elasticity of the atrium as the slope of the two curves is essentially the same.

The mechanism responsible for lower intracardiac pressure with atrial fibrillation is not clear. If one assumes that the atria are roughly ellipsoid in shape, it could be further assumed that they would become more spherical in form with fibrillation due to the increase in wall tension. If this change in shape occurred, the internal volume would increase, thereby lowering intracardiac pressure. However, this explanation does not seem entirely adequate. Inspection of the volume-pressure plots indicates that a drop of 1 mm of Hg pressure would require an increase in volume of about 12 cc. A volume change of this magnitude seems too great to be accomplished by variations in atrial geometry. Furthermore, increasing the internal volume would tend to change the slope of the volume-pressure curve which does not occur.

Summary. The effect of atrial fibrillation on left atrial pressure was studied in the living dog during brief periods of ventricular standstill. The data indicate that left atrial pressure decreases with atrial fibrillation in the order of 1 mm Hg. This decrease causes a shift of the volume-pressure plot for the pulmonary-left heart segment toward the volume axis without change of slope. The mechanism of this shift is not clear.

† The break in the plot at a volume change of 12 ml has been described elsewhere(1).

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Ethionine-Induced Resorption of the Rat Conceptus.* (26018)

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Various investigators have reported that amino acid analogues have specific detrimental effects on growth and differentiation of embryonic primordia in the chick(1,2). It has been proposed that the effect is primarily on the protein of the embryonic cell. In light of this, we have established a program to determine effects of amino acid analogues on the rat embryo.

Ethionine, the amino acid analogue of me-

* This project was initiated at Univ. of Oregon; it has been supported by U. S. Public Health grants and by funds from the Graduate School, University of Oregon.

TABLE I. Gross Effects of Ethionine* and/or Methionine* on 12-Day Rat Embryo.

Treatment (total dose)	Total No. rats	Embryonic resorption — No. complete	No. partial	% complete + partial	% embryos reduced in size or resorbed
Saline controls	39	2	3	12.8	5.6
.8 mg ethionine/g body wt	41	23	14	90.2	62.3
.8 mg methionine/g body wt	12	0	0	0	1.4
.8 mg ethionine + .8 mg methionine/g body wt	24	7	6	54.2	26.4

* Nutritional Biochemicals.

thionine, was the first compound chosen for this investigation since its effects on the non-pregnant rat have been studied(3-6). This paper describes gross and histologic effects of ethionine on the pregnant rat with particular reference to resorption of embryos and induced abnormalities of placentae and uteri.

Materials and methods. A total of 116 pregnant albino rats (Sprague-Dawley strain) within a weight range of 230 to 270 g was used. Pregnancies were timed by vaginal smears, the day in which sperm were found being considered as day 0. Animals were treated as shown in Table I. The total dose of ethionine and/or methionine was administered over a 3-day period, starting on day 7. Animals were sacrificed on day 12 of pregnancy. After autopsy, uteri were removed and conceptuses and embryos were measured. Several conceptuses from each animal were fixed in Bouin's solution for histological observations.

Results. A summary of the gross observations is shown in Table I. Resorption of the conceptus was considered as complete when the embryo had been completely resorbed and the placenta either was present as a remnant of tissue or as an implantation site. Partial resorption was indicated by a definite reduction in size of the embryos and presence of large amounts of blood in the uterine lumen. In the calculation of the % embryos reduced in size or resorbed, average litter size of 11 was used for those animals in which complete resorption had occurred.

The pattern of the resorption was apparently similar in ethionine-induced resorption and spontaneous resorption observed in the controls. The sequential destruction of the various regions of the placenta was as follows: The allantoic mesoderm was destroyed 1st (Fig. 1B), followed by the labyrinth and compact layers of the hemoendothelial placenta (Fig. 1C). The embryo was destroyed next as indicated by a loss of cohesion of the cells and an increase in pycnosis, then the yolk sac splanchnopleure disappeared (Fig. 1D), and finally the giant cell trophoblast. The giant cell layer often formed a prominent spherical nest of cells in the center of the conceptus. The decidua basalis was found to be very resistant to breakdown.

There appeared to be no selective effect of ethionine on the embryo, but rather an overall breakdown of embryonic tissue. It was frequently noted that the neural tube had a spiral or wavy appearance, especially noticeable in the late stages of destruction of the embryo.

Discussion. An increase in number of embryonic resorptions and still births in pregnant rats following administration of ethionine has been reported by Lee *et al.*(7). Although the pancreases of the mothers were severely damaged by ethionine injections, those of the fetuses remained essentially normal. Therefore the authors questioned the passage of the ethionine across the placenta. However, when C^{14}-ethionine was administered to pregnant rats 4 days before parturition, the label was isolated from the newborn rat in the form of choline and creatinine(3). The passage of the ethionine across the rat placenta is being investigated in this laboratory by autoradiographic technics. Since it has been shown that ethionine can be incorporated into proteins in the non-pregnant rat (4), it is assumed at present that ethionine exerts its effect by being incorporated into proteins of the embryo and/or placenta and therefore interferes with the normal protein metabolism of these tissues.

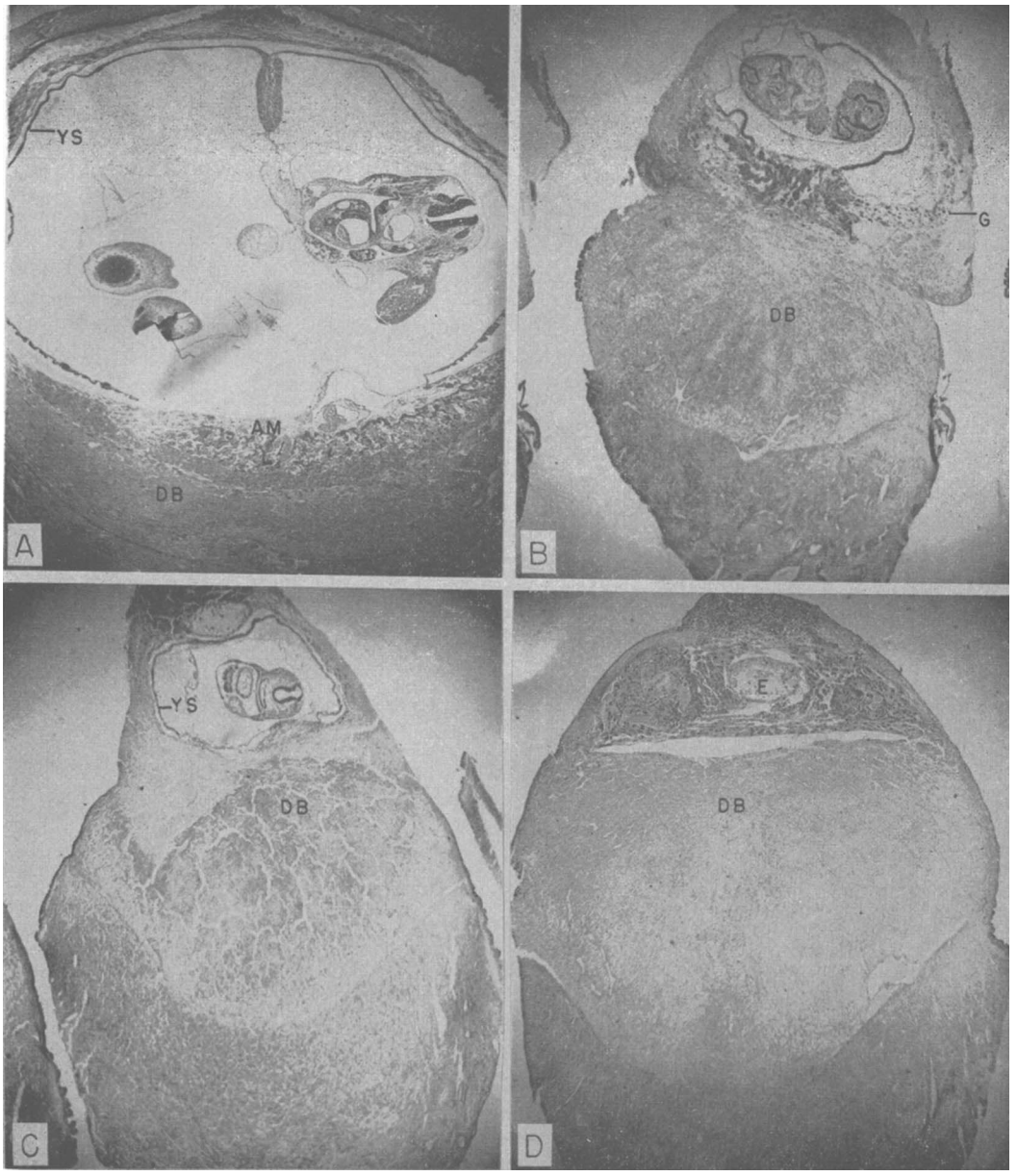

FIG. 1. Sections of 12-day pregnant rat conceptuses. A, control. B, C, D, stages in resorption following treatment with ethionine. DB, decidua basalis; E, embryonic remnant; G, giant cell layer; L, placental labyrinth; YS, yolk sac; AM, allantoic mesoderm. Hematoxylin and eosin stain. × 15.

Further evidence for this assumption is the observation that simultaneous administration of methionine and ethionine causes a reduction of approximately 50% in the embryonic resorption and decreased size of the rat embryos. Several workers(5,6) have demonstrated that a higher amount of methionine is required to completely reverse the ethionine effect on the liver. Therefore, it may be that the partial reversal of the resorptive effects of ethionine shown here indicates that the ethionine effect involves competitive incorporation between the analogue and the amino acid.

Summary. A marked increase in resorption

of the embryos and placentae was observed following administration of high doses of ethionine to pregnant rats. A similar dose of methionine had no apparent effect by itself while a combination of methionine with ethionine resulted in about a 50% reduction in the resorptive effect of ethionine. The sequential destruction of the tissues of placenta and embryo associated with the ethionine-induced resorption is described.

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Adrenergic Inhibition and Lethal Effect of Bacterial Endotoxin in Mice. (26019)

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Participation of epinephrine or related substances in the sequelae of bacterial endotoxin administration has been suggested(1-3). Adrenergic blocking agents such as phenoxybenzamine HCl have been used against traumatic shock with some success in laboratory animals, though with less in man. They have been largely ineffective against bacterial endotoxin. Recently several new ways of affecting sympathetic reactivity have been described. The following study tests the ability of some of the presently available types of adrenergic inhibition to alter lethal effects of injected epinephrine and of bacterial endotoxin administration.

Methods. Survival after intraperitoneal epinephrine was determined by the technic of Loew and Micetich(4) and results were evaluated by the method of Litchfield and Wilcoxon(5). Data from selected dose levels were used for comparison in Table I. High doses of epinephrine with low expected survivals were used when protection was anticipated and the reverse when sensitization was indicated. The significance of difference between results from these selected doses was judged by the Rank Correlation method of Wilcoxon(6).* Doses of synthetic l-epinephrine bitartrate were calculated as mg/kg free base. The blocking agents were given as salts, also on a mg/kg basis. Difco crystalline lipopolysaccharide from *E. coli* was used in the endotoxin studies. It was dissolved in pyrogen-free saline and given intraperitoneally on the basis of total mg/mouse (not/kg). Average weight of the male CF-1 mice used in this study was about 20 g. For reference purposes 2 SD_{50}, or 50% survival, doses were determined one hour after epinephrine in normal untreated male CF-1 mice. These were 8.0 (5.41-11.8) and 7.8 (6.45-9.44) mg/kg i.p. respectively. Another series received an intraperitoneal saline blank (0.1 cc/10 g of mouse) 24 hours before epinephrine. SD_{50} here was 7.6 (6.39-9.04) mg/kg i.p. Obviously, the susceptibility of the animals to epinephrine was essentially unchanged. We did find that mice were adversely affected if one intraperitoneal injection followed soon after another. For short term testing we used subcutaneous or oral premedication followed by intraperitoneal epinephrine.

Results. A. *Effects on lethal action of injected epinephrine.* It is recognized that lethal actions of toxic doses of epinephrine are very different from circulatory collapse and shock. However, as a preliminary step in our study we tested the ability of the several

* Kindly computed by Dr. Irving Sher of Smith Kline and French Labs.