also highly reactive with castor pollen extract. By utilization of the phenomenon of reagin neutralization (specific desensitization) with castor pollen extract, sites passively sensitized with these 6 sera were rendered non-reactive to the pollen allergens; the pollen-desensitized sites were still highly reactive to the seed protein. The results appear to support the conclusion that allergy to castor bean pomace may be hypersensitivity to one or more of several components of the seed, pollen, or female blossoms.

The exchange of materials was approved by the U. S. Department of Agriculture and the U. S. Public Health Service. The U. S. Customs Service approved entry of the sera, duty free, for research purposes. William G. Murray performed the photographic services.

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Altered Mesothelial Permeability in the Guinea Pig Following Bilateral Vagotomy.* (28218)

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The acute hemorrhagic pulmonary edema observed after bilateral vagotomy in certain species is probably part of a generalized edema involving many tissues(1). Mechanisms proposed for the lung edema(2) can be considered under 2 headings: (a) increased filtration pressure at the pulmonary capillary-alveolar barrier, and (b) increased permeability of the membranes making up the capillary and alveolar walls. This study subjected the latter proposal to analysis.

Methods used to study the permeability of vascular walls are usually indirect and only semi-quantitative. A technique has been developed in this laboratory(3,4) for measuring *in vitro* the permeability of rabbit mesentery. These studies emphasized similarities between the permeability characteristics of capillary walls and of this mesothelial membrane. The method was modified slightly to determine the influence of vagotomy, alone and in combination with other treatments, on the permeability of mesentery excised from guinea pigs. Quantitative data are presented here to show that vagotomy does influence mesentery permeability.

Methods. Guinea pigs, 400 to 600 g, anesthetized with ether were subjected to midcervical bilateral vagotomy or a sham operation. Sham-operated animals were sacrificed at appropriate times by a blow on the back of the head. Immediately after sacrifice or death due to pulmonary edema, a portion of mesentery free of macroscopically visible blood vessels and fat was excised and mounted in a diffusion cell free of hydrostatic or osmotic gradients(5). The ions Rb^{86} and p^{32}-orthophosphate migrate independently across the mesentery apparently by passive diffusion(3, 4). Krebs-Ringer bicarbonate (pH 7.4) with trace amounts of the radioisotopes made up the superfusion solution. Tracer substances passing from the superfusate (source solution)

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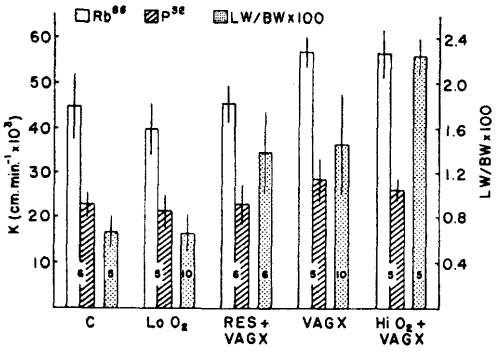

FIG. 1. Mean permeability coefficients (left ordinate) and mean lung-to-body weight ratios (right ordinate) for all groups of guinea pigs studied. The treatment to which each group was subjected is indicated on abscissa. Vertical lines at top of each bar indicate standard deviations. Numerals within the bars indicate number of animals in each group. C = controls; RES = reserpine-treated; VAGX = vagotomized; Lo O_2 = exposure to an atmosphere low in oxygen; Hi O_2 = exposure to an atmosphere high in oxygen.

to the sink solution (initially Krebs-Ringer bicarbonate free of radioactivity) were counted by circulating the sink solution continuously through a small plastic capsule in the well of a scintillation detector which was connected to an analytical rate meter and recorder. The mesothelial tissue was oxygenated constantly at 38°C. Results are expressed in terms of a permeability coefficient K in cm min^{-1}, representing the proportionality constant in the formula which equates instantaneous tracer ion flux to the concomitant tracer ion concentration gradient(5).

At autopsy the heart and lungs were removed, and the lungs were stripped of mediastinal tissue and weighed. Lung weight as a percent of body weight (LW/BW × 100) indicated the extent of pulmonary edema(2). Analyses of brain, heart, and adrenal catecholamines were performed by the trihydroxyindole method(6). The stomach and intestines were examined for congestion and ulceration.

Reserpine acetate (0.25 mg/kg/day) was injected intraperitoneally in one group of animals for three days prior to the above procedures. Other groups of guinea pigs were subjected to atmospheres of 4% oxygen-96% nitrogen or 70% oxygen-30% nitrogen. A nearly airtight box housing the animals was flushed continuously for 4 or more hours with the appropriate gas mixture. Oxygen concentrations were determined in a Scholander apparatus.

Several other techniques were used in an attempt to show permeability changes of membranous tissues in vagotomized guinea pigs: (a) the rate of diffusion of Evan's blue or trypan blue into the peritoneal cavity after intravenous injection of the dye; (b) the whole-blood/peritoneal-wash ratio of radio-iodinated serum albumin administered intravenously, as determined just after death due to vagotomy or sacrifice of sham-operated animals; (c) histological examination of mesentery by the method of Shelley and Florence(7) to observe the integrity of mast cells.

Results. Fig. 1 illustrates mean values of the permeability coefficients (K) and the mean lung-to-body weight ratio (LW/BW × 100) for each group of guinea pigs. Comparison of untreated (C) and vagotomized animals (VAGX) reveals statistically significant differences. The increases in K for Rb^{86} and in LW/BW × 100 were highly significant ($P < 0.01$), while the increase in P^{32} permeability was just significant ($P < 0.05$) as determined by the Student "t" test.

Because hypoxia developing concurrently with pulmonary edema might influence mesentery permeability, other guinea pigs were subjected to 4% oxygen at atmospheric pressure (Lo O_2 in Fig. 1) for at least 4 hours. This procedure was fatal to about one-third of the animals. Neither the mean K values for Rb^{86} or P^{32} nor the mean LW/BW × 100 differed from those of control animals. Another group of pigs was vagotomized and subsequently maintained in 70% oxygen until death (Hi O_2 + VAGX in Fig. 1). Control animals survived in this atmosphere for 6-8 hours without developing lung pathology. Effects of vagotomy were not retarded by high oxygen concentration in the inspired air; in fact, LW/BW × 100 for this group was significantly greater than for the group vagotomized and left in room air ($P < 0.01$). The mean K value for Rb^{86} was greater than the value of the control animals ($P < 0.01$), but the mean P^{32}-orthophosphate K value did not change significantly ($P > 0.05$).

Guinea pigs pretreated with reserpine for 3 days lost weight but were only slightly lethargic by the fourth day. After vagotomy these

animals died with pulmonary edema in the same time as non-reserpinized controls. The mean LW/BW × 100 of the group vagotomized after reserpine (RES + VAGX) was significantly elevated over that of the non-vagotomized control group C ($P<0.01$) and was virtually the same as for the group that was vagotomized without pretreatment (VAGX). The mean K values for Rb^{86} and P^{32} in reserpinized and vagotomized animals did not differ from the values of the untreated Group C. The Rb^{86} permeability coefficient, however, was significantly lower ($P<0.01$) than in vagotomized animals which did not receive reserpine. Because of large individual variation, the mean value for P^{32} of the drug-treated group was not significantly different from that of the group tested with vagotomy alone ($P>0.05$). Analysis of the organs from reserpinized guinea pigs demonstrated complete depletion of catecholamines in heart and brain and reduction of adrenal levels to about 25% of normal. In animals pretreated with reserpine but not vagotomized, the lungs were normal in weight, and no pathology of lungs, stomach, or intestines was discernible.

Postmortem examination of vagotomized animals often revealed ulceration, congestion, and hemorrhages in the gastric and intestinal mucosae. In general, the more intense and extensive these lesions were, the greater were the observed values of mesenteric permeability. Reserpine pretreatment protected vagotomized guinea pigs against the lesions of abdominal viscera, even though these animals exhibited diarrhea in response to the drug.

The integrity of cellular membranes in the guinea pig as determined by the less direct procedures described in the last paragraph of *Methods* was not measurably altered as a result of vagotomy.

Discussion. Vagotomy-induced increases in permeability of mesentery appear to support the hypothesis that post-vagotomy hemorrhage and edema in the lungs result from increased permeability of capillary-alveolar membranes. Exposure of non-vagotomized guinea pigs to low oxygen tensions (Lo O_2) did not alter lung weight or mesenteric permeability. Therefore, hypoxia developing concurrently with vagotomy-induced pulmonary edema is not a primary factor in producing these changes. The Hi O_2 + VAGX animals showed much greater lung weights than the VAGX group. Since exposure of non-vagotomized guinea pigs to 70% oxygen did not cause lung pathology, the increased level of inspired oxygen enhanced the development of lung edema initiated by vagotomy. Breathing 95-100% oxygen for prolonged periods (guinea pigs) or oxygen under high pressure (rats) causes pulmonary hemorrhage and edema(8,9). Perhaps the mechanisms by which vagotomy and oxygen poisoning produce lung edema are related.

Reserpine has been reported to inhibit the development of vagotomy-induced pulmonary edema in guinea pigs, but survival time compared to vagotomy controls was appreciably shortened(10). Vagotomy was performed shortly after administration of a single large dose of reserpine. In the present investigation smaller multiple doses of reserpine were injected in order to avoid marked depression, because anesthesia protects vagotomized guinea pigs from lung edema(11). This dosage schedule was still adequate to deplete tissues of catecholamines and probably also of 5-hydroxytryptamine (5-HT). Since reserpine pretreatment did not prevent pulmonary infiltration following vagotomy, body stores of catecholamines and 5-HT appear to be unrelated to the edema-producing process in the lungs.

On the other hand, reserpinized guinea pigs did not exhibit increased mesentery permeability as a consequence of vagotomy. This difference may have been due to the inability of the reserpinized animal to release large quantities of catecholamines. The stress of restraint greatly increases the incidence and severity of gastric ulceration in vagotomized guinea pigs(11). Furthermore, epinephrine may increase mesentery permeability when applied to the *in vitro* preparation(5).

An alternative explanation involves differential peripheral effects of an edema-producing factor postulated to be released from the brain stem as a result of vagotomy(12,13). This blood-borne substance might alter the gastrointestinal vasculature and the mesentery by activating catecholamine or 5-HT stores. The effect of the centrally-released substance on the pulmonary tissues might not

involve sympathetic amines, but might be mediated directly or through some other intermediate process. The above data certainly indicate that vagotomy-induced pathological processes in lung and mesentery are not identical.

Summary. The Rb^{86} and P^{32}-orthophosphate permeability of mesentery removed from vagotomized guinea pigs in terminal stages of pulmonary edema was greater than the permeability of mesentery from control animals. The exposure of guinea pigs to air diluted with nitrogen, producing a sometimes fatal anoxia, did not alter mesothelial permeability or lung weight. Exposure of vagotomized animals to an atmosphere rich in oxygen failed to prevent an increase in mesentery permeability or in lung weight. Vagotomy, however, did not alter the permeability of mesentery taken from reserpine-pretreated animals, although high lung weights indicated pulmonary edema. Because it is improbable that vagotomy affected the permeability *only* of mesenteric mesothelium, increased permeability of pulmonary membranes may play a role in vagotomy-induced pulmonary edema, whether or not hemodynamic abnormalities are also important. The results with reserpine, however, prove that the mechanism is not identical in lungs and mesentery.

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Rapid Appearance of Injected Fat in the Gut of the Rat. (28219)

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In studies undertaken to develop a method of measuring reticuloendothelial function in man, intravenous injections of fat emulsions were given to rats. This material was chosen since it has been used extensively for intravenous alimentation in man(1). The emulsion was specially prepared "Lipomul I.V.,"* a 15% emulsion of cottonseed oil, dispersed with Pluronic F-68 (non-ionic detergent) and lecithin in 5% dextrose. An oil soluble dye, "Fluorescent Green H. W. 185%"† was added to the oil prior to emulsification (20 mg/g cottonseed oil). At this low concentration the dye did not affect the stability of the emulsion and the ultimate distribution of the oil could be determined by following the distribution of fluorescent material.

The emulsion was injected into the femoral veins of rats (0.1 ml/100 g rat) and 0.1 ml samples were removed from the tail at time intervals. The samples were diluted to 25 ml with acetone and shaken for one hour. This

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† Supplied by Wilmot and Cassidy, Inc., New York.