whether the difference in porphyrin concentration in the kidney is due to differences in tubular reabsorption of uro- and coproporphyrin.

The high concentration of protoporphyrin in the liver parenchyma adjacent to the gallbladder suggests that considerable amounts of this porphyrin are reabsorbed from the gallbladder by way of the lymphatics.

Summary and conclusions. 1. Allylisopropylacetylcarbamid ("Sedormid") produces an hepatic form of porphyria in rabbits. 2. The livers of these animals contain large amounts of proto-, copro- and uroporphyrin, the latter chiefly in the form of non fluorescing precursors. Porphobilinogen is also present. 3. The protoporphyrin is excreted only, and the coproporphyrin chiefly, in the bile, most of the uro- type porphyrins appearing in the urine, in amounts ranging up to 60 mg in 24 hours. The latter consists mainly of type III isomers, but type I has also been identified in small amount. Large amounts of porphobilinogen are excreted in the urine. 4. The porphyrin content of erythrocytes, bone marrow, spleen, and brain is within normal limits. 5. Transient paresis of hind limbs, dilatation of the stomach, and constriction of the pylorus are noted, with irregular small bowel spasm. Death is invariably due to rupture of the stomach. 6. The possibility is discussed that the genesis of the porphyria is related to a primary effect of the Sedormid on the formation of iron porphyrin enzymes in the liver cell.

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Histamine Sensitivity and Anaphylaxis in the Pertussis-Vaccinated Rat.* (19988)

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The intact, white rat is known to be relatively insensitive to both histamine and anaphylactic shock. The resistance to both these insults can be significantly diminished by adrenalectomy(1-3) or hypophysectomy(3,4). This behavior is not unlike that exhibited by the mouse(5,6). In the latter species it has been reported that a preliminary inoculation of *Hemophilus pertussis* likewise diminishes the resistance to both histamine(7) and anaphylactic shock(8). The present report is concerned with the effect of *H. pertussis* vaccination on these insults in the white rat.

Methods and results. (1) Female, white rats of about 100 g weight were injected intra-

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TABLE I. Effect of Pertussis Vaccination on the Resistance of the Rat to Histamine.

Histamine phosphate, mg/kg	Mortality rate*	
	Control	Pertussis-vaccinated
187.5	0/10	0/10
375	0/10	
750	0/10	3/10
1500	2/10	13/17

* Mortality rate = number of animals dead after 24 hr/No. animals tested.

peritoneally (i.p.) with 25,000 million phase I *H. pertussis* organisms contained in a volume of 1 ml. On the fourth day after inoculation groups of animals were injected i.p. with various concentrations of histamine diphosphate solution in saline. As controls, unvaccinated animals were treated concurrently. The figures in Table I indicate the mortality rate, determined as the number of animals dead after 24 hr number of animals tested. It is apparent that *H. pertussis* is effective in lowering the resistance of the rat to histamine.

(2) A series of white rats of approximately the same weight received a single i.p. inoculation of 1 ml of a mixture containing 25,000 million *H. pertussis* organisms and 0.1 ml of horse serum. A control group received only the 0.1 ml of horse serum diluted to a 1.0 ml volume. On the tenth subsequent day both groups were challenged by the intravenous injection of 0.1 ml of horse serum. The results show a mortality rate of 0/27 for the control group as compared to 47/50 for the pertussis-inoculated group. Although the three surviving animals in the pertussis-vaccinated series showed symptoms of severe shock, only an occasional animal in the control group exhibited shock symptoms, always minimal. Thus, it has been shown that pertussis vaccination possesses the capacity of markedly increasing the anaphylactic sensitivity of the rat to an antigen.

(3) Two small groups of rats, vaccinated with pertussis and sensitized to horse serum, were given 25 mg cortisone subcutaneously 4 and 18 hr before challenge, respectively. The mortality rates were 6/6 and 2/5, respectively, thus suggesting that cortisone, in proper doses and at correct time intervals, may have the capacity of protecting the sensitized rat against fatal anaphylactic shock. The surviving animals all exhibited marked shock symptoms.

(4) Three rats of each of 5 experimental groups were sacrificed by asphyxiation with chloroform and immediately autopsied. These groups consisted of (a) normal, untreated animals, (b) animals inoculated with pertussis vaccine and sensitized to horse serum 10 days previously, (c) animals treated as in (b) but sacrificed during anaphylactic shock, (d) animals in histamine shock after pertussis vaccination and (e) unvaccinated, horse serum sensitized animals following challenge with horse serum. No pathological post mortem findings, gross or microscopical, were evident in rats of groups (a), (b) and (e). The animals of group (c) showed grossly, right heart dilation, collapsed lungs, congested liver, gut and brain and essentially normal adrenals and spleen. The gross post mortem findings of the animals in group (d) showed dilation of the right auricle, markedly hemorrhagic and somewhat collapsed lungs, markedly congested liver and brain and essentially normal adrenals and spleen. The microscopical changes of the latter two groups were strikingly similar. The vessels of the heart were distended with blood cells; there was some vacuolization with separation of the muscle fibers. The lungs were congested and there were areas of atelectasis, edema and dilated alveoli. Occasionally, about the bronchi was seen an infiltration of cells. The liver showed minimal congestive changes. The brain was edematous with meningeal congestion. There was marked congestion of the medulla of the adrenals with minimal cortical congestion. The spleens were essentially normal.

Summary. Inoculation of the white rat with *Hemophilus pertussis* increases its sensitivity to histamine. Pertussis mixed with horse serum markedly enhances the ability of the antigen to produce anaphylactic sensitivity.

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Mechanism of Anaphylaxis in the Rabbit. Further Evidence Against Plasma Protease Mechanism.* (19989)

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The theory that the development of anaphylaxis depends upon the activation of plasma protease (plasmin, or fibrinolysin) has numerous adherents. Although this theory lacks the support of direct and unequivocal evidence, and in spite of direct evidence in opposition(1), it enjoys sufficiently wide acceptance to be indicated as the probable mechanism of anaphylaxis in a recent review(3). The literature pertinent to the activation of plasma protease by immune reactions was recently reviewed briefly by Geiger(4), who, as a result of his own careful experiments, considered it "unlikely that anaphylactic symptoms in rabbits can be attributed solely to activation of plasma protease." In our studies of the mechanism of the anaphylactic reaction in the rabbit, we have utilized as a criterion the release of histamine from blood cells, which follows the addition of antigen to the blood from a sensitized rabbit *in vitro*. In an earlier publication(1), we indicated that the participation of plasma protease in the *in vitro* release of histamine in rabbit blood was doubtful because: 1. Excessive quantities of soybean trypsin inhibitor failed to inhibit the histamine release, and 2. Large amounts of bovine fibrinolysin failed to release significant amounts of histamine.

To obtain an even more direct type of evidence, we have now activated plasma protease of rabbit blood by means of streptokinase both *in vitro* and *in vivo*, and have compared the effects of antigen and streptokinase with respect to the activation of protease, the release of histamine *in vitro*, and the development of anaphylactic symptoms *in vivo*. The results of the *in vitro* experiments, Table I, indicate that there is a complete lack of correlation between histamine release and protease activation. Homologous antigen released a large amount of histamine and failed to activate a detectable amount of plasma protease; conversely, streptokinase markedly activated plasma protease and in so doing did not release significant amounts of histamine. From the data in Table II, it is apparent that there is no correlation between protease activation *in vivo* and the development of anaphylaxis. There is no significant difference in protease level between the blood of normal rabbits and blood withdrawn from challenged rabbits at the time of anaphylactic death, prior to death, or during severe anaphylactic symptoms. Conversely, rabbits treated with streptokinase showed no anaphylactic symptoms even though there was a several-fold elevation of the plasma protease level in all cases but one. The evidence presented here not only casts extreme doubt upon the plasma protease theory of the mechanism of anaphylaxis in the rabbit, but also calls for a more critical attitude toward this theory in relation to other species.

Experimental. The streptokinase (SK) preparation, kindly supplied by Mr. Frank Ablondi, of Lederle Laboratories, was dissolved in physiological sodium chloride solution immediately before use. The SK units indicated are Lederle units.

The details of rabbit sensitization, and the *in vitro* histamine release technic were presented previously(1,2). The *in vitro* histamine release was carried out both at 37.5°C,

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