chick and monkey, the former possibility being the more likely. In any case, the demonstration that *CPT* is distinctly less active than chlorguanide against infections with *P. cynomolgi* explains previous failures to isolate the hypothetical "active metabolite" of chlorguanide.

In conclusion some comment on the practical implications of the current findings should be made. The high activities of CPT and especially *DCPT* against infections with *P. gallinaceum* might suggest that these drugs would be a striking improvement over chlorguanide in the treatment of human malaria. Such optimism is not justified by the findings in *P. cynomolgi* infections, which in a wide experience have proved to be a highly reliable indicator of the value of drugs against human malaria. The demonstrations that in the simian disease *CPT* is distinctly less effective than chlorguanide and that *DCPT* has essentially the same effectiveness as this biguanide suggest that with respect to inherent antimalarial activity these metabolites would have little to offer in the treatment of human malaria.

Summary. The activities of the triazine metabolites of chlorguanide and dichlorguanide have been studied in *P. cynomolgi* infections in the rhesus monkey. The results show that the chlorguanide metabolite, *CPT,* has only one-half to one-fourth the activity of the parent drug, whereas the dichlorguanide metabolite, *DCPT,* has activity equal to that of chlorguanide. These findings are in marked contrast to reported results on *P. gallinaceum* infections in the chick, against which *CPT* and *DCPT* are respectively 10 and 100 times as effective as chlorguanide.

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Occurrence of Acute Pulmonary Edema in Experimental Alkalosis. (19626)

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In previous studies of experimentally induced tetany(1,2), it was found that venoclysis of solutions of sodium carbonate and sodium bicarbonate for the production of alkalotic tetany in cats frequently resulted in the appearance of gross lung edema. This edema resembled that produced by the administration of toxic doses of ammonium salts previously described and studied by several of us(3,4). The purpose of this report is to describe the experimental production of acute pulmonary edema with the alkaline salts of sodium together with some preliminary observations on the mechanism of its production.

Material and methods. The data presented in this paper are based on the study of 25 adult cats anesthetized with sodium pentobarbital (35 mg/kg). The trachea was cannulated in all experiments. In a number of experiments artificial respiration was provided

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through the tracheal cannula as positive pressure blasts from a Harvard type respirator pump. Alkalosis was produced in 20 cats by the continuous infusion of a 5% solution of sodium carbonate or an 8% solution of sodium bicarbonate into the femoral vein. From time to time venous blood was collected under mineral oil in a hypodermic syringe and the pH determined with the Beckman glass electrode pH meter. Hypocalcemic tetany was produced in 4 cats by venoclysis of a phosphate buffer with a pH of approximately 7.4 (3 g of monobasic sodium phosphate, 30 g of dibasic sodium phosphate in 600 cc of solution). In the fifth cat, hypocalcemic tetany was produced by venoclysis of a 2% sodium citrate. The rate of infusion was adjusted so that manifest tetany was present from 10 to 20 minutes and then slowed to maintain a steady state of tetany until the termination of the experiment. In 5 experiments the cats were pretreated with dibenamine (25 mg/kg in 2 cats, 40 mg/kg in 3 cats by intraperitoneal administration), an adrenergic blocking agent, 3 to 4 hours before the administration of sodium carbonate. Analysis of edema fluid for total protein content was carried out in 5 experiments with a modification of the Koch-McMeekin micro-Kjeldahl method(5) for nitrogen. Postmortem examination was performed with special reference to the thoracic viscera in all experiments. In a number of experiments a lobe of lung was ligated and fixed by immersion in 10% formalin, sectioned and stained with hematoxylin and eosin for microscopic examination.

Results. The characteristics of the tetany produced by this method have been described elsewhere(2). Seven cats were given an 8% solution of sodium bicarbonate by venoclysis. Of this group, 5 cats received 50 to 100 cc of solution over a period ranging from 20 to 100 minutes. The blood pH was raised from a normal of 7.45 $\pm$ 0.05 to 7.85-7.95. Gross pulmonary edema appeared in all 5 experiments. The remaining 2 cats were given 40 and 45 cc respectively of the sodium bicarbonate solution over a period of 2 hours. The pH of their blood did not exceed 7.75 and the degree of tetany developed was moderate. Pulmonary edema did not occur in these 2 animals.

Eight cats were given 35 to 100 cc of a 5% solution of sodium carbonate by venoclysis over periods ranging from 25 minutes to 120 minutes. Six of the 8 cats developed acute pulmonary edema. The pH of the blood was raised to 7.80 – 7.90 or more in these animals. Artificial respiration did not appear to influence the production of lung edema. The hypocalcemic tetany produced in four cats by venoclysis of a phosphate buffer, in one by a 2% solution of sodium citrate was not accompanied by pulmonary edema.

Because of the efficacy of dibenamine in preventing the lung edema produced by ammonium salts(4), dibenamine was employed in this study. Of five cats treated with dibenamine, four developed lung edema in the usual fashion upon administration of 5% sodium carbonate. The presence of the full effect of dibenamine was demonstrated in one of these animals by injection of 0.5 cc of a 1:10,000 solution of epinephrine intravenously, which produced a marked reduction in arterial pressure instead of the usual elevation.

In most of these experiments, the presence of lung edema first made itself known by the appearance of edema fluid in the tracheal cannula. This fluid was usually straw-colored and clear with a variable amount of foam, although occasionally the fluid was blood-tinged. Analyses for total protein carried out on samples of edema fluid collected in 3 experiments yielded the following: 0.8%, 1.0% and 1.4%. Edema fluid in 2 experiments in which animals were pretreated with dibenamine contained 4.6% and 4.9% protein. Upon autopsy and microscopic examination the lungs had the usual appearance of acute pulmonary edema with areas of congestion and hemorrhage.

Discussion. The administration of solutions of sodium bicarbonate and sodium carbonate by venoclysis in cats results quite consistently in the appearance of acute pulmonary edema. This phenomenon seems to have escaped notice. Other routes of administration for the sodium salts and other animal species have not been studied. The lung edema does not appear to be related to the tetany which is present in these animals, but

rather to the elevation in blood pH. Hypocalcemic tetany produced by venoclysis of solutions of phosphate or sodium citrate is indistinguishable from alkalotic tetany but does not eventuate in pulmonary edema. In our experience, the blood pH has to exceed 7.80 and has to be maintained for five minutes or longer before lung edema appears. Artificial respiration with positive pressure does not seem to inhibit this form of lung edema, although it has been reported to inhibit other types of experimental lung edema(6).

The relatively low protein content of the edema fluid indicates that a significant increase in alveolar capillary permeability was not present at the time the fluid was formed. However, the anoxia which follows the obstruction of alveolar spaces and the duct system by edema fluid quickly produces an increase in capillary permeability allowing an appreciable leakage of plasma proteins and often culminating in the rupture of capillary walls with consequent hemorrhage. The high protein content of the edema fluid in animals pretreated with dibenamine may be attributable to a more fulminating onset of lung edema with earlier anoxia. These results indicate that an increase in alveolar capillary permeability is not involved in the initiation of lung edema in alkalosis. The acute lung edema occurring in alkalosis resembles that produced by ammonium salts. Both are preceded by and associated with abnormal neuromuscular phenomena, tetany in the former and tonic and clonic convulsions in the latter (3) and the protein content of the edema fluid is relatively low(4). However, dibenamine, which blocks the excitor effects of sympathetic nerve impulses at the effector organs(7), is exceedingly effective in preventing ammonium lung edema(4), but is quite ineffectual in alkalosis lung edema. An understanding of the pathogenesis of this form of acute pulmonary edema awaits further investigation.

Summary. 1. Venoclysis of solutions of sodium carbonate and sodium bicarbonate in quantities sufficient to produce a severe alkalosis and tetany produced acute pulmonary edema in most cats. 2. This lung edema was not inhibited by artificial respiration nor by pretreatment with dibenamine. 3. The edema fluid contained very small concentrations of proteins, ranging from 0.8% to 1.4%. In two animals that had been pretreated with dibenamine the total protein approached 5%. 4. Severe hypocalcemic tetany produced by venoclysis of a phosphate buffer and citrate solution did not result in lung edema.

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Nature of an Accelerator of Prothrombin Activation Arising During Storage of Purified Prothrombin.* (19627)

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A most fruitful approach to the study of the mechanisms of blood coagulation has been the purification of some of its important components. For example, our laboratory has devoted much effort to the purification of prothrombin and to a study of its conversion to thrombin(1-4). Prothrombin has been separated from bovine plasma in sufficient quantity

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