15030 P

Clotting of Blood *In vivo* by Aqueous Homologous Lung Extract, Some Clinical Implications.*

A. B. Baker, H. H. Noran, and W. P. Larson.

From the Department of Neuropsychiatry and Bacteriology, University of Minnesota Medical School.

Pathological studies of the brain in patients dying of pneumonia encephalitis revealed primarily vascular thrombi and hemorrhages. The cerebral lesions were similar regardless of the etiological agent causing the pneumonia, thus suggesting that the cerebral lesions were probably produced by some product of the injured lung tissue.

In an attempt to produce experimentally the lesions of pneumonia encephalitis, rabbit lungs were homogenized with a tissue homogenizer which reduced the tissues to the consistency of a gruel. This homogenized tissue was then diluted 1 to 25 with saline solution and filtered through paper. When this saline extract was injected intravenously into rabbits in amounts of .5 to 1 cc, death ensued in from 30 seconds to 2 minutes. This rabbit lung extract proved to be rapidly fatal to all animals of the species producing nystagmus, ataxia, convulsions, and death. Intravenous injections of similar or larger amounts of extracts of other organs such as brain, liver, kidney, intestine, spleen, and nasal mucosa produced no untoward effect. In order to determine whether or not the toxic action of lung was species specific, rabbits were inoculated intravenously with a 1 to 25 aqueous extract of beef, pork, sheep, guinea pig, and human lung. Of these heterologous lung extracts only the beef lung proved toxic to rabbits, giving a delayed reaction with subsequent death of the animal. Additional proof of the species specificity of the lung extract was demonstrated by intravenous inoculation into guinea pigs and dogs of an aqueous extract of the homologous lung tissue. In each case the inoculated material caused rapid death of the animals. From these experiments it is apparent that lung tissue extract when injected intravenously is fatal to the homologous species. Subcutaneous and intraperitoneal injections even in massive doses were innocuous.

Animals sacrificed after receiving repeated sublethal intravenous doses of lung extract and finally killed with a lethal dose, revealed within the cerebral tissues lesions resembling those seen in human cases of pneumonia encephalitis. The vessels showed early thrombosis with a deposition of fibrin clot. Further proof that the observed reaction was due to clotting is supported by the observation that all symptoms were prevented by preliminary intravenous injection of 10 mg of heparin.

We were intrigued by the fact that lung extracts from animals of other species were innocuous even when given in much larger doses than the homologous lung tissue. Extracts of lung tissue, whether from the rabbit or guinea pig, cause blood to gel in a test tube almost instantly, regardless of the animal species from which the blood is derived. The contractility of these clots is rapid and extensive, often contracting to one-half of the original volume of the clots within 2 or 3 hours. It is, therefore, apparent that some factors are operative in the animal body which prevent clotting, which are not present in the test tube experiment. Rabbits which had received an intravenous injection of guinea pig lung extract were found to be protected when given intravenous doses of homologous lung tissue extract, provided an interval of about 10 minutes elapsed between the two injections. When the extracts of guinea pig and rabbit lungs were mixed and given simultaneously, death ensued promptly. It is, therefore, apparent that the guinea pig lung extract sets up a protective mechanism against the homologous lung extract within a period of 10 minutes. The same mechanism may be mobil-

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ized by the injections of fresh human and guinea pig sera. The protection is transient, lasting more than one hour but less than 4 hours. Inactivated human and guinea pig sera afford no protection. Whether the protective action is due to the complement in the fresh sera, or whether other thermolabile enzymes are responsible for the reaction, has as yet not been determined. We are not prepared at this time to identify the substance in the aqueous extract of lung tissue which initiates the clotting. Lung tissue extract which has been heated at 56°C for 30 minutes is inactive. This would suggest that either pro-thrombin or thrombin may be the substances responsible for the clotting since they are thermolabile, while kinases as a class are thermostabile. Further studies are now under way which, it is hoped, will throw light on this subject.

15031

Effects of Thiouracil on the Mammary Gland.*

J. F. SMITHCORS. (Introduced by S. L. Leonard.)
From the Department of Zoology, Cornell University, Ithaca, N.Y.

The thyroid-inhibiting substances, thiourea and thiouracil, induced hyperplasia of the thyroid, attended by typical symptoms of hypothyroidism as indicated by lowered metabolism, decreased food intake and retarded growth.[1-5] In treated animals no other tissues except the anterior lobe of the pituitary were reported altered histologically.[1,5] The weights of the pituitary, gonads, and adrenals of treated animals were in proportion to the decreased body weights. The physiological effects of the thyroid-inhibiting substances were nullified by giving thyroid hormone simultaneously.[2,3]

Since thyroidectomy in both male[6] and female[7] rats favored the stimulation of lobule-alveolar development and the inhibition of the extension of the ducts of the mammary glands, an investigation was made to compare the effects of thiouracil with those following thyroidectomy on the mammary structure of the rat.

Methods. Rats of the Long-Evans strain were arranged in groups of similar age and body weight, and as far as possible comparisons were made between animals of the same litter. Eighty-five rats of both sexes, with body weights ranging from 37-238 g, were used. In some experiments rats of both sexes were castrated before treatment and a few animals were thyroidectomized for additional controls. Since previous experience had shown that injections of estrogen magnified the effects of thyroidectomy on mammary growth,[6] several experiments were made in which total dosages of 50 γ of *a*-estradiol dipropionate† were injected during the last 10 days of the experimental period. In one group, thyroxin was administered at the rate of 5 γ daily to determine if the effects of thiouracil would be counteracted. This dose of thyroxin was found to nullify the effect of the doses of thiouracil given on the metabolic rate and thyroid

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† The estrogen alpha-estradiol dipropionate (Di-Ovocylin) was obtained through the courtesy of Dr. E. Oppenheimer of the Ciba Pharmaceutical Co., Summit, N.J.