that had not received any sodium salicylate, 15 showed anti-Rh agglutinins following the injection of rhesus blood. In the case of the rabbits these were stronger which suggests that the methods used on these animals were better suited for such experiments.

Of 18 animals which had received sodium salicylate during the period of immunization only 2 showed microscopic agglutination of Rh positive cells.

No free salicyl radical was found in any of the sera tested which suggests that *in vivo* salicylate inhibits the formation of agglutinins rather than their effect in the plasma.

These findings call for confirmation and salicylate prophylaxis for erythroblastosis fetalis is not suggested here. On the contrary, the toxicity of this drug is again[7] emphasized. However, these experiments intimate the possibility of a chemotherapeutic approach to the subject of iso-immunization.

Summary. In guinea pigs and in rabbits the formation of anti-Rh agglutinins following the injection of rhesus monkey blood cells appears to be diminished when sodium salicylate has been administered 3 days prior to and during the period of immunization.

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Biochemical Changes Following Poisoning of Rats by Alpha-naphthylthiourea.

K. P. DUBOIS, L. W. HOLM, AND W. L. DOYLE.
*From the University of Chicago Toxicity Laboratory.**

Alphanaphthylthiourea (ANTU) has been proposed as a rodenticide because of its effectiveness against Norway rats. Richter[1] has shown that poisoning by this compound is characterized by (a) development of intense pulmonary edema and pleural effusion, (b) marked resistance of herbivores in comparison to carnivores, (c) greater resistance of younger animals, (d) a rapid development of tolerance after repeated sublethal doses. These factors are individually significant in the action of many drugs. The present study indicates that ANTU profoundly alters the carbohydrate metabolism in poisoned animals and that the administration of cysteine counteracts these effects in rats.

Experimental. Purina Chow was used as diet for adult albino rats. ANTU was administered intraperitoneally in propylene glycol (5 mg ANTU per ml solvent). The solvent alone produced no observable effects. Under these conditions the LD-50 was approximately 3.0 mg per kilo. A dose of 10 mg per kg killed all rats between 6 and 24 hours after injection. Glucose was determined by the method of Folin and Malmros[2] and glycogen according to Good *et al.*[3] Our initial experiments consisted blood glucose determinations on rats prior to and 2.5 hours after injection of 10 mg per kg of ANTU. In 6 rats the average normal blood glucose rose from 68 ± 2 mg % to an average of 173 ± 18 mg % in 2.5 hours after poisoning. It was later observed that this initial hyperglycemia was followed by hypoglycemia which might be due to depletion of liver glycogen. Eight rats were fasted for 7 hours after which time 4 received 10 mg per kg of ANTU intraperitoneally. Food was withheld from both groups for another 8 hours after which

* This work was carried out under contract with the Medical Division of the Chemical Warfare Service.

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[2] Folin, O., and Malmros, H., *J. Biol. Chem.*, 1929, **83**, 115.

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TABLE I.
Effect of ANTU on Synthesis of Liver Glycogen.

Glucose schedule	Controls		ANTU—10 mg/kg	
	Rat No.	Glycogen %	Rat No.	Glycogen %
None	15	0.14	22	.11
	16	0.14	23	.07
0.15 g/hr for 2 hr before death	17	0.48	24	.09
	18	0.28	25	.12
" " " 4 " " "	19	0.95	26	.03
	20	1.20		
" " " 6 " " "	21	1.20	27	.10
			28	.05

TABLE II.
Effect of Cysteine on the Toxicity of ANTU.

Group	ANTU (mg/kg)	Cysteine (mg/kg)	Mortality	% Mortality
1	10	0	5/5	100
2	10	200	2/2	100
3	10	400	3/5	60
4	10	700	1/5	20
5	10	1000	0/5	0

time all of the animals were sacrificed by decapitation. The livers were removed and frozen on dry ice. Decapitation and removal of the livers was accomplished within 1 minute to prevent glycogenolysis. Whereas the average liver glycogen values for the control animals was 1.13% ± .25, that of the ANTU-poisoned group was only 0.019% ± .006, clearly indicating a depletion of liver glycogen in rats poisoned with ANTU.

The glycogenic activity of the liver of ANTU-poisoned animals was then examined. Fourteen female rats were fasted 16 hours after which time 7 rats were given 10 mg per kg of ANTU intraperitoneally. A 10% glucose solution was injected intraperitoneally at hourly intervals into the fasted controls and the ANTU-poisoned animals. All the animals were killed 6 hours after ANTU was injected and liver glycogen was determined as previously described. The quantity of glucose injected per rat and the results of the liver glycogen determinations are given in Table I. The animals which had received 10 mg per kg of ANTU were unable to deposit liver glycogen, while controls deposited glycogen after glucose injections.

Possible methods of counteracting ANTU poisoning are of interest not only with respect to the mechanism of action but also from the standpoint of obtaining therapeutic measures for accidental poisoning. It appeared possible that ANTU reacts with sulphydryl groups. Cysteine was the first sulphydryl compound tested. Rats were given 10 mg per kg of ANTU (5 mg per ml in propylene glycol) intraperitoneally. Varying amounts of cysteine (100 mg per ml in saline) were injected intraperitoneally into 5 groups of rats immediately after injection of ANTU. The results given in Table II show that cysteine, at a level of 1 g per kg effectively counteracted the lethal action of an LD-100 dose of ANTU, and partial protection was obtained by lower doses of cysteine in rats. Additional results indicate that intraperitoneal injection of cysteine is equally effective against ANTU administered by stomach tube. Protection to the same degree was not obtained in dogs receiving a lethal dose of ANTU.

Summary and Conclusions. The intraperitoneal injection of 10 mg per kg of ANTU into rats caused a marked rise in blood sugar from an average value of 68 mg % and 173 mg % in 2.5 hours. Liver

glycogen values fell from a normal of 1.13% to 0.019%. ANTU-poisoned animals were unable to deposit liver glycogen. While these experiments demonstrate a disturbance in carbohydrate metabolism, they do not prove that death from ANTU is due to these changes. In rats large doses of cysteine (1000 mg per kg) afforded protection from death against 10 mg per kg of ANTU. The relation between lung damage and impairment of glycolysis and/or respiration is under investigation.

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Modification of Anaphylaxis by Benadryl.*

J. A. WELLS, H. C. MORRIS, AND CARL A. DRAGSTEDT.

From the Department of Pharmacology, Northwestern University Medical School, Chicago, Ill.

It has been recently shown that beta-dimethyl aminoethyl benzhydryl ether hydrochloride (Benadryl) inhibits the action of histamine on the bronchi and ileum of the guinea pig.[1] The subsequent demonstration that this drug is capable of reducing the severity of anaphylaxis in the guinea pig[2] is in accordance with the repeated demonstration that anaphylaxis in the guinea pig is due, in large part, to bronchospasm resulting from the action of histamine which is liberated from the lung.[3-8]

We have demonstrated that Benadryl inhibits the vasodepressor action of histamine in the anesthetized dog and have suggested that this inhibition is due to competition of Benadryl with histamine for its site of action.[9,10] The purpose of the present investigation was to determine the effect of Benadryl against anaphylaxis in the dog, a condition which, as in the guinea pig, is intimately connected with the release and action of histamine.[11-15]

It has been shown that in fatal anaphylaxis in the dog from 3.2 to 4.7 mg of histamine per kilo (measured as acid phosphate) is liberated from the liver.[16] It is also known that such doses of histamine injected intravenously in dogs produce fatal shocks.[13,17] Therefore, preliminary to studies of anaphylaxis, a series of 8 dogs were injected intravenously with 4.5 mg of histamine acid phosphate per kilo. These animals were pretreated with a dose of Benadryl (10.0 mg

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