are necessary for the activation of thromboplastin: one supplied by the plasma and the other by the platelets. Our results confirm the finding that the platelet factor is quantitatively and qualitatively normal in hemophilia(2) and suggest that the plasma precursor of thromboplastin is normal in thrombocytopenic blood.

A few other data require comment. It will be seen that the addition of 1/20 volume of thrombocytopenic blood to hemophilic blood was sufficient to reduce the clotting time to normal but influenced only slightly the consumption of prothrombin. This indicates that the clotting time of whole blood is less accurate than the prothrombin consumption test as a procedure for the study of hemophilia.

The "accelerator effect" of serum was found to be very low in both hemophilic and thrombocytopenic sera, as previously shown by Alexander and de Vries(8,9). A normal "serum accelerator effect" could, however, be obtained by allowing thrombocytopenic and hemophilic bloods clot in the presence of thromboplastin. In our experiments, the "accelerator effect" of serum appeared to be indirectly proportional to the prothrombin activity of serum.

Summary. In both hemophilic and thrombocytopenic blood the defect of the clotting mechanism reflects a deficiency of active thromboplastin. Addition of thrombocytopenic blood to hemophilic blood results in a mixture in which the clotting time, clot retraction, prothrombin activity and "accelerator effect" of serum all become normal.

These findings support the theory that at least two factors are necessary for the formation of active thromboplastin: a plasmatic agent, deficient in hemophilia, and a platelet factor, defective in thrombocytopenic purpura.

8. Alexander, B. and de Vries, A., *Blood*, 1949, v4, 747.

9. Alexander, B. and de Vries, A., *Blood*, 1949, v4, 752.

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Tuberculin Reaction. IV. Failure of Pyribenzamine to Protect Against Systemic Tuberculin Shock.* (17663)

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The suppressing effect of antihistaminics on allergic reactions involving histamine or histamine-like substances is well established. Although there is no good evidence to indicate that histamine plays a role in the tuberculin reaction, it naturally becomes of interest to inquire whether antihistaminics will suppress the allergic reaction of tuberculin type sensitivity. Information on this point should be helpful in elucidating the mechanism of tuberculin-type reactions as well as being of possible immediate value in the treatment of diseases in which this type of sensitivity is present. These objectives have led to a limited number of investigations on the effect of various antihistaminics on the course of tuberculosis and cutaneous tuberculin sensitivity in experimental animals and man. The conflicting results of the French investigators have recently been summarized by Wissmer(1) who, in his own experiments, observed that oral administration of 500 mg/day of the powerful antihistaminic R. P. 3015 (dimethylaminoethylthio-diphenylamine) did not suppress cutaneous reactivity to tuberculin in either tuberculous or non-tuberculous patients. Sar-

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1. Wissmer, B., *La Revue d'Immunol.*, 1947, v11, 183.

ber(2) reported that subcutaneous doses of 50 mg/kg/day of Benadryl exert a definite suppression on the cutaneous tuberculin reaction of tuberculous guinea pigs. Friedman and Silverman(3) observed that Pyribenzamine given orally to a large group of tuberculin-positive pre-adolescent children in doses of 60 and 240 mg daily for 4 days did not exert any inhibiting effect on the cutaneous response to tuberculin. Millner and Hurst(4) have reviewed much of the recent literature on the use of antihistaminics in tuberculosis and presented their own observations that prolonged treatment of tuberculous adults with a combination of Neo-antergan and Phenergan in daily dosage of 300 mg and 25 mg respectively did not provide any conclusive evidence that the drugs were beneficial. These authors called attention to the observation emphasized by Rich(5) and many others that the cutaneous tuberculin test is often unreliable because of the lowering of the reactive capacity of the skin by nonspecific factors especially those which affect the circulation. It is apparent that the effects which antihistaminics may exert on the course of tuberculosis and tuberculin sensitivity have not been established.

The present investigation was conducted as part of a project on the mechanism of the tuberculin reaction. The systemic tuberculin test was employed as the measure of tuberculin sensitivity because it is commonly observed to be a more reliable measure of tuberculin sensitivity in experimental animals than the cutaneous test(6).

Experiments. In the first experiment 15 large guinea pigs weighing 600 to 1000 g were given an intraperitoneal dose of 2.8 mg of a young culture of the B.C.G. strain of *M. tuberculosis* var. *bovis*. Twenty-four days later the animals responded to the intracutaneous test with 1:100 Old Tuberculin† with strong reactions, 4 of which showed central areas of necrosis. On the 34th day, 11 of the animals were "protected" with a series of subcutaneous injections of Pyribenzamine‡ in doses expressed per kg body weight and timed with respect to the shock dose of tuberculin as follows: 2 mg 1 hour before shock; 4 mg 20 minutes before shock; 2 mg 1 hour after shock; 2 mg 2 hours after shock; 2 mg 3 hours after shock and finally 2 mg 4 hours after shock to the surviving pigs. All animals were given an intraperitoneal shock dose of 5 ml of 1:5 O. T. There was no difference in the reactions of the two groups and all animals developed typical severe tuberculin shock in from 3 to 4 hours. Of the Pyribenzamine-treated animals, one died during the 4th hour, one during the 5th hour, 2 during the 6th hour, 4 during the 8th hour, and 3 sometime between the 8th and 20th hours. The 4 unprotected controls died during the 4th, 5th, 9th, and 10th hours respectively.

A second experiment was conducted with 18 large guinea pigs similarly infected with B.C.G. They all gave 3+ to 4+ cutaneous reactions to 1:100 deglycerinated O.T. when tested on the 22nd day after infection. Twelve of the animals were given "protective" doses of Pyribenzamine at 2, 1, and 0 hours before the shock dose of 10 ml of 1:5 O.T., and 1 and 3 hours later. The remaining 6 unprotected controls were given the shock dose of tuberculin at the same time. All of these animals developed severe shock between the 2nd and 3rd hour. There was no significant difference in survival time of the treated and untreated animals. Further details on methods and the results of the experiment are given in Table I. Three non-tuberculous controls which received the same Pyribenzamine dosage as the animals of Group II shown in the table

2. Sarber, R. W., *Am. Rev. Tub.*, 1948, v57, 504.

3. Friedman, E., and Silverman, I., *Am. Rev. Tub.*, 1949, v60, 354.

4. Millner, T., and Hurst, A., *Dis. Chest*, 1949, v16, 870.

5. Rich, A. R., *The Pathogenesis of Tuberculosis*, pp. 368, 369, Charles Thomas, Springfield, Illinois, 1st Edition, 1944.

6. Hehre, E., and Freund, J., *Arch. Path.*, 1939, v27, 289.

† The Old Tuberculin used in these experiments was kindly supplied by the Lederle Laboratories of Pearl River, N. Y.

‡ The Pyribenzamine HCl was kindly supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE I.
Attempt to Protect Tuberculous Guinea Pigs Against Systemic Tuberculin Shock with Pyribenzamine.

No. of animals	Total dosage Pyribenzamine, mg/kg body wt	Time of death—hr after shock dose of O.T.
	Group I*	
2	5	8 to 20
4	5	4
	Group II†	
1	10	8 to 20
3	10	4
1	10	5
1	8	3
	Group III (controls)	
4	0	4
2	0	5

* Group I pigs received 1 mg/kg at each injection.
† Group II pigs received 2 mg/kg at each injection.

were unaffected by the shock dose of tuberculin.

Additional experiments were conducted on some 50 guinea pigs in which the total dosage of Pyribenzamine was varied from 4 to 12 mg/kg and spaced at intervals between 2½ hours before to 7½ hours after the shock dose of tuberculin. The shock dose of tuberculin was varied from 3.3 to 10 ml of 1:5 O.T. In no instance was there any evidence of protection by Pyribenzamine.

Summary. The results of the various experiments did not provide any evidence that Pyribenzamine protects against systemic tuberculin shock in the tuberculous guinea pig.

This is in contrast to the marked protection Pyribenzamine affords against active anaphylactic shock where as little as 1 mg/kg given subcutaneously 10 minutes before the shock dose of antigen may give full protection against fatal anaphylaxis(7). In our own experience, several properly-spaced doses of Pyribenzamine totalling 4 to 8 mg/kg given subcutaneously at intervals before and after a large shock dose of antigen prevents severe shock and death from both acute and protracted active anaphylaxis in the majority of highly sensitive guinea pigs(8).

The failure of Pyribenzamine to protect against systemic tuberculin shock is perhaps to be expected since no smooth muscle reaction or shock organ has ever been identified as taking part in this type of shock.

The results of the present experiments indicate that histamine or histamine-like substances do not play a significant role in tuberculin shock and support the concept that anaphylactic and tuberculin sensitivities are basically different.

7. Mayer, R. L., Huttrer, C. P., and Scholz, C. R., *Science*, 1945, v102, 93.

8. Weiser, R. S., unpublished work.

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