proffered in these experiments.

Summary and conclusions. The L.E. cell phenomenon has been produced experimentally in the skin of two normal human volunteers following inoculation of windows with the plasma of a patient with acute disseminated lupus erythematosus. *In vivo,* under the conditions of our experiments, the neutrophilic L.E. cell usually developed as the result of ingestion of other neutrophilic nuclear lobes or nuclei which had undergone a previous partial peculiar lysis. Less commonly the L.E. cell may represent the originally affected neutrophilic leukocyte in which lobar lysis is out of step in the individual nuclear lobes. The experiments described should provide a means of testing the proposed identity of the L.E. cells and the "hematoxylin staining bodies" of the diseased tissues in acute disseminated lupus erythematosus, an identity recently suggested by several workers(11,12).

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Received August 7, 1950. P.S.E.B.M., 1950, v75.

The Antipyretic Effect of Cortisone.* (18166)

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(Introduced by R. F. Loeb.)

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In various febrile illnesses, clinical improvement following the use of adrenocorticotrophic hormone (ACTH) or cortisone is usually associated with a decline in temperature to normal or near-normal levels(1). The decline occurs together with a striking diminution in the clinical and laboratory evidences of inflammatory activity. There have been several reports illustrating an antipyretic effect of ACTH without appreciable alteration in the course of the underlying disease. Thus, in pulmonary tuberculosis(2), pneumococcal pneumonia(3) and subacute bacterial endocarditis(4), the administration of ACTH was followed by apparent clinical well-being and rapid defervescence of fever, but cultures of the blood or sputum continued to be positive. Indeed, in one instance extension of the tuberculous process has been noted to occur during ACTH administration. In view of these observations, it became of interest to determine whether an antipyretic effect of cortisone could be experimentally demonstrated.

Exp. I. Thirty chinchilla rabbits of about 2 kg body weight were divided into two groups of equal number. Each animal of one group received an initial injection of 10 mg of cortisone acetate† intramuscularly, fol-

* This work is supported in part by the Helen Hay Whitney Foundation and the Masonic Foundation for Medical Research and Human Welfare.

‖ Fellow of the Commonwealth Fund.

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† Obtained from Merck and Company on recommendation of the Committee on Cortisone of the National Academy of Sciences, through funds allocated by the U. S. Public Health Service.

TABLE I. Effect of Cortisone on the Febrile Response of Rabbits to Pneumococcus Vaccine.

	1. (Day 3)		2. (Day 10)		3. (Day 12)	
	Control	Cortisone	Control	Cortisone	Control	Cortisone
No. of animals	15	15	12	13	10	5* 8 13†
Mean temp. °F before pyrogen	—	—	102.4	102.0	102.0	102.3* 101.4 101.8†
Mean temp. °F 2 hr after pyrogen	104.3	102.9	105.1	103.8	104.5	103.5* 103.1 103.3†
Mean temp. increment ± stand. error of mean	2.3 ± .25§	0.9 ± .15§	2.7 ± .17	1.8 ± .20	2.5 ± .18	1.2 ± .25* 1.7 ± .22
‡Diff. between means of control and cortisone-treated groups divided by stand. error of this diff.	4.8		3.6		4.1* 2.8	

All animals received 2 cc of pneumococcus polyvalent vaccine on Day 1, and 4 cc on Days 10 and 12. Cortisone-treated animals received 2.5 mg a day except as indicated.

* 10 mg a day for 3 days.

† Mean temp. of entire group, including animals receiving both 10 mg and 2.5 mg cortisone.

‡ Highly significant when the ratio is greater than 2.6.

§ For convenience of presentation, 102°F was used as the baseline temperature in this part.

lowed thereafter by a daily injection of 2.5 mg. On the third day of cortisone administration, both groups of animals received 2 cc of a polyvalent pneumococcal vaccine‡ intravenously. Rectal temperatures were found to reach a peak about two hours after the injection and to approach baseline in seven hours. Subsequently, eight and ten days later, after continued cortisone administration to the treated group of animals, 4 cc of pneumococcal vaccine was given intravenously to both groups and the rectal temperatures were again recorded. Therefore, the first febrile response was initiated after three days of cortisone administration, and the last one after twelve days of cortisone to the same animals. Five of the treated group of animals were given an increased amount of cortisone (10 mg per day) for the three days preceding the last injection of pneumococcus vaccine.

The febrile responses of the rabbits are presented in Table I. The temperatures are recorded in degrees Fahrenheit, less 100°, for convenience. It is evident that on each of the three occasions studied, the average febrile response of the cortisone-treated animals was 1.2° to 1.5° less than the control animals two hours after injection of the vaccine. These differences, although small, are highly significant statistically as indicated in the table. The differences between the mean temperatures of the control and cortisone-treated groups divided by the standard error of these differences range from 2.8 to 4.8. When the ratio is greater than 2.6, the probability of exceeding the difference by chance factors alone is less than 1 in 100.§ As further indicated in part 3 of Table I, the animals receiving 10 mg of cortisone for the last three days of the experiment showed a smaller increment in temperature from their baseline temperature than did the animals maintained on 2.5 mg daily, namely, 1.2° ± .25 as opposed to 1.7° ± .22.

Exp. II. A standardized pyrogenic assay procedure was employed(5). Two groups of 9 rabbits each (A and B) were given a pseu-

‡ Obtained from Dr. F. Kauffmann of the State Serum Institute, Copenhagen for use in experiments to be reported with Dr. M. Bjørneboe and Dr. H. C. Stoerk. (*J. Exp. Med.*, 1950, v93, No. 1).

§ We are indebted to Dr. J. Fertig, Professor of Biostatistics, Columbia University School of Public Health, for his help and criticism.

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TABLE II. Effect of Cortisone on the Febrile Response of Rabbits to Pseudomonas Vaccine.

Group	No. of rabbits	Procedure	Mean temp. rise in °F
A	9	Initial dose of pyrogen	2.5 ± .23
		2nd dose of pyrogen + cortisone*	1.3 ± .14
B	9	Initial dose of pyrogen	2.0 ± .20
		2nd dose of pyrogen + saline†	2.0 ± .18

* Received 5 mg cortisone subcut. for 3 days prior to the second dose of pyrogen.

† Received 1 ml 0.5% pyrogen-free saline for 3 days prior to the second dose of pyrogen.

An interval of 2 mo. elapsed between the 1st and 2nd doses of pyrogen.

domonas pyrogenic vaccine and their febrile response was recorded. Two months later the pyrogen was administered for the second time. The second febrile response could be expected to reproduce the first(5). However, on this second occasion, group A was pretreated for three days with 5 mg of cortisone (saline suspension 5 mg/ml/rabbit subcutaneously) while group B received subcutaneously 1 ml of a pyrogen-free 0.5% saline solution for three days prior to the administration of the pyrogen. Rectal temperatures were recorded. As is evident from Table II, the animals of group B reacted with striking conformity to their pattern of two months previously. The cortisone-treated group A, although previously found to have a slightly higher average febrile response than group B, manifested much less of a rise on this occasion. This result is statistically significant and in keeping with the observations in Exp. I.

Discussion. It is apparent that cortisone exerts a moderate antipyretic action. The quantitative aspects of this action have not been investigated. It seems likely, however, that the degree of antipyretic effect is related to the dose of cortisone administered. This is suggested by the fact that the animals receiving the larger dose of cortisone showed a smaller febrile response to the same dose of pyrogen.

Antipyretic drugs may exert their effects by a peripheral action on the tissues or a central action on the thermo-regulator centers of the hypothalamus. There is increasing evidence that cortisone alters and often inhibits the inflammatory reaction of tissues to injury(6), although this may not always occur(7). Fever as a sequel to inflammation is thought to result from the products of the inflammatory exudate(8), and inhibition of the latter may be expected to decrease the febrile response. In addition, cortisone is known to act upon the central nervous system as evidenced by the electroencephalographic changes and psychic disturbances(9) noted in treated patients. It would seem possible that both an anti-inflammatory and central action of cortisone may be responsible for the antipyretic effect.

Summary. In a controlled study, cortisone has been found to be antipyretic in rabbits given pneumococcal vaccine and a pseudomonas pyrogen. The mechanism for this effect is not known.

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Received July 31, 1950. P.S.E.B.M., 1950, v75.