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Prevention of Experimental Allergic Encephalomyelitis by Combination of Epinephrine and a Phenothiazine Derivative, Propiomazine* (33969)

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Experimental allergic encephalomyelitis (EAE) is an experimental autoallergy which has similarities to certain human disease. One such disease is acute disseminated encephalomyelitis that sometimes follows viral infections such as mumps or vaccinia. The disease cannot be transferred by serum from a sensitized animal, but can be transferred by sensitized lymphoid cells (1). The possible role of humoral antibody in the disease cannot be ruled out (2). The disease has been prevented by treatment with cortisone (3), corticotropin (4), and 6-mercaptopurine (5).

In other studies epinephrine given to newborn rabbits inhibited development of lymphoid tissue and humoral antibody but did not inhibit homograft rejection (6). A phenothiazine derivative, propiomazine (Largon, Wyeth), known to possess antihistaminic and other protective properties (7), produced similar results; moreover, there was prolonged homograft survival in newborn rabbits (8). When given alone, neither epinephrine nor propiomazine produced these effects in adult rabbits; however, the two drugs given as a mixture to adult rabbits inhibited production of humoral antibody (9). In the latter studies peripheral leukocyte counts (total and differential) and serum complement levels were unaltered by the drug mixture. The above prompted further study of the effects of the drugs on a tissue reaction such as EAE which is considered to be mediated primarily by cell bound antibody (1).

Materials and Methods. Thirty-six adult rabbits weighing 1.5–2 kg were used. These were divided into 3 groups of 12 each. The first was given an initial daily intraperitoneal injection of 20 mg of propiomazine and 0.5 mg of epinephrine for a period of 3 weeks. At the end of this time, the dose was increased to 40 mg of propiomazine and 1.0 mg of epinephrine for an additional 2 weeks prior to sensitization and until completion of the experiment. The second group received intraperitoneally 40 mg of propiomazine and 1.0 mg of epinephrine on the day of injection of antigen and daily throughout the duration of

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TABLE I. Prevention of Experimental Allergic Encephalomyelitis in Rabbits Treated with Propiomazine and Epinephrine.

Manifestation of disease[a]	Untreated	Treated 5 weeks prior to sensitization[b]	Treated from day of sensitization[c]
Paralysis	7	0	1
Neurologic signs[d]	3	0	2
No signs	2	12	9
Total no. of animals	12	12	12

[a] Animals were observed for presence of disease 18 days after sensitization.

[b] Treated with a daily injection of 20 mg of propiomazine and 0.5 mg of epinephrine for 3 weeks prior to sensitization. Beginning 2 weeks prior to sensitization the dose was increased to 40 mg of propiomazine and 1 mg of epinephrine and continued until completion of the experiment.

[c] Treated from day of sensitization with a daily injection of 40 mg of propiomazine and 1 mg of epinephrine until completion of the experiment.

[d] Spastic movements with tremors but without paralysis.

the experiment. The third group, used as controls, was given a daily intraperitoneal injection of normal saline. All injections were in a volume of 3.0 ml.

Antigenic material (homologous spinal cord and Freund adjuvant) for sensitization was prepared and administered by modification of methods previously described (5). The animals were observed through the eighteenth day after injection for evidence of paralysis, tremors, spasticity, or extreme hypertonicity. At the end of that time, sections of the brain and spinal cord were taken, processed, and stained with hematoxylin and eosin.

Results. Table I summarizes the effects of the drug mixture on EAE. When treated with the drug mixture for 5 weeks prior to injection of the antigen, none of the animals developed evidence of the disease. Of the 12 animals receiving the drug mixture on the same day as injection of antigen only 3 developed signs of the disease. In contrast, 10 of the 12 control animals demonstrated evidence of the disease and 7 of these developed frank paralysis of one or more of the extremities.

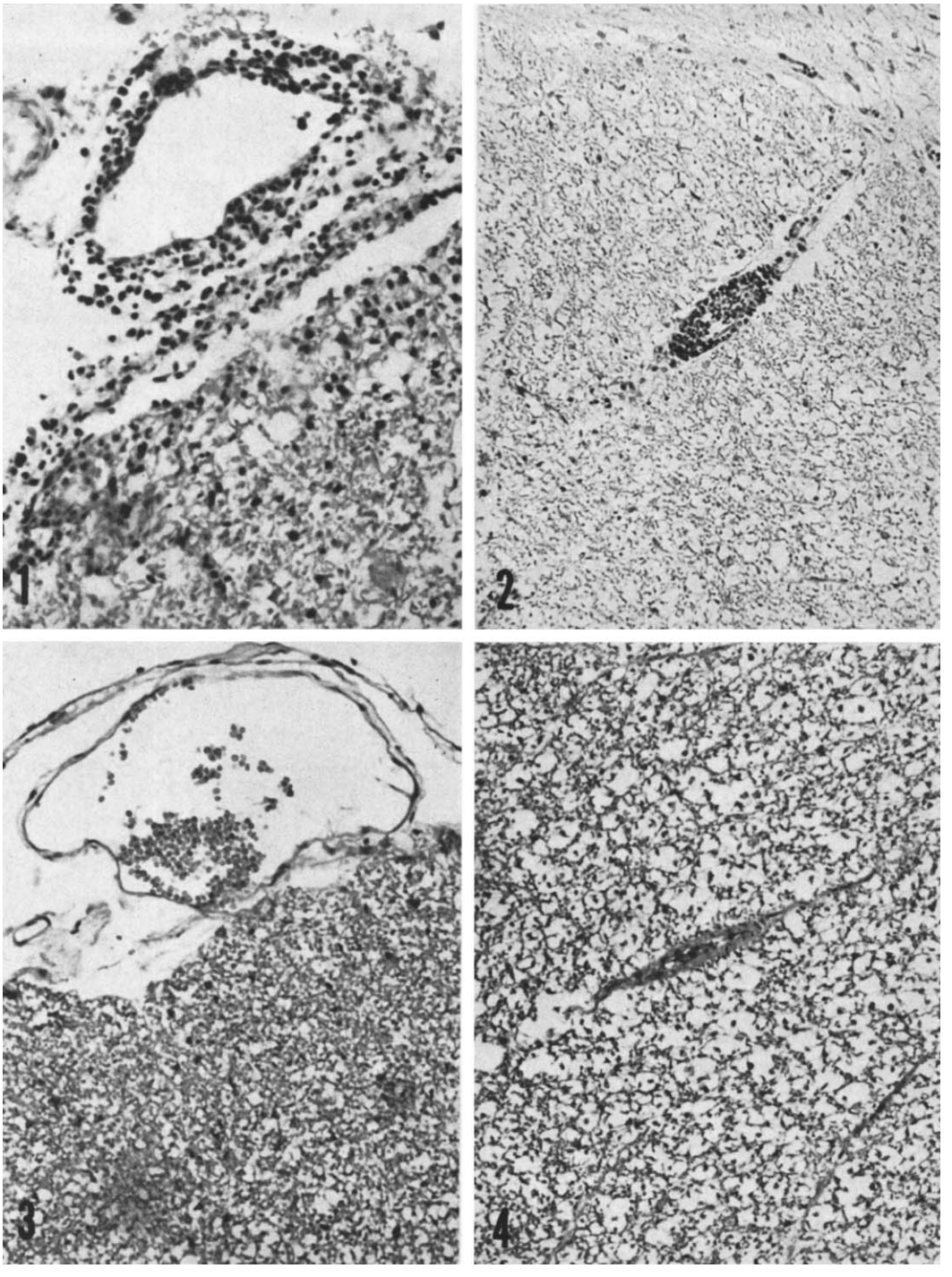
Figure 1 shows a peripheral area of brain from one of the control animals in which there is a distinct mononuclear leukocytic (lymphocytes and plasma calls) reaction about a meningeal vein and extending into the underlying brain. Similar perivascular cuffing was observed in other sections from deeper areas of the brains of the control animals (Fig. 2). Microscopic examination of similar areas from animals without clinical evidence of disease treated from 5 weeks prior to sensitization showed an absence of these changes (Figs. 3 and 4).

Discussion. The antihistaminic and other protective properties of phenothiazine derivatives alone are ineffective in preventing antigen–antibody mediated lesions as expressed by both actively and passively induced reactions (11).

Early investigators concluded that epinephrine acted as a specific trigger substance for release of adrenocorticotropic hormone and thereby caused release of cortisone (12). This concept has since been refuted (13, 14). It is recognized that prolonged stress will inhibit development of the immune response. Epinephrine is released in animals undergoing stress. Epinephrine alone fails to prevent formation of humoral antibody (9, 10).

Our observations (Table I) indicate that the propiomazine–epinephrine mixture possesses a strong inhibitory action upon development of EAE. This action is considered to be due to the ability of epinephrine to act on lymphoid cells to make them more susceptable to the actions of the propiomazine. A similar action may be the means by which epinephrine enhances the effects of cortisone (13, 15). These results suggest an approach to immunosuppression with less toxic effects than those caused by conventional drugs used for this purpose.

Summary. Rabbits treated with a mixture of propiomazine (a phenothiazine derivative) and epinephrine 5 weeks prior to sensitization with homologous spinal cord and adjuvant suspension failed to develop experi-



FIGS. 1 and 2. Brain sections from untreated rabbits sensitized by administration of homologous spinal cord and Freund adjuvant. Figure 1 shows a meningeal vein with surrounding mononuclear inflammation; ×220. Figure 2 shows a vein from the white matter with characteristic mononuclear perivascular cuffing; ×134. (All sections were stained with hematoxylin and eosin.)

FIGS. 3 and 4. Brain sections from rabbits sensitized with homologous spinal cord and Freund adjuvant but treated with propiomazine and epinephrine from 5 weeks prior to sensitization. Figure 3 shows a meningeal vein without perivascular inflammation; ×220. Figure 4 shows a vein from the white matter also without inflammation; ×134.

mental allergic encephalomyelitis (EAE). Of 12 animals begun on the drug mixture on the day of sensitization only 3 developed signs of the disease. Ten of 12 control animals showed evidence of the disease process while 7 of these showed frank paralysis of one or more extremities.

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