# Effects of Antihistamine–Epinephrine Combinations on Adjuvant Arthritis in Rats

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**Abstract** □ Three antihistaminic agents—diphenhydramine, doxylamine, and methapyrilene—alone and in combination with epinephrine, were examined for their effectiveness against adjuvant arthritis in Wistar–Lewis inbred rats. Simultaneous administration of diphenhydramine (75 mg./kg. p.o.) and epinephrine (0.4 mg./kg. s.c.) reduced adjuvant-injected and contralateral noninjected hind-paw volumes during a 21-day dosing period as compared to saline-treated controls; however, considerable toxicity was evident at these doses. Protective activity was minimal or absent when lower dosage combinations, which produced no overt evidence of toxicity, were employed. Doxylamine and methapyrilene combinations with epinephrine were effective only against the primary response to adjuvant administration, *i.e.*, early swelling of the injected paw. The individual agents were largely ineffective against adjuvant disease in rats. Sustained protective activity could be achieved only with dosage combinations that elicited toxic manifestations; thus, the potential utility of antihistamine–epinephrine combinations appears limited.

**Keyphrases** □ Antihistamine–epinephrine combinations—effect on adjuvant arthritis, rats □ Diphenhydramine with epinephrine—effect on adjuvant arthritis, rats □ Doxylamine with epinephrine—effect on adjuvant arthritis, rats □ Methapyrilene with epinephrine—effect on adjuvant arthritis, rats □ Arthritis, adjuvant—effect of antihistamine–epinephrine combinations, rats

Adjuvant arthritis in rats is a widely investigated animal model of chronic inflammation. This experimental disorder, induced by the injection of Freund's complete adjuvant or of mycobacteria suspended in oil, is considered to be an example of delayed hypersensitivity reactions against antigen(s) associated with the peptide-glycolipids of the wax D fraction of mycobacteria (1). The disease cannot be transferred by serum from a sensitized animal, but transmission *via* lymphoid cells has been achieved (2). Certain manifestations of adjuvant-induced arthritis resemble those of clinical disorders such as rheumatoid arthritis, ankylosing spondylitis, and Reiter's disease (3–6). Immunosuppressants and several other classes of drugs (7–9) have been employed to modify this inflammatory process.

Histamine has been implicated as one mediator of the early stages of allergic and inflammatory reactions (10). Experimental evidence exists that histamine antagonism can alter the development of adjuvant arthritis. Pelczarska (11) reported that hypostamine, a histidine decarboxylase inhibitor, reduced the inflammation and edema associated with the developing disease. Perrine and Takesue (12) and Walz *et al.* (9) demonstrated a similar effect with chlorpheniramine. In a series of publications, Henson and coworkers (13–15) examined the inflammatory suppressive effect of a combination of epinephrine and propiomazine, a phenothiazine derivative with antihistaminic and other "protective" properties (16). Henson and his associates postulated that epinephrine might enhance the anti-inflammatory activity of propiomazine by increasing lymphoid cell susceptibility to the actions of the latter drug. An inhibitory effect was demonstrated on the development of adjuvant arthritis (13), the Arthus reaction (14), and experimental allergic encephalomyelitis (15), and the suggestion was made that similar drug combinations might offer an alternative approach to treatment with toxic immunosuppressants.

The purpose of this study was to examine the effects of three antihistaminic agents—diphenhydramine, doxylamine, and methapyrilene—alone and in combination with epinephrine, on adjuvant arthritis in rats.

## EXPERIMENTAL

Male Wistar–Lewis inbred rats[1], weighing initially between 100 and 130 g., were used throughout this study. Food and water were supplied *ad libitum*. The animals were assigned randomly to treatment groups. Adjuvant arthritis was produced by a single subcutaneous injection (20-gauge needle) of 0.3 mg. of *Mycobacterium butyricum*[2], suspended in 0.06 ml. of light mineral oil NF, into a foot pad of the left hind paw. Normal control animals were injected with an identical volume of mineral oil vehicle.

Hind-paw volumes were determined plethysmographically by a modified method of Van Arman *et al.* (17). A mercury well was connected to a pressure transducer[3], and output from the transducer was led to a polygraph[4] equipped with a low-level d.c. preamplifier[5]. Throughout the study the instrument was calibrated repeatedly by the addition and withdrawal of a known volume of mercury. For measurement of hind-paw volumes, the hind limbs were immersed up to the hairline in the mercury pool. Determinations of paw volumes were made at regularly spaced intervals throughout each experiment; body weights were recorded daily.

The following drugs were studied: diphenhydramine hydrochloride[6], doxylamine succinate[7], methapyrilene hydrochloride[8], and epinephrine bitartrate. Phenylbutazone[9] was included as a positive control. Doses of all compounds are expressed as the base. Antihistaminic agents were dissolved in purified water; phenylbutazone was suspended with 2.5% (w/v) tragacanth with the aid of a blender[10]. Saline (0.9% NaCl), prepared with 0.15% sodium metabisulfite as a catecholamine antioxidant, was used as the solvent for epinephrine bitartrate.

Volumes administered were 10 ml./kg. orally and 2 ml./kg. subcutaneously. In each animal the oral dosing immediately preceded subcutaneous injection. Drugs were administered once daily for 21 consecutive days, beginning 1 day before adjuvant injection, with the exception of phenylbutazone in the methapyrilene–epinephrine study, in which the dosage schedule was reduced to 15 days. Normal control (mineral oil injected) and adjuvant control animals received 10 ml./kg. oral doses of water and 2 ml./kg. subcutaneous injections of saline–metabisulfite solution daily for the specified duration of each drug treatment schedule.

Six series of experiments were performed, four with diphenhydramine and epinephrine in various combinations and two with

[1] Obtained from Charles River Laboratories.
[2] Difco Laboratories, Detroit, Mich.
[3] Statham Model P23BC, 0–5 cm. Hg.
[4] Grass model 7B.
[5] Model 7P1B.
[6] Donated by Parke-Davis & Co., Detroit, Mich.
[7] Donated by Merrell-National Laboratories, Cincinnati, Ohio.
[8] Donated by Eli Lilly & Co., Indianapolis, Ind.
[9] Donated by Ciba Pharmaceutical Co., Summit, N. J.
[10] Waring.

Table I—Effect of Diphenhydramine and Epinephrine on Paw Edema and Body Weight Gain in Adjuvant Arthritic Rats

| Treatment | Dose, mg./kg. | Hind-Paw Volume, ml.[a] Injected (Left) Paw Day 4 | Injected (Left) Paw Day 11 | Injected (Left) Paw Day 18 | Injected (Left) Paw Day 26 | Noninjected (Right) Paw Day 11 | Noninjected (Right) Paw Day 18 | Noninjected (Right) Paw Day 26 | Body Weight Increase, g., Day 18 | Number Surviving at Day 26 / Number Tested |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphenhydramine | 75 | 1.48 | 1.93 | 2.78 | 3.46 | 1.43 | 2.16 | 2.65 | 31.5 | 11/14 |
| Diphenhydramine + epinephrine | 75 0.4 | 1.31[d] | 1.64[d] | 2.24[b] | 3.15 | 1.24[d] | 1.65[b] | 2.20[b] | 38.0 | 7/14 |
| Diphenhydramine | 37.5 | 1.63 | 2.07 | 2.87 | 3.65 | 1.56 | 2.29 | 3.00 | 28.4 | 8/15 |
| Diphenhydramine + epinephrine | 37.5 0.4 | 1.38[d] | 1.90 | 2.70 | 3.57 | 1.34[c] | 2.01 | 2.38 | 51.2 | 9/14 |
| Epinephrine | 0.4 | 1.54 | 2.00 | 2.79 | 3.75 | 1.47 | 2.20 | 3.07 | 38.9 | 12/14 |
| Phenylbutazone | 50 | 1.50 | 1.76[b] | 2.05[d] | 2.94[d] | 1.41 | 1.67[d] | 2.33[b] | 55.0 | 12/12 |
| Normal control | | 1.21[d] | 1.45[d] | 1.45[d] | 1.53[d] | 1.38[c] | 1.41[d] | 1.49[d] | 83.9 | 14/14 |
| Adjuvant control | | 1.57[e] (1.4–1.9) | 2.00 (1.7–2.4) | 2.91 (1.9–4.2) | 3.66 (2.3–4.6) | 1.55 (1.3–2.0) | 2.15 (1.4–2.7) | 2.83 (1.9–3.5) | 42.0 (13–77) | 14/14 |

[a] All values represent means of the number of rats surviving to Day 26. [b] Differs from adjuvant control at $p < 0.05$. [c] Differs from adjuvant control at $p < 0.01$. [d] Differs from adjuvant control at $p < 0.001$. [e] Mean (range in parentheses).

Table II—Effect of Diphenhydramine and Epinephrine on Paw Edema and Body Weight Gain in Adjuvant Arthritic Rats

| Treatment | Dose, mg./kg. | Hind-Paw Volume, ml.[a] Injected (Left) Paw Day 4 | Injected (Left) Paw Day 11 | Injected (Left) Paw Day 18 | Noninjected (Right) Paw Day 11 | Noninjected (Right) Paw Day 18 | Body Weight Increase, g., Day 18 | Number Surviving at Day 18 / Number Tested |
|---|---|---|---|---|---|---|---|---|
| Diphenhydramine + epinephrine | 75 0.4 | 1.66[d] | 1.89[c] | 2.93[b] | 1.32[d] | 2.15[b] | 49.3 | 11/11 |
| Diphenhydramine + epinephrine | 75 0.2 | 1.64[d] | 1.95[b] | 3.33 | 1.37[d] | 2.50 | 54.1 | 11/11 |
| Diphenhydramine + epinephrine | 75 0.1 | 1.68[d] | 1.97 | 3.20 | 1.37[d] | 2.32 | 55.4 | 13/13 |
| Diphenhydramine + epinephrine | 75 0.05 | 1.79 | 2.03 | 3.47 | 1.35[d] | 2.64 | 42.2 | 12/12 |
| Adjuvant control | | 1.93[e] (1.6–2.3) | 2.17 (1.8–2.6) | 3.63 (2.8–4.7) | 1.63 (1.4–2.1) | 2.89 (1.5–4.0) | 42.5 (24–72) | 11/11 |

[a] All values represent means of the number of rats surviving to Day 18. [b] Differs from adjuvant control at $p < 0.05$. [c] Differs from adjuvant control at $p < 0.01$. [d] Differs from adjuvant control at $p < 0.001$. [e] Mean (range in parentheses).

either doxylamine–epinephrine or methapyrilene–epinephrine. The selection of doses was based upon preliminary dose-range studies, wherein the drugs were administered from 1 to 4 days. In these studies, the minimum symptomatic doses were approximated for each of the three antihistamines, alone and in combination with epinephrine (0.4 mg./kg.). Henson and Brunson (13) stated that repeated administration of epinephrine, at a dose of 0.5 mg./kg. s.c., produced about a 50% incidence of mortality. In the present experiments, epinephrine was employed at doses ranging from 0.05 to 0.4 mg./kg.

All paw volumes and body weight data represent mean values derived from the number of rats surviving at the termination of the experimental period. Statistical significances of differences between drug-treated and adjuvant control animals were determined by an analysis of variance.

## RESULTS

**Development and Course of Adjuvant Disease**—Subcutaneous injection of adjuvant produced swelling of the injected hind paw within 24 hr. This initial inflammatory reaction (primary response) usually reached a peak at Day 4 and became stabilized at Days 7–11. Thereafter, a rapid and marked further increase in swelling developed. Progression of the disease was followed to Day 26, at which time hind-paw volumes had increased 110–280% above normal paw volumes prior to adjuvant injection. Swelling of the contralateral noninjected limbs and nodules on the ears and tail appeared in approximately 90% of the animals between Days 7 and 11 and increased progressively in severity to Day 26. Paw volumes of the noninjected hind limbs ranged from 60 to 235% above normal. Enlargement of both noninjected and injected paws, which occurred from Day 7 and thereafter, was designated as the secondary response and constituted the disseminated disease. In rats with adjuvant disease, the gain in body weight was significantly diminished in comparison to normal control animals.

**Diphenhydramine in Adjuvant Disease**—Table I contains a summary of results obtained with diphenhydramine administered alone and in conjunction with epinephrine. The hind-paw and body weight gain values represent data pooled from two replicate experiments.

A combination of diphenhydramine (75 mg./kg. p.o.) and epinephrine (0.4 mg./kg. s.c.) significantly reduced noninjected and injected paw volumes during the 21-day period of dosing as compared to saline-treated adjuvant control animals. On Day 26, injected paw volumes of drug-treated animals were not significantly different from controls. A lower dose of diphenhydramine (37.5 mg./kg.), in combination with epinephrine, was active only against the primary response. The apparent effectiveness of these treatments was tempered by the observed toxicity.

Additional studies were performed to determine whether protective activity could be obtained at essentially nontoxic doses of the drug combination. Epinephrine, at doses ranging from 0.05 to 0.4 mg./kg., was administered in conjunction with diphenhydramine at doses of 75 mg./kg. (Table II) and 18.8 mg./kg. (Table III). Mortality did not occur in either of these 18-day studies, in contrast to the previous 26-day experiments (Table I).

The duration of protective activity of epinephrine with diphenhydramine, 75 mg./kg. (Table II), was related to the dose of epinephrine. The regimen of diphenhydramine, 75 mg./kg., with epinephrine, 0.4 mg./kg., was effective throughout the 18-day experimental period. Doses of 0.2 and 0.1 mg./kg. of epinephrine in conjunction with 75 mg./kg. of diphenhydramine reduced paw volumes only to Day 11; the lowest dose of epinephrine (0.05 mg./kg.) in combination with 75 mg./kg. of diphenhydramine was largely ineffective. With the exception of a statistically significant decrease

Table III—Effect of Diphenhydramine and Epinephrine on Paw Edema and Body Weight Gain in Adjuvant Arthritic Rats

| Treatment | Dose, mg./kg. | Hind-Paw Volume, ml.[a] Injected (Left) Paw Day 4 | Injected (Left) Paw Day 11 | Injected (Left) Paw Day 18 | Noninjected (Right) Paw Day 11 | Noninjected (Right) Paw Day 18 | Body Weight Increase, g., Day 18 | Number Surviving at Day 18 / Number Tested |
|---|---|---|---|---|---|---|---|---|
| Diphenhydramine + epinephrine | 18.8 0.4 | 1.64[b] | 2.28 | 3.52 | 1.56 | 2.42 | 54.7 | 11/11 |
| Diphenhydramine + epinephrine | 18.8 0.2 | 1.66 | 2.29 | 3.45 | 1.52 | 2.44 | 49.1 | 11/11 |
| Diphenhydramine + epinephrine | 18.8 0.1 | 1.73 | 2.31 | 3.98 | 1.51 | 2.47 | 45.8 | 11/11 |
| Diphenhydramine + epinephrine | 18.8 0.05 | 1.89 | 2.52 | 4.00 | 1.60 | 2.64 | 35.0 | 11/11 |
| Diphenhydramine | 18.8 | 1.85 | 2.66 | 4.02 | 1.51 | 2.59 | 33.6 | 11/11 |
| Adjuvant control | | 1.92[c] (1.5–2.6) | 2.44 (1.6–4.1) | 3.58 (2.1–4.4) | 1.53 (1.2–1.9) | 2.46 (1.5–3.2) | 42.4 (14–87) | 11/11 |

[a] All values represent means of the number of rats surviving to Day 18. [b] Differs from adjuvant control at $p < 0.05$. [c] Mean (range in parentheses).

Table IV—Effect of Doxylamine and Epinephrine on Paw Edema and Body Weight Gain in Adjuvant Arthritic Rats

| Treatment | Dose, mg./kg. | Hind-Paw Volume, ml.[a] Injected (Left) Paw Day 4 | Injected (Left) Paw Day 11 | Injected (Left) Paw Day 18 | Injected (Left) Paw Day 26 | Noninjected (Right) Paw Day 11 | Noninjected (Right) Paw Day 18 | Noninjected (Right) Paw Day 26 | Body Weight Increase, g., Day 18 | Number Surviving at Day 26 / Number Tested |
|---|---|---|---|---|---|---|---|---|---|---|
| Doxylamine | 100 | 1.64 | 2.11 | 3.21 | 3.59[b] | 1.37 | 2.21 | 2.70 | 39.1[b] | 7/8 |
| Doxylamine + epinephrine | 100 0.4 | 1.30 | 1.90 | 3.10 | 4.20 | 1.20 | 1.50 | 2.20 | 36.0 | 1/8 |
| Doxylamine | 50 | 1.83 | 2.19 | 3.38 | 3.90 | 1.49 | 2.31 | 2.60 | 33.5 | 8/8 |
| Doxylamine + epinephrine | 50 0.4 | 1.53[c] | 2.20 | 3.30 | 4.15 | 1.45 | 2.33 | 2.75 | 47.3[b] | 6/6 |
| Epinephrine | 0.4 | 1.47[b] | 1.93 | 2.90 | 3.80 | 1.37 | 2.30 | 2.97 | 48.3 | 3/8 |
| Phenylbutazone | 50 | 1.56[d] | 1.85 | 2.50[d] | 3.41[d] | 1.34 | 1.79[b] | 2.27[b] | 43.5[b] | 8/8 |
| Normal control | | 1.38[d] | 1.54[d] | 1.61[d] | 1.73[d] | 1.45 | 1.48[d] | 1.57[d] | 98.9[d] | 7/8 |
| Adjuvant control | | 1.85[e] (1.6–2.2) | 2.00 (1.7–2.3) | 3.51 (2.8–4.1) | 4.11 (3.4–4.6) | 1.44 (1.2–1.8) | 2.37 (1.3–3.0) | 3.16 (1.5–4.4) | 29.7 (21–39) | 7/8 |

[a] All values represent means of the number of rats surviving to Day 26. [b] Differs from adjuvant control at $p < 0.05$. [c] Differs from adjuvant control at $p < 0.01$. [d] Differs from adjuvant control at $p < 0.001$. [e] Mean (range in parentheses).

in injected paw volumes at Day 4 in rats treated with the high dose of epinephrine (0.4 mg./kg.) in conjunction with 18.8 mg./kg. of diphenhydramine, combinations of epinephrine with this dose of diphenhydramine did not evidence protective activity against adjuvant arthritis (Table III).

**Doxylamine and Methapyrilene in Adjuvant Disease**—Evaluation of doxylamine and methapyrilene, alone and in combination with epinephrine, revealed that these treatments had little effect on the progression of adjuvant disease. For example, doxylamine (50 mg./kg.) in combination with epinephrine (0.4 mg./kg.) reduced the primary edema only at Day 4 (Table IV). Similarly, methapyrilene (15 and 30 mg./kg.) in combination with epinephrine, and methapyrilene alone (30 mg./kg.) reduced inflammation of the injected hind paw at Day 4 (Table V). No other significant differences from adjuvant controls were noted with respect to primary or secondary reactions. Animals treated with doxylamine (100 mg./kg.) and doxylamine (50 mg./kg.) in combination with epinephrine evidence significantly greater body weight gain than the adjuvant controls; a similar pattern was observed with methapyrilene (30 mg./kg.) and methapyrilene (15 mg./kg.) in combination with epinephrine. The combination of doxylamine (100 mg./kg.) and epinephrine (0.4 mg./kg.) was extremely toxic; 87% of the animals in this group died prior to termination of the experiment.

In all experiments, phenylbutazone (50 mg./kg.) significantly reduced both injected and noninjected hind-paw volumes as compared to adjuvant control animals. When phenylbutazone was given for 21 days, activity persisted during the latter stages of the 26-day experimental period (Tables I and IV); when the dosage schedule was reduced to 15 days, activity was noted only against the primary response (Table V). Extended treatment with 50 mg./kg. of phenylbutazone was not associated with grossly apparent toxicity. Epinephrine (0.4 mg./kg.) alone was essentially inactive against adjuvant disease; however, this dose produced overt toxicity.

## DISCUSSION

The combination of epinephrine and diphenhydramine afforded the greatest degree of protection against adjuvant arthritis in this series of experiments. However, this protective activity was frequently associated with evidence of drug-induced toxic effects. Animals treated with high dose combinations (diphenhydramine, 37.5 and 75 mg./kg., with epinephrine, 0.4 mg./kg.) lost their well-groomed appearance, became lethargic, and exhibited respiratory difficulties. Alopecia of the neck and back (epinephrine injection site) was apparent after 8–12 days of dosing and was not reversible upon cessation of treatment. When mortality occurred, it was preceded by dyspnea, cyanosis, loss of righting reflex, and clonic convulsions. Autopsy revealed macroscopic cardiac lesions and pulmonary hemorrhage, a profile that suggests that lethality might be due primarily to epinephrine rather than to the antihistamine.

Attempts to dissociate drug toxicity from protective activity by reducing the dose levels of both diphenhydramine and epinephrine proved largely unsuccessful. Although lower dosage combinations of diphenhydramine and epinephrine did not produce overt toxicity (based on gross appearance, behavior, body weight gain, and survival incidence), they failed to provide sustained inhibition of adjuvant disease.

Henson and Brunson (13) proposed that the enhanced activity of propiomazine with epinephrine resulted from an epinephrine-induced increase in lymphoid cell susceptibility to anti-inflammatory actions of propiomazine. The possibility exists that antihistamine–epinephrine combinations may act through a similar

Table V—Effect of Methapyrilene and Epinephrine on Paw Edema and Body Weight Gain in Adjuvant Arthritic Rats

| Treatment | Dose, mg./kg. | Hind-Paw Volume, ml.[a] Injected (Left) Paw Day 4 | Injected (Left) Paw Day 11 | Injected (Left) Paw Day 18 | Noninjected (Right) Paw Day 11 | Noninjected (Right) Paw Day 18 | Body Weight Increase, g., Day 18 | Number Surviving at Day 18 / Number Tested |
|---|---|---|---|---|---|---|---|---|
| Methapyrilene | 30 | 2.09[b] | 2.60 | 4.05 | 1.67 | 2.93 | 5.9[c] | 9/9 |
| Methapyrilene + epinephrine | 30 0.4 | 1.97[d] | 1.97 | 3.73 | 1.40 | 2.78 | −0.5 | 9/10 |
| Methapyrilene | 15 | 2.66 | 2.56 | 3.94 | 1.73 | 2.94 | −3.0 | 9/9 |
| Methapyrilene + epinephrine | 15 0.4 | 2.04[b] | 2.18 | 4.15 | 1.47 | 2.95 | 8.6[d] | 8/10 |
| Phenylbutazone | 50 | 2.08[b] | 2.38 | 3.44 | 1.64 | 2.51 | 13.7[b] | 9/9 |
| Normal control | | 1.64[d] | 1.68[d] | 1.87[d] | 1.58 | 1.78[d] | 71.9[d] | 9/9 |
| Adjuvant control | | 2.42[e] (2.0–2.9) | 2.18 (1.7–2.6) | 3.69 (2.9–4.3) | 1.54 (1.3–2.1) | 2.89 (1.4–3.4) | −12.0 (−35–+5) | 9/9 |

[a] All values represent means of the number of rats surviving to Day 18. [b] Differs from adjuvant control at $p < 0.05$. [c] Differs from adjuvant control at $p < 0.01$. [d] Differs from adjuvant control at $p < 0.001$. [e] Mean (range in parentheses).

mechanism, but alternative explanations are also plausible. Their effectiveness may be due to competitive inhibition of histamine by the antihistaminic agent, together with physiological antagonism by epinephrine of certain critical effects of histamine, *i.e.*, microvascular dilation and increased capillary permeability. In support of this concept, all antihistamine–epinephrine dosage combinations examined in this study significantly reduced the primary or early response to adjuvant, a phase during which histamine mediation of the inflammatory reaction is reputedly prominent (18). Of the three antihistaminic drugs evaluated, only diphenhydramine in combination with epinephrine produced extended protection; the reason for this longer duration of activity is not apparent. This protective effect against adjuvant disease could be achieved only at dosage levels that elicited overt toxic manifestations. Thus, the potential usefulness of such a drug combination appears limited.

## REFERENCES


(1) C. M. Pearson, F. D. Wood, and A. Tanaka, *Prog. Ann. Meet. Amer. Rheum. Ass., Abstr.*, **1968**, 57.

(2) B. H. Waksman and C. Wennerstein, *Int. Arch. Allergy Appl. Immunol.*, **23**, 129 (1963).

(3) C. M. Pearson, *Arthritis Rheum.*, **7**, 80(1964).

(4) C. M. Pearson and F. D. Wood, *ibid.*, **2**, 440(1959).

(5) R. S. Jones and J. R. Wood, *ibid.*, **6**, 23(1963).

(6) E. M. Glenn, B. J. Bowman, W. Kooyers, T. Koslowska, and M. L. Myers, *J. Pharmacol. Exp. Ther.*, **155**, 157(1967).

(7) M. L. Graeme, E. Fabry, and E. B. Sigg, *ibid.*, **153**, 373(1966).

(8) C. A. Winter and G. W. Nuss, *Arthritis Rheum.*, **9**, 394 (1966).

(9) D. T. Walz, M. J. DiMartino, and A. J. Misher, *J. Pharmacol. Exp. Ther.*, **178**, 223(1971).

(10) W. W. Douglas, in "The Pharmacological Basis of Therapeutics," 3rd ed., L. S. Goodman and A. Gilman, Eds., Macmillan, New York, N. Y., 1965, pp. 621, 622.

(11) A. Pelczarska, *J. Pharm. Pharmacol.*, **21**, 692(1969).

(12) J. W. Perrine and E. I. Takesue, *Arch. Int. Pharmacodyn. Ther.*, **174**, 192(1968).

(13) E. C. Henson and J. G. Brunson, *Ann. Rheum. Dis.*, **29**, 185(1970).

(14) E. C. Henson, C. G. Evers, and J. G. Brunson, *Int. Arch. Allergy Appl. Immunol.*, **34**, 458(1970).

(15) E. C. Henson and J. G. Brunson, *Proc. Soc. Exp. Biol. Med.*, **131**, 752(1969).

(16) M. Brunaud, V. Segal, J. Navarro, and M. Aurousseau, *Arch. Int. Pharmacodyn. Ther.*, **119**, 367(1959).

(17) C. G. Van Arman, A. J. Begany, L. M. Miller, and H. H. Pless, *J. Pharmacol. Exp. Ther.*, **150**, 328(1965).

(18) H. O. Schild and D. A. Willoughby, in *Proc. Int. Pharmacol. Meet. 3rd, Vol. II*, "Immunopharmacology," H. O. Schild, Ed., Pergamon Press Ltd., London, England, 1968, pp. 104, 105.


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