regular 2-week intervals. It is apparent that the response of reticulocytes, red cells, and hemoglobin is influenced slightly by the dosage of cobalt but that the average figure for the 3 groups is close to that elicited by the maximum dose of 10.0 mg per kg of body weight. The curves for body weight and leucocyte count similarly show no marked differences as affected by the 3 doses given. While the experimental animals failed to gain as much weight as the controls, no other deleterious effects were noted, which indicates a low systemic toxicity from cobaltous chloride in adult animals in the dosage administered.

Table I presents the numerical data for each animal relative to the blood volume at the end of 32 weeks. The striking increase in total red cell mass and the slight but consistently lower plasma volumes are worthy of note.

Table II contains data derived from cell counts, measurements of the mean cell diameter, hematocrit and hemoglobin content. The cell size, cell volume, cell thickness, absolute hemoglobin content and hemoglobin concentration were calculated according to Wintrobe.[12] Regarding the size, shape and hemoglobin content of erythrocytes from animals with cobalt polycythemia the following facts have come to light as a result of this study: 1. Although the mean cell diameter remains normal the cell volume increases by about one-third, a change which is proportionate to the increase in cell thickness. 2. The absolute amount of hemoglobin per red cell remains unchanged.

The blood volume per kilogram of body weight of these animals compares favorably with that found in the more extreme cases of polycythemia vera in man.[13]

Detailed histopathologic studies are in progress as well as further work on the components of red cells and plasma.

Conclusions. 1. Injections of cobaltous chloride continued over a period of 8 months without apparent serious toxicity has resulted in persistent polycythemia during this period of a degree comparable to that occurring in polycythemia vera in man. 2. The average increases in blood volume and total erythrocyte mass as compared with controls was 80% and 192% respectively, due entirely to increase in erythrocytes since plasma volume decreased 16% on the average. 3. The erythrocyte of polycythemic animals as compared with the normal increased in volume 41% due almost entirely to an increase in the thickness of the cell. The hemoglobin content remains essentially unchanged.

[12] Wintrobe, M. M., *Clinical Hematology*, Lea & Febiger, 1942.

[13] Gibson, J. B., 2d, Harris, A. W., and Swigert, V. W., *J. Clin. Invest.*, 1939, **18**, 621.

15250

Influence of Dimethylaminoethylbenzhydryl Ether Hydrochloride Upon Histamine Flare Reactions.

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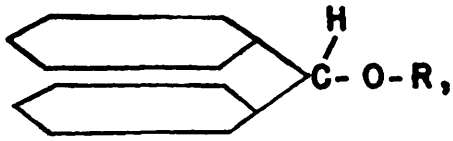
The alleviation of histamine induced anaphylaxis in guinea pigs has been described following the use of a number of benzhydryl alkamine ethers of the general formula, where R represents a carbon chain carrying a primary, secondary or, in most cases, a tertiary nitrogen atom.[1,2,3] In one of the

[1] Loew, E. R., Kaiser, M. E., and Moore, V., *J. Pharm. and Exp. Therap.*, 1945, **83**, 120.

[2] Loew, E. R., and Kaiser, M. E., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 235.

[3] Sharp, E. A., personal communication.



most potent of these preparations, the R grouping is beta-dimethylaminoethyl.[1,2]

The present experiments have been conducted to determine the degree to which histamine flare reactions in the skin can be influenced by the oral administration of dimethylaminoethyl benzhydryl ether hydrochloride* to human subjects.

Methods and Materials. Human beings who were not known to have any allergic disease or other condition associated with a recognizable disturbance of the autonomic nervous system were subjected to histamine flare tests before, during, and after the oral administration of varied amounts of dimethylaminoethyl benzhydryl ether hydrochloride.

To examine skin sensitivity to histamine, a drop of 1% aqueous histamine solution and a drop of physiological saline for control purposes were each applied to the volar surface of the forearm. A slight depression of the skin under each drop was then made by pressure from a sterilized ordinary pin, care being taken not to cause any bleeding. After 5 minutes, the drops were gently wiped away, and the size and shape of the wheal and erythema were outlined with ink. This outline was accurately transferred for permanent record by the use of transparent paper and india ink. At the end of 10 minutes a similar reading and recording of the wheal and erythema was made. The size of the wheal and of the erythema were approximated by multiplying the diameters at right angles by each other. The values thus obtained in each subject in the fore period were arbitrarily taken as 100%, and all subsequent values computed as fractions or multiples thereof.

Results. The data (Table I) reveal that a daily dose of 150 mg of dimethylaminoethylbenzhydryl ether hydrochloride was capable of a definite reduction in the sensitivity of the skin to histamine, and that 300 mg daily might effect a maximum response if sufficiently long continued. A diminution in both wheal and erythema has been observed after 3 days of treatment with 150 mg daily. A complete disappearance of both wheal and erythema has been noted in some cases after 10 days of treatment with 300 mg. The continued administration of the drug, at least for periods up to 18 weeks apparently does not alter the striking anti-histamine action. As a rule a maximum effect can be attained with a dose of 300 mg daily, although this may not be reached quite so promptly as when 400 mg are given.

When the drug is discontinued, the response to histamine is accentuated as compared with the control period. In one instance, the "release" phase was associated with a flare and wheal that were approximately 500% of the original. In every case, this phasic effect is seen, but the response to histamine usually returns to normal within a few days after dimethylaminoethy benzhydryl ether hydrochloride has been stopped. In no previously normal subject was this increased response to histamine associated with any clinical allergic manifestation.

Discussion. Undoubtedly the anti-histamine action of dimethylaminoethylbenzhydry ether hydrochloride accounts for the clinic success attendant upon its application to several types of skin condition.[4,5] The high therapeutic index, the failure for tolerance

* Generous supplies of this material under the name, Benadryl, have been made available through the courtesy of Dr. E. A. Sharp, of Parke, Davis & Co., Detroit, Mich.

4 Curtis, A. C., and Owens, B. B., *Univ. Hosp. Bull.*, Ann Arbor, 1945, **11**, 25.

5 O'Leary, P. A., and Farber, E. M., *Proc. Staff Meetings of the Mayo Clinic*, 1945, **20**, 429.

6 McElin, T. W., and Horton, B. T., *Proc. Staff Meetings of the Mayo Clinic*, 1945, **20**, 417.

7 Koelsche, G. A., Prickman, L. E., and Carryer, H. M., *Proc. Staff Meetings of the Mayo Clinic*, 1945, **20**, 432.

8 Williams, H. L., *Proc. Staff Meetings of the Mayo Clinic*, 1945, **20**, 434.

9 Logan, G. B., *Proc. Staff Meetings of the Mayo Clinic*, 1945, **20**, 436.

10 McGavack, T. H., Elias, H., and Boyd, L. J., *J. Lab. and Clin. Med.*, in press.

TABLE I.
Erythema and Wheal Reactions to the Intracutaneous Administration of Dimethylaminoethyl Benzhydryl Ether Hydrochloride.

No. subjects	Dosage (mg/daily)	Duration treatment (weeks)	Degree of Reaction (% of control)‡ Erythema 5 min.	Erythema 10 min.	Wheal 5 min.	Wheal 10 min.
10	0	—	100	100	100	100
5	150	0.6	105	63	63	75
5	300	2.0	4	37	3	7
3	400	2.3	24	33	4	8
6	—	0.5†	138	155	185	168
2*	—	1.0†	493	300	104	104

* Both of these patients had received treatment for more than 11 weeks, and at the 400 mg dosage level for not less than 2 weeks.
† Length of time since treatment was discontinued.
‡ Figures represent averages for the number of subjects indicated.

to develop, even on long continued administration, and the clinical results thus far attained,[4-10] warrant further extensive clinical trial of the drug in a wide variety of allergic conditions.

Summary. Dimethylaminoethylbenzhydryl ether hydrochloride orally administered in sufficient amounts is capable of completely suppressing the sensitivity of the skin to histamine, at least as expressed by the wheal and flare reaction. In limited trials, this effect appears to have widespread clinical application.

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The Reputed Antipyretic Action of Camphor.*

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Many current textbooks of pharmacology contain statements to the effect that camphor is antipyretic and useful in the symptomatic treatment of fevers. Thus for example, in Sollmann's treatise[1] we find, "Camphor Spirit is a household remedy in colds, bronchitis, etc. It is thought to be somewhat expectorant, diaphoretic and antipyretic (Binz, 1875 and 1877)." In older books, published 100 years or more ago, less cautious statements are made, for there the virtues of camphor as an antipyretic are panegyrised. Camphor was first used in China and brought to Europe by the Arabians.[2] Its introduction as an antipyretic seems to have been based upon at least two properties, first that it has some antidiarrheic activity and secondly that spirit of camphor, applied to the skin, has a cooling effect. There has been no recent work done to check these ancient conceptions of the antipyretic value of camphor.

In the work described in this report, some 500 animals, including albino rats, guinea pigs, rabbits and cats, were rendered febrile by the intramuscular injection of peptone (B.D.H.) in a dose of 1 g per kilo body

* This research was aided financially by a grant from the Committee of Scientific Research, Queen's University. A report of the work was presented at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics, Inc., Atlantic City, March, 1946.

1 Sollmann, T., *A Manual of Pharmacology*, 6th ed., Saunders, London, 1942.

2 Flückiger, F. A., and Hanbury, D., *Pharmacographia*, Macmillan, London, 1879.