rhage in shock dogs reported in this investigation supports this interpretation.

Summary. 1. Seven control dogs anesthetized with morphine sulfate and sodium barbital were bled to death at the rate of 2 cc/kg/minute. Six dogs similarly anesthetized were first subjected to a standardized hemorrhagic shock procedure and were then reinfused with all blood previously withdrawn. They were bled to death 60 minutes after reinfusion at the same rate as the normal dogs. In each instance, the residual blood volume was determined after death by perfusion with a sodium chloride-sodium citrate solution under 150 mm Hg pressure. The residual volume was partitioned into fractions obtained from (1) the superior cava-azygos, (2) the inferior cava, and (3) the cardio-pulmonary systems.

2. The average total blood volume of the control animals slightly exceeded that of the shock animals, but the difference is not believed significant. The bleeding volume was significantly greater in the control animals, and correspondingly the residual volume was greater in the shock animal.

3. There was a significant shift in the distribution of the residual volume in the animal dying in shock. As compared to the controls, there was a marked increase in the residual volume of blood retained in the inferior vena cava territory and an accompanying decrease in the superior cava-azygos system.

4. The conclusion is reached that the reduced lethal bleeding volumes after transfusion of dogs in hemorrhagic shock are not significantly due to reduction in total blood volume but to pooling of greater volumes of residual blood in the splanchnic vessels. Changes in the cardio-pulmonary residual volumes are too small to affect lethal bleeding volumes.

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15856

Anesthetic Action of Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in the Skin of Human Beings.*

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Beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) is one of the recent members of a series of synthetic antihistamine compounds which currently are receiving clinical trial and are showing promise of usefulness in the treatment of some types of allergy.[1-7] In regard to anesthetic action, only the first of this series of compounds, thymoxyethyldiethylamine (929 F), has been studied in detail. This compound was shown by Bovet and Staub[8,9] to possess antihista-

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1 McElin, T. W., and Horton, B. T., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 417.

2 O'Leary, P. A., and Farber, E. M., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 429.

3 Koelsche, G. A., Prickman, L. E., and Carryer, H. M., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 432.

4 Williams, H. L., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 434.

5 Logan, G. B., *Proc. Staff Meet., Mayo Clin.*, 1945, **20**, 436.

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7 Feinberg, S. M., *J. A. M. A.*, 1946, **132**, 702.

8 Bovet, D., and Staub, A.-M., *C. R. Soc. de biol.*, 1937, **124**, 547.

9 Staub, A.-M., and Bovet, D., *C. R. Soc. de biol.*, 1937, **125**, 818.

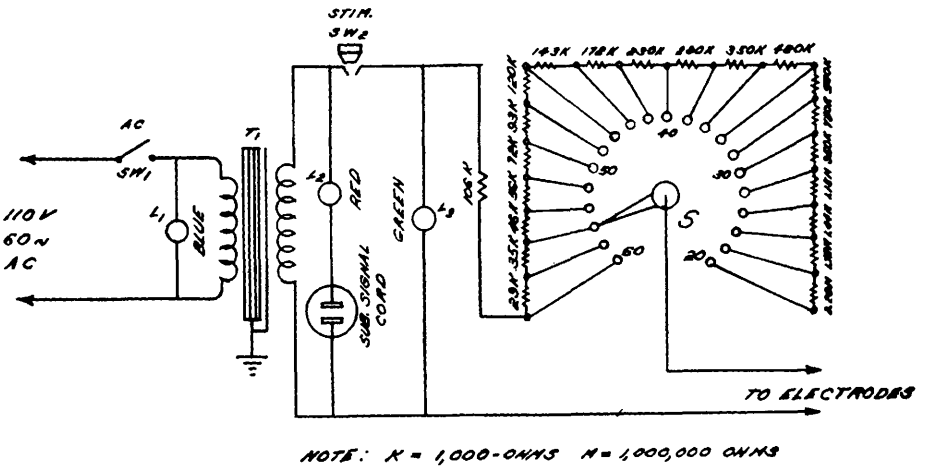

FIG. 1.

Schematic diagram of circuit of algesimeter. T_1, isolating transformer 1:1 ratio; S, calibrating attenuator for adjusting current; L_1, blue pilot lamp indicating current to the primary of T_1; L_2, red pilot lamp which lights when subject signal button is pushed; L_3, green pilot lamp which lights when stimulating switch SW_2 is closed.

mine and antianaphylactic properties. The anesthetic action of thymoxyethyldiethylamine was discussed by Staub[10] who noted also the marked intolerance of various animal species, including man, to its administration both locally and by mouth. Burchell and Varco[11] observed that large doses of the drug given subcutaneously to dogs produced a general analgesic effect which, according to their tests, was incomplete. In the skin of man they found no evidence of local anesthesia after subcutaneous injection, while intracutaneous injection produced anesthesia only in the raised portion of the epidermis. Rosenthal and Minard[12] noted a generalized elevation of the cutaneous threshold for pain in dogs which received thymoxyethyldiethylamine, and Rosenthal, Minard and Lambert[13] obtained similar results when studying visceral sensation in the dog. During these investigations it was reported that thymoxyethyldiethylamine in 0.5% solution, when given intracutaneously, possessed the anesthetic potency of a 1.0% solution of procaine.[12] Climenko, Homburger and Messer,[14] studying the pharmacologic action of thymoxyethyldiethylamine, noted that extremely inflammatory reactions, erythema, edema, necrosis and sloughing were produced in the skin when the drug was administered subcutaneously to mice, a result which confirmed similar studies made by Staub.

During an investigation of the antihistamine action of β-dimethylaminoethyl benzhydryl ether hydrochloride, hereafter referred to as benadryl, in the skin of human subjects, it was found that this drug also exhibits a pronounced local anesthetic action. A study then was undertaken to determine the effectiveness of the compound as a local anesthetic agent in the skin and to compare its potency in this regard with that of procaine.

Methods and Procedures. The anesthetic action of benadryl injected into the skin was tested in 10 healthy men and women whose ages ranged from 18 to 30 years. All tests were made at a constant room temperature

10 Staub, A.-M., *Ann. Inst. Pasteur*, 1939, **63**, 400, 485.

11 Burchell, H. B., and Varco, R. L., *J. Pharm. and Exp. Therap.*, 1942, **75**, 1.

12 Rosenthal, S. R., and Minard, David, *J. Exp. Med.*, 1939, **70**, 415.

13 Rosenthal, S. R., Minard, David, and Lambert, Edward, PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 317.

14 Climenko, D. R., Homburger, E., and Messer, F. H., *J. Lab. and Clin. Med.*, 1941, **27**, 289.

of 78°F and a relative humidity of 40%. The subjects lay supine on comfortable beds in the presence of minimal extraneous stimuli during the tests and for at least 30 minutes before the beginning of the tests.

Pain thresholds were determined by use of a simple type of algesimeter. The apparatus consisted of the necessary components to convert 110 volt, 60 cycle alternating current to an adjustable constant current at the subject electrodes. The current range of the device was from 10 microamperes to 1 milliampere subdivided in 20 steps such that each step gave approximately 26% (2 db) greater current than the preceding lower step (Fig. 1). Stimulation was applied by means of a smaller monopolar electrode approximately 3 mm in diameter; the large indifferent electrode was held in the hand of the subject on the side opposite to that being tested for anesthesia. The stimulating electrode was applied firmly but with minimal pressure to the skin.

An area approximately 2 by 12 cm midway between the elbow and the wrist on the flexor surface of either forearm was used in all tests. All stimuli were applied for one second and repeated 2 times with 3-second intervals between periods of stimulation. The subject then reported on the presence or absence of pain. As a rule, groups of 3 stimuli were repeated each minute, throughout the test. The strength of stimulus which was uniformly painful over the designated area was first established. Injections were then given and their effect on the sensation elicited by the threshold stimulus of the area determined. To assist the subject, sensation in intact skin was repeatedly compared with that in injected skin. When no sensation was felt the area was regarded as anesthetized. In most tests, as confirmation of the presence of anesthesia, one or two stimuli of 400 microamperes were applied. In many instances, as anesthesia subsided a period of altered sensation occurred during which stimuli sufficient to produce pain in normal skin were perceived as dull or blunt but not painful sensations in injected skin.

All injections were made intracutaneously, the amount of each was 0.3 cc and all were delivered from a 1 cc tuberculin syringe through a 27-gauge needle. Each injection produced a wheal about 1.5 to 2 cm in diameter. All dilutions of drugs to be injected into the skin were prepared in physiologic saline solution.

Since both benadryl and procaine were to be given intracutaneously, it was first necessary to determine the effect of the intracutaneous injection of an inert solution on cutaneous sensation. For this purpose physiologic saline solution was used and pain thresholds in normal skin and in skin injected with saline solution were determined on 3 successive days for each of the 10 subjects. Then the effects of benadryl and procaine were studied. In each test a similar procedure was followed. On one forearm a control wheal was made by injection of saline solution and 5 wheals were made by injection of benadryl in dilutions of 1:500, 1:1,000, 1:5,000, 1:10,000 and 1:20,000. Sensation in the benadryl-induced wheals was compared to that in the surrounding intact skin and in the control wheal induced by injection of physiologic saline solution. Each wheal was tested every 60 to 90 seconds. The duration of complete anesthesia and the duration of altered sensation were noted for each dilution of benadryl. When these tests were completed, a similar series was carried out on the other forearm, using procaine in dilutions of 1:100, 1:200, 1:400, 1:800, 1:1,600 and 1:3,200.

To determine the local irritant effects of benadryl, each of the 10 subjects received intracutaneous injections of 0.3 cc of benadryl in dilutions of 1:100, 1:500 and 1:1,000. Occurrence of immediate local reactions was noted and daily observations were made until all effects had subsided.

Results. Control determinations of pain thresholds. Control tests of pain thresholds were made on 3 successive days on the forearms of each subject. The minimal stimulus which consistently gave a sensation of pain in the forearms was quite constant from day to day in each subject, although there was considerable variation between subjects. In

TABLE I.
Comparison of Anesthetic Properties of Benadryl and Procaine.
(Both drugs and all dilutions tested on the same 10 subjects.)

	Mean duration of action in minutes					
	Procaine in dilutions of					
Action	1:100	1:200	1:400	1:800	1:1,600	1:3,200
Anesthesia	15.8 ± 0.7*	12.2 ± 0.6	9.8 ± 0.4	5.4 ± 0.6	0.3 ± 0.2	
Altered sensation	7.5 ± 1.5	6.4 ± 0.7	5.3 ± 0.7	5.0 ± 1.0	6.0 ± 0.7	2.1 ± 0.8
Total effect	23.3 ± 1.6	18.6 ± 0.8	15.1 ± 0.8	10.4 ± 0.8	6.3 ± 0.7	2.1 ± 0.8
	Benadryl in dilutions of					
Action		1:500	1:1,000	1:5,000	1:10,000	1:20,000
Anesthesia		12.3 ± 1.2	9.2 ± 0.6	2.8 ± 0.6	0.6 ± 0.2	
Altered sensation		6.4 ± 1.0	5.8 ± 0.6	7.4 ± 1.1	5.1 ± 1.1	2.4 ± 0.7
Total effect		18.7 ± 1.8	15.0 ± 0.9	10.2 ± 0.8	5.7 ± 1.0	2.4 ± 0.7

* The figure after the ± is the standard error of the mean.

the group of 10 subjects the strength of stimulus required consistently to produce pain ranged from 100 to 158 microamperes, with a mean value of 130.7 ± 8.1 microamperes for the group. The intracutaneous injection of physiologic saline solution did not appreciably alter the pain threshold of any of the subjects studied. An instrument capable of a finer adjustment than that of 26% in the strength of stimuli might have indicated some effect.

Anesthetic action of benadryl. In dilutions ranging up to 1:5,000, benadryl consistently produced complete anesthesia. On the average, the anesthetic effect of benadryl in dilutions of 1:500, 1:1,000 and 1:5,000 lasted about 12 minutes, 9 minutes and 3 minutes, respectively (Table I). Injection in dilution of 1:10,000, on the other hand, produced anesthesia in only half the subjects which lasted for only one or 2 minutes; all subjects, however, experienced some altered sensation which persisted for about 5 minutes. Given in dilution of 1:20,000 benadryl did not produce anesthesia in any of the subjects, although in the majority sensation was altered for some minutes.

Anesthetic action of procaine compared with that of benadryl. Procaine in dilutions up to 1:800 consistently caused complete anesthesia in the area in which it was injected (Table I). In general equianesthetic effects were produced by benadryl 1:500 and procaine 1:200; benadryl 1:1,000 and procaine 1:400; benadryl 1:5,000 and procaine 1:800; benadryl 1:10,000 and procaine 1:1,600, and, finally, benadryl 1:20,000 and procaine 1:3,200 (Fig. 2).

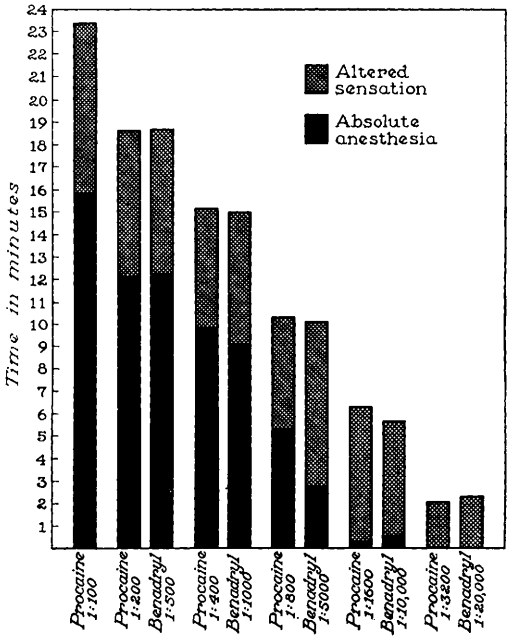

FIG. 2.
Comparison of local anesthetic effect of benadryl and procaine when injected into the skin of human subjects. Height of column gives average duration of anesthesia and altered sensation in the skin of 10 subjects after injection of the drugs in various dilutions.

Irritant effects of benadryl. Results of tests performed by injection of benadryl intracutaneously indicated that the drug possesses definite irritant properties when administered in concentrations greater than 1:500 (2 mg per cubic centimeter). Six of the 10 persons to whom benadryl in 1:100

dilution was given presented an immediate reaction at the site of injection; the reaction consisted of marked, burning pain which lasted several minutes and of diffuse local edema with pronounced redness. Four of these 6 individuals exhibited a severe delayed reaction in which sloughing and ulceration occurred at the site of injection. The ulcers, which never exceeded 1 cm in diameter, were superficial and painless; they healed within 10 days. In the other 2 of the 6 subjects the local reaction subsided within 24 hours without evidence of necrosis. Injection of benadryl in dilution of 1:100 caused no reaction in 4 subjects.

Administration of benadryl intracutaneously in dilution of 1:500 caused transient burning pain, redness and slight edema in 2 subjects; this reaction disappeared in 4 to 6 hours. Both of these subjects also had experienced a severe local reaction after administration of benadryl in dilution of 1:100. Eight subjects did not present signs of cutaneous irritation after injection of benadryl in dilution of 1:500.

None of the 10 subjects exhibited more than transient local redness in response to injection of benadryl in dilution of 1:1,000, although 3 reported the occurrence of mild burning pain, lasting only one or 2 minutes, at the time of injection.

Comment. As pointed out previously by others, methods for determining the local anesthetic effects of a drug are not entirely satisfactory. The results obtained may vary widely with the method used. Sinha,[15] after investigation of various technics used in the bio-assay of anesthetic agents designed for local administration, concluded that the human wheal method afforded greatest accuracy and was one of the most practical procedures for determination of anesthetic effect. Chance and Lobstein[16] have reported that quantitative inaccuracies of this method render it unsuitable for bio-assay of drugs, yet agree that the technic is of qualitative value in that it immediately discloses whether or not a given drug acts in the living body and also allows one to detect the occurrence of undesirable side effects. In the human wheal method the anesthetic agents act on the most minute nerve fibrils and nerve endings. Although the end-point in this method, the absence of sensation, is not too delicate and is entirely subjective in nature, it was sufficient for the purposes of this study of the relative anesthetic potency of benadryl and its irritant effects when introduced into human skin. Also, with a change of 26% in the strength of stimulus delivered by each adjustment of the algesimeter, the stimulus which consistently gave a pain response in the skin of the forearm remained quite constant from day to day and no differences between normal skin and skin infiltrated with saline solution were noted. An instrument which would permit finer adjustments of current strength might have indicated some variability.

It is possible that injections of benadryl in concentrations greater than 1:500 may produce anesthesia by virtue of injury to the tissue at the site of injection. However, in those wheals produced by intracutaneous injection of relatively dilute solutions of benadryl, the anesthetic reaction was reversible; complete return to normal sensitivity occurred at time intervals ranging from 2 to 18 minutes, depending on the concentration of drug employed. Local anesthetic action in the skin is, therefore, a definite property of the drug. Because of the irritant effects produced by benadryl administered locally it is unlikely, however, that this drug will have practical value as a local anesthetic agent.

In this study no correlation between anesthetic and antihistamine properties has been made. Do other antihistamine compounds possess anesthetic properties? Ray and Rieveschl[17] suggested the possibility that anesthetic properties might be possessed by a group of alkamine compounds which they had synthesized and the fundamental chemical structure of which is similar to that of

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[16] Chance, M. R. A., and Lobstein, H., *J. Pharm. and Exp. Therap.*, 1944, **82**, 203.

[17] Ray, F. E., and Rieveschl, George, Jr., *J. Am. Chem. Soc.*, 1943, **65**, 836.

benadryl. The possibility of correlation between anesthetic action and antihistamine effect deserves further study.

Summary. A study was made of the local anesthetic effect of β-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) when injected into the skin of human beings. The results were as follows: 1. By means of electric algesimetric determinations, benadryl in dilutions of 1:500, 1:1,000, 1:5,000, 1:10,000 and 1:20,000 was found to possess anesthetic potencies similar to those of procaine in dilutions of 1:200, 1:400, 1:800, 1:1,600 and 1:3,200 respectively. 2. Benadryl in concentrations greater than 1:500 (2 mg per cubic centimeter) proved to be exceedingly irritating when injected into human skin, causing tissue necrosis and ulceration in 4 of 10 subjects tested.

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Comparative Inhibitory Effect of Penicillin and Streptomycin Upon the Action of Staphylocoagulase.*

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One of the properties of pathogenic staphylococci is the capacity to induce the formation of a fibrin clot when the organisms are added to citrated human plasma. Though the significance of this biologic phenomenon is not clear, Hale and Smith[1] have pointed out that the *in vitro* phagocytosis of coagulase-positive staphylococci is inhibited in the presence of coagulable plasma and suggested that the invasiveness of these strains is associated with the *in vivo* production of a coagulum around the cocci which prevents efficient phagocytosis and destruction of the bacteria. Spink and Vivino[2] showed that the sulfonamides had a variable effect on the action of staphylocoagulase.

The present study revealed that streptomycin had a marked inhibitory effect on the action of staphylocoagulase in contrast to the results obtained with penicillin.

Material and Methods. Eighteen strains of coagulase-positive staphylococci were utilized; 5 strains being stock cultures, and 13 of them recently isolated from the lesions of patients. The strains were grown for 24 hours in tryptose phosphate broth and then 1 ml of each culture was added to a series of 11 sterile test tubes. Serial dilutions of penicillin and streptomycin were freshly prepared in physiologic saline solution and 1 ml amounts of the desired dilutions were added to each of the tubes containing organisms. The initial concentrations per ml of each antibiotic were 50,000 units, or 15 mg of crystalline penicillin G sodium, and 250 mg of streptomycin (base equivalent). The coagulase tests were performed by adding 0.2 ml of each culture-antibiotic mixture to 0.5 ml of citrated human plasma contained in small test tubes. The tubes were placed in a water bath at 37°C and examined for the presence of a coagulum after 2, 12 and 24 hours. Coagulation was graded from 1+ to 4+, 1+ indicating a coagulum that was just visible, while 4+ meant the formation of a solid clot, and 2+ and 3+ were designated as intermediate coagulation. The contents of each tube of antibiotic-culture mixture were tested for the presence of viable cells by streaking standard loopful amounts on agar plates, and incubating at 37°C for 24 hours.

* Aided by grants from Sharp and Dohme, Inc., and the Graduate School, University of Minnesota.

1 Hale, J. H., and Smith, W., *Brit. J. Exp. Path.*, 1945, **26**, 209.

2 Spink, W. W., and Vivino, J. J., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 37.