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CHEMICAL CORPS MEDICAL LABORATORI

SPECIAL REPOR

Report No. 10

EVALUATION OF INTRAMUSCULAR SELF-INJECTION OF 2 MG. ATROPIN

A. Comparison of Effectiveness of Ampin Versus Syrette for Intramuscular Self-Injection by Healthy Adult Males.

B. Subjective Findings Resulting from 2 mg. Atropine Intramuscularly in Healthy Adult Males.

C. Objective Study of Effects of 2 mg. Atropine Intramuscularly in Healthy Adult Males.

by

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March 1952

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ARMY CHEMICAL CENTER, MARYLAND

CHEMICAL CORPS
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MARYLAND

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University of Chicago, Ill.

* Under a grant from the Army Chemical Center Medical Laboratories, Edgewood, Md.

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ABSTRACT

OBJECT.

A. To ascertain the ability of normal, healthy, adult males to self-inject intramuscularly 2 mg. atropine, as might be necessary if exposed to nerve gas poisoning.

B. To evaluate the comparative efficiency of self-injection by means of ampins versus syrettes.

C. To note the subjective effects and objective findings resulting from a 2 mg. injection of atropine.

METHOD.

Normal, healthy male Liberal Arts and Physical Education students at the University of Illinois Urbana campus* were asked to volunteer for the study and were then indoctrinated with the methods to be used. During two days of testing, carried on during physical education classes, one hundred and eighty-eight students volunteered to participate. Ninety-six of these used the ampin and ninety-two used the syrette, each loaded with 2 mg. atropine (the quantity of atropine salt used is equivalent to 1.66 mg. of atropine base per cc. of solution). They were carefully monitored during the self-injection, then observed for physiological changes resulting from the atropine, and questioned regarding their subjective experiences.

GENERAL CONCLUSIONS:

1. The test, as carried out under the exigencies of this situation, does not represent an ideally controlled study for the following reasons:

a. The group was composed entirely of college students and results may not be representative of findings in a completely military population or in a more typical section of the entire civilian population.

b. All one hundred and eighty-eight participants were <u>volunteers</u>. Accordingly, they are representative only of the segment of this special group

*We wish to express our appreciation to the staff of the Department of Physical Education, University of Illinois, for their willing cooperation in this study.

who were willing, because of curiosity, interest, group association, or some other factor, to attempt self-injection of 2 mg. atropine. The ability to administer a self-injection and the reactions of the non-volunteers have not been assayed.

c. For an accurately controlled study each man should have used both an ampin and a syrette. This is possible only if (1) both syrettes and ampins are loaded with isotonic physiologically inactive solution or (2) one-half of the devices are so loaded and one-half with 2 mg. atropine. Since, for this study, both the ampins and the syrettes contained 2 mg. atropine--and it was deemed undesirable to have participants receive double amounts of atropine intramuscularly--each volunteer used only one device. The efficacy of use of the devices is comparable, then, only insofar as the groups using each apparatus are comparable. For most particulars the groups of 96 and 92 are too small for significant comparisons.

2. No significant difference in efficiency between use of the ampin and the syrette is noted in most areas. Neither device is completely satisfactory in its present form.

3. In appraising the apparatus, more men rate the device they actually used as being superior. This is to be expected. However, there is a general trend in favor of the ampin.

4. During the period of 90 to 120 minutes immediately following the self-injection of 2 mg. atropine, no serious physiological effects were noted in the volunteers:

a. However, there were indications that circulatory compensatory mechanisms were significantly disturbed, especially in the individuals of smaller size. These included tachycardia, erect hypotension, and increased skin temperature. All electrocardiographic findings were essentially normal.

b. The most common subjective complaints were: dryness, tiredness and dizziness.

RECOMMENDATIONS.

1. Decisions regarding final preference for the ampin versus the syrette for routine use as the method of choice in self-injection of 1.66 mg. atropine base should await further, more adequately controlled tests.

2. In future tests, the following conditions must be arranged:

a. The population tested should be a military group.

b. All members of the group must attempt self-injection. Since it is essential to know how many men can actually accomplish self-injection, the use of only a volunteer group is completely invalidating.

c. All men must use both devices, in order to allow direct comparison. Accordingly, both ampins and syrettes must be loaded with an inactive solution, or one device with such a solution and one with 2 mg. atropine.

3. Regardless of the device finally accepted, both ampin and syrette can and should be improved, as detailed in the following report.

4. Further studies on the effects resulting from this dose of atropine should be accomplished, especially as pertains to the relationship of the subjective feelings and objective findings to military performance under field conditions.

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INTRODUCTION

At the request of Dr. D. B. Dill, Scientific Director, Army Chemical Center Medical Laboratories and Dr. Gustave Freeman, Chief, Clinical Investigation Branch, a study has been made of the efficiency of intramuscular self-injection of 2 mg. atropine by means of standard ampins and syrettes.

When the study was proposed, it was recognized by all interested parties that an ideally controlled test should include:

(1) Use of a military population;

(2) Attempts at self-injection by all members of the group; and

(3) Use of both an ampin and a syrette by each participant.

In order for all of these conditions to be satisified it would have been necessary to use ampins and syrettes loaded with isotonic physiologically inactive solution, or one of the devices so loaded and the other with 2 mg. atropine.

However, at the time of proposal of the study, only atropine-loaded ampins and syrettes were available in adequate quantities for testing purposes. Since it was deemed unwise to have subjects, who were not exposed to nerve gases receive double amounts of atropine intramuscularly at one time, criterion 3 above could not be fulfilled. The deadline for completion of the study precluded the use of a military group since it did not allow sufficient time for arranging clearance and details of self-administration of 2 mg. atropine to military personnel. Therefore, criterion 1 above could not be satisfied.

Inability to use armed forces for testing purposes necessitated the recruitment of undergraduate college students. It was impossible to require all students to participate in the self-injection, so the final test group consisted only of student volunteers. Criterion 2, above, therefore could not be complied with.

Despite the recognition of these limiting factors, exigencies of the situation made it seem worthwhile to perform the study nevertheless and to secure the following information:

(1) Comparison of efficiency of intramuscular self-injection of atropine by ampin versus syrette;

(2) Subjective findings resulting from 2 mg. atropine intramuscularly in normal healthy adult males; and

(3) Objective study of effects of 2 mg. atropine intramuscularly in normal healthy adult males.

GENERAL PROCEDURE

Male Liberal Arts and Physical Education students at the University of Illinois Urbana campus were asked to cooperate in the study during their physical education classes. They were indoctrinated with the facts that: they would be participating in a test sponsored by the Department of Defense; that they would be required to self-inject, intramuscularly, a chemical antidote for nerve gas poisons; that they would probably notice certain side-effects from the injection; but, that these would be minor and not incapacitating.

The volunteers were then assembled in the testing area, where they received a ten to fifteen minute lecture-demonstration detailing the correct use of the ampin and the syrette. Thereafter they were randomly assembled in groups before each of three booths. A trained monitor in each booth evaluated their use of either the syrette or the ampin.

A short time before he entered the booth each volunteer was presented with a sample ampin and a syrette. He did not know which device he would be called upon to use in the booth, but he had several minutes to familiarize himself with the apparatus of both types. In the booths, the monitors alternated their assignment of ampins and syrettes so that a random assortment of approximately one-half of each group used each device. When the men entered the booth, they were told which device to use and to select an injection site on the anterior surface of their thigh and prepare it with an antiseptic solution. Following the signal "Now" by the monitor, the volunteer injected himself with 1.66 mg. atropine base. He was closely checked for the number of insertions required, the time lapse (in seconds) from "Now" to adequate insertion, and from insertion to time of actual injection. The total amount of dose taken and the reasons for failure at any point were also noted.

The students received no coaching while in the booths, and were allowed only three minutes in which to complete the injection. If they had failed at the end of this time they were considered total failures. They received the syrette in a previously opened cardboard syrette container (figure 1); and they were given the ampin in its conical shaped plastic container. Here the decision to use the case for a syrette and the cover for an ampin rested upon the fact that it appeared desirable to have a set of rules available in case the participant forgot how to use the device. The ampin has the directions for use on the plastic cover; the syrette has them on the cardborad box. For field use, and in future tests, the individual will be given one syrette contained in a single vial with the instructions printed thereon. The total time necessary for self-injection will thus be shortened since removal from the cardboard box will not be a factor. The monitors completed their rating summary following each man's performance.

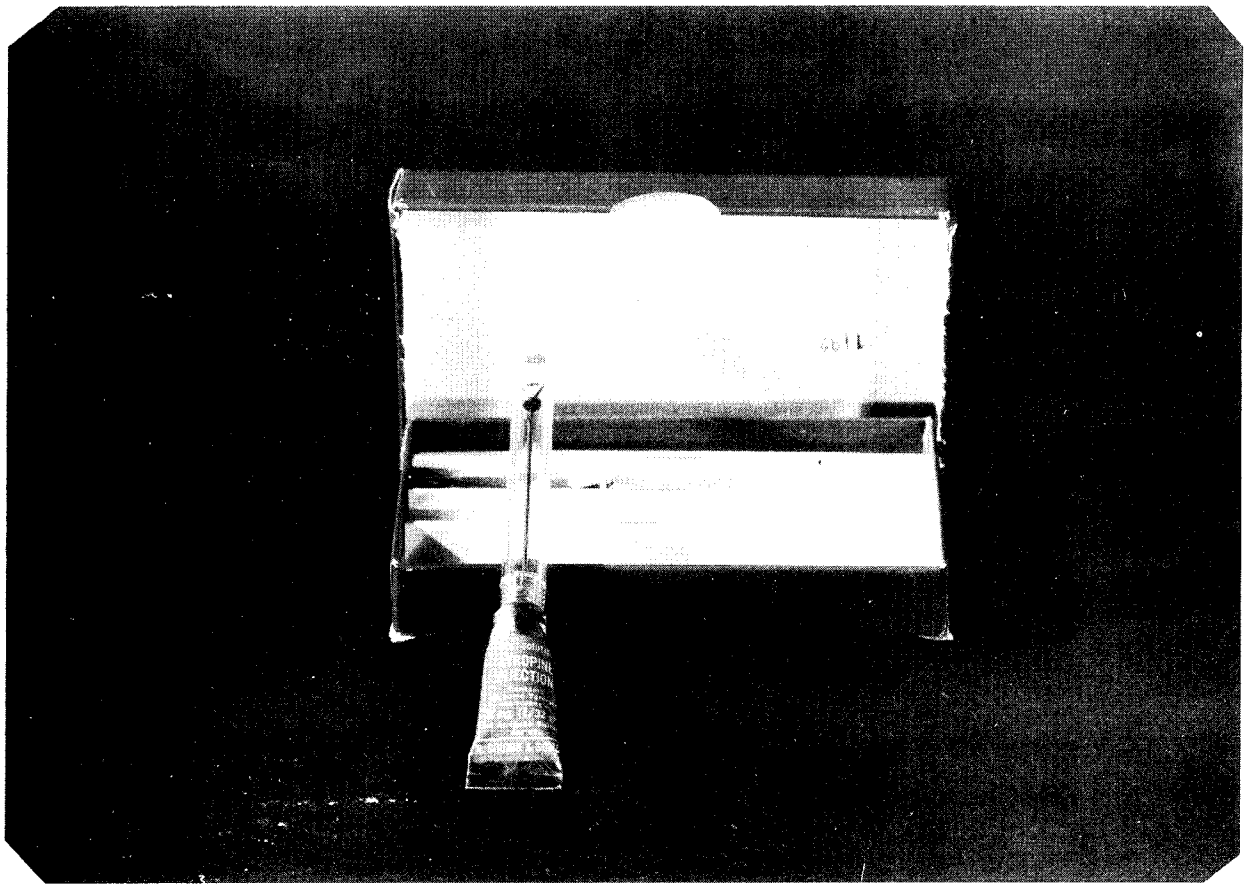

Figure 1 Standard Syrette (Squibb)

With 1 cc. of injectable solution containing atropine tartrate. Note screw type plastic needle-cover and wire stylet for breaking seal.

Following the injection the men returned to the assembly area where objective studies were begun about thirty minutes later. The participants were kept here for a minimum of one hour following the injection, and most of them for 90 to 120 minutes. During this time the men were retained in the area and a number of observations were made. General neurological and gross coordination tests were performed on some of the volunteers. Most of them had standing and recumbent pulse and blood pressure taken. Those who had alterations in blood pressure had sitting, standard-lead electrocardiograms taken. Skin temperatures were recorded before and after the injection. These were taken by placing a standard 0-100° Centigrade thermometer between the thumb and index finger of the subject.

As each student left, he received an Exit Interview during which he was probed to volunteer any and all symptoms he had noted since the atropine injection. The interviewer suggested no symptoms, but merely allowed the student to describe his feelings. At sometime within the next few days all participants were requested to fill out a Final Questionnaire on which they noted symptoms, time of onset and duration of these, as well as their personal appraisal of ampins versus syrettes.

PART A

COMPARISON OF EFFECTIVENESS OF AMPIN VERSUS SYRETTE OR INTRAMUSCULAR SELF-INJECTION BY HEALTHY ADULT MALES.

RESULTS

Two groups of Physical Education majors and two groups of General Curriculum and Liberal Arts students were used for the testing. One hundred and eighty-eight of the three hundred and forty-five men in these classes volunteered for and participated in the study. The two groups were comparable and the assignment of students to use the ampin or the syrette was apparently well-randomized since they were comparable as regards class in the University, and median age, height and weight, (Table B).

Table A reveals that only one individual failed to insert the needle with each device. Equal numbers of ampin users and syrette users were able to insert the needle and start the injection, whereas, there were a few more cases with the ampin than the syrette in which the needle was successfully inserted but the injection was not begun. However, this latter point was not statistically significant. Most of the men accomplished the insertion with the first attempt. Several cases required two or three attempts with each device.

The time required for self-administration of a unit dose of atropine by ampins and syrettes is shown in Table C. There was s statistically significant difference in the time requirement for needle-insertion with the two devices. The median time for needle insertion with all classes using the ampins was seven seconds less than the similar group using the syrette. However, it is necessary to make two qualifying statements as regards this difference: (1) although the seven second difference was significant, the insertion with either device was accomplished in twenty-five seconds, which is a reasonable time for performing an atropine injection after exposure to nerve gas; and (2) since

TABLE A

Number of participants and outcome of their attempt at self-injection with atropine devices

	Men Using Ampin					Men Using Syrette				
	Class 1	Class 3	Class 2	Class 4	All Classes	Class 1	Class 3	Class 2	Class 4	All Classes
Total Number in class	60	55	150	80	345	60	55	150	80	345
Number of volunteers	19	12	34	31	96	17	11	34	30	92
Monitor: S.	6	4	12	12	34	5	4	12	11	32
F.	6	4	11	9	29	6	3	12	8	29
G.	7	4	11	11	33	6	4	10	11	31
Outcome:										
Needle not inserted	1	-	-	-	1	-	-	-	1	1
Inserted, no inj.	-	3	3	1	7	-	-	3	-	3
Injection begun	18	9	31	30	88	17	11	31	29	88
No. of Insertions:										
None	1	-	-	-	1	-	-	-	1	1
One	17	12	34	30	93	16	11	31	29	87
Two	1	-	-	1	2	-	-	3	-	3
Three	-	-	-	-	-	1	-	-	-	1

Monitors: S = Silberberg; F = Frye; G = Gordon

Classes: 1 and 3 = Physical education majors
2 and 4 = Liberal arts majors

TABLE B

Comparison of groups using ampin and syrettes

	Men Using Ampin					Men Using Syrette				
	Class 1	Class 3	Class 2	Class 4	All Classes	Class 1	Class 3	Class 2	Class 4	All Classes
Subject's class:										
Freshman	9	8	20	22	59	6	7	19	16	48
Sophomore	3	1	12	7	23	7	1	13	9	30
Junior	5	1	1	1	8	4	2	2	3	11
Senior	2	2	-	1	5	-	1	-	1	2
Not reported	-	-	1	-	1	-	-	-	1	1
Subject's major:										
Phys. Ed.	19	12	-	-	31	17	11	-	-	28
Engineering	-	-	12	9	21	-	-	5	6	11
Lib. Art & Science	-	-	5	9	14	-	-	9	7	16
Commerce	-	-	4	7	11	-	-	6	9	15
Agriculture	-	-	6	5	11	-	-	8	2	10
Pre-Medical	-	-	3	1	4	-	-	1	2	3
All other	-	-	3	-	3	-	-	5	3	8
Not reported	-	-	1	-	1	-	-	-	1	1
Subject's age:										
17	-	-	5	2	7	-	-	-	1	1
18	3	3	12	17	35	5	6	19	14	44
19	5	5	11	8	29	4	-	12	6	22
20	4	1	3	1	9	4	3	3	6	16
21	3	2	2	1	8	2	1	-	1	4
22 and over	4	1	-	2	7	2	1	-	1	4
Not reported	-	-	1	-	1	-	-	-	1	1
Median age	20.4	19.6	19.0	18.8	19.2	19.9	18.9	18.8	18.9	19.2
Subject's height:										
Under 5'7"	1	1	3	1	6	1	1	4	1	7
5'7"	-	-	1	2	3	1	1	6	-	8
5'8"	4	3	4	3	14	1	1	6	1	9
5'9"	3	1	4	5	13	1	1	4	4	10
5'10"	1	-	7	6	14	3	3	3	3	12
5'11"	3	3	4	4	14	3	1	2	6	12
6'0"	1	1	2	4	8	6	1	5	9	21
6'1"	1	3	4	1	9	-	2	3	2	7
6'2"	3	-	3	3	9	-	-	1	2	3
Over 6'2"	2	-	1	2	5	1	-	-	1	2
Not reported	-	-	1	-	1	-	-	-	1	1
Median height	5'10"	5'11"	5'10"	5'10"	5'10"	5'11"	5'10"	5'9"	5'11"	5'10"
Subject's weight:										
Under 130 lbs.	-	1	1	2	4	1	-	1	-	2
130-139 lbs.	-	-	4	2	6	-	1	4	3	8
140-149 lbs.	2	-	3	7	12	1	2	7	8	18
150-159 lbs.	4	3	8	7	22	1	3	11	1	16
160-169 lbs.	4	3	8	4	19	5	2	7	4	18
170-179 lbs.	4	-	4	2	10	3	1	2	7	13
180-189 lbs.	2	2	2	4	10	4	1	1	2	8
190-199 lbs.	1	1	1	1	4	1	-	1	2	4
200-209 lbs.	1	2	-	2	5	-	1	-	1	2
210 lbs and over	1	-	2	-	3	1	-	-	1	2
Not reported	-	-	1	-	1	-	-	-	1	1
Median weight	169	167	161	156	162	172	158	155	166	161

TABLE C

Time required for self-administration of 2 mg. atropine by ampins and syrettes.

	Men Using Ampin					Men Using Syrette				
	Class 1	Class 3	Class 2	Class 4	All Classes	Class 1	Class 3	Class 2	Class 4	All Classes
Time till needle in:										
Never in	1	-	-	-	1	-	-	-	1	1
Under 10 seconds	2	-	1	-	3	-	-	-	-	-
10-19 seconds	7	4	22	16	49	3	2	12	7	24
20-29 seconds	5	4	6	8	23	6	5	15	8	34
30-39 seconds	3	2	1	4	10	6	2	4	9	21
40-49 seconds	1	-	2	2	5	1	1	2	2	6
50-59 seconds	-	1	-	1	2	-	-	-	2	2
60 seconds or more	-	1	2	-	3	-	1	1	1	3
Not reported	-	-	-	-	-	1	-	-	-	1
Median time	19.5	24.5	16.8	19.2	18.6	27.6	26.5	22.8	28.9	25.7
Time till inj. begun:										
Needle never in	1	-	-	-	1	-	-	-	1	1
Injec. not begun	-	3	3	1	7	-	-	3	-	3
Under 10 seconds	-	-	-	-	-	-	-	-	-	-
10-19 seconds	4	1	10	11	26	1	1	5	5	12
20-29 seconds	4	1	13	8	26	6	4	18	9	37
30-39 seconds	4	5	4	7	20	5	3	4	8	20
40-49 seconds	4	1	1	3	9	2	1	2	4	9
50-59 seconds	-	-	-	1	1	1	-	1	2	4
60 seconds or more	1	1	3	-	5	1	1	1	1	4
Not reported	1	-	-	-	1	1	1	-	-	2
Median time	30.7	34.5	23.7	24.5	26.2	31.5	29.5	25.3	30.1	27.9
Net time from needle in to inj. begun:										
Needle never in	1	-	-	-	1	-	-	-	1	1
Inj. not begun	-	3	3	1	7	-	-	3	-	3
no seconds	2	1	-	-	3	-	1	1	8	10
1 second	-	-	3	4	7	1	2	6	1	9
2 seconds	-	-	7	5	12	2	3	9	2	16
3 seconds	1	1	4	2	8	-	-	4	12	16
4 seconds	1	-	4	2	7	2	1	1	4	8
5 seconds	-	-	2	4	6	5	1	4	1	11
6 seconds	2	1	4	6	13	-	-	1	1	2
7 seconds	2	-	2	1	5	1	-	-	-	1
8 seconds	1	-	-	1	2	2	1	-	-	3
9 seconds	1	-	1	-	2	-	-	1	-	1
10-19 seconds	5	7	3	5	19	2	1	4	-	7
20 seconds or more	2	-	1	-	3	2	-	1	-	3
Not reported	1	-	-	-	1	-	1	-	-	1
Median time	8.0	12.0	3.9	4.9	5.8	5.2	2.2	2.6	2.8	3.1

the instructions were on the box rather than on the individual unit, personnel received the syrette in a boxed form. Opening the box for access to the unit was a maneuver not necessary for injection with the ampin, and undoubtedly accounts for a major portion of the extra time requirement. In field use and future tests, men will receive individual syrettes and this factor will be eliminated.

The time from starting the test to actual injection of the drug was almost the same for the ampin and the syrette. But the net time between insertion of the needle and beginning of drug injection was less for the syrette than for the ampin. The latter was statistically significant. Thus, the actual time of beginning the atropine injection was essentially the same whether ampin or syrette was used (26.2 and 27.9 seconds, respectively, in Table C, Part II), while the syrette, in a box, took significantly longer for intramuscular injection, but the ampin took statistically longer for beginning the injection following insertion. The causes of these delays suggest possible improvements for both injectors, and these will be discussed in the following section.

Analysis of the actual amount of drug taken and the points of failure are very interesting and are shown in Table D. The most important overall finding is that there is no statistically significant difference between the number of men receiving three-fourths or more of the dose with the ampin or with the syrette (79 to 72). In contrast to this, there were twice as many absolute failures with the ampin as with the syrette (8 to 4). Furthermore, five students received "almost none" of the injection from the ampin, whereas only one case using the syrette obtained "almost none". These latter data are not statistically significant with the small number of cases used but it may indicate a consistent and suggestive trend.

In those cases in which insertion of the needle was accomplished, but not injection of the drug, the primary error was breakage of the body of the ampin rather than the tip resulting in drug loss rather than drug-injection. However, as regards incomplete dosage, faulty tilting of the ampin and faulty squeezing of the syrette overshadowed all other possibilities in accounting for the inadequacy. This again suggests improvements for both devices. The main reason for failing to begin injection once the needle was inserted is listed as memory failure, such as forgetting to break the seal on the syrette. This may reflect a personal inadequacy of the participant, poor indoctrination, lack of interest of volunteer, or certain mechanical difficulties with the apparatus. The first three factors could not be appraised here, but the mechanical difficulties encountered do suggest improvements, which will be discussed later.

In no case was there any serious immediate physiologic or psychologic reaction to the injection per se and, all men proceeded at once to the next step of the investigations.

DISCUSSION AND CONCLUSIONS

1. This study was not controlled to the desired extent, but a great deal of interesting and valuable data can be gleaned from it. A certain amount of caution must be exercised in assuming that these results can be applied to a military population. Although the age level and physical status are about

TABLE D

Amount of dose taken and reasons for failure with ampins and syrettes

	Men Using Ampin					Men Using Syrette				
	Class 1	Class 3	Class 2	Class 4	All Classes	Class 1	Class 3	Class 2	Class 4	All Classes
Amount of dose taken:										
Essentially all	12	5	25	27	69	10	5	18	22	55
About 3/4	2	1	3	3	9	5	4	7	1	17
About 1/2	-	-	2	-	2	1	2	5	4	12
About 1/4	2	-	1	-	3	1	-	1	1	3
Almost none	2	3	-	-	5	-	-	-	1	1
Absolutely none	1	3	3	1	8	-	-	3	1	4
Point of Failure:										
No insertion:										
Not reported	1	-	-	-	1	-	-	-	1	1
No injection:										
Failed to squeeze S. or break A.	-	-	1	-	1	-	-	-	-	-
Broke A. at top	-	3	2	-	5	-	-	-	-	-
Not reported	-	-	-	1	1	-	-	3	-	3
Incomplete dose:										
Faulty needle ins.	-	-	-	-	-	-	-	3	-	3
Faulty squeezing of S. or tilting of A	5	4	6	3	18	6	6	10	5	27
Premature needle removal	1	1	-	-	2	-	-	2	-	2
Began squeezing S. before insertion	-	-	-	-	-	-	-	1	3	4
Not reported	1	-	-	-	1	1	-	-	-	1
Dosage complete	12	5	25	27	69	10	5	18	22	55
Reason for failure to begin injection:										
Didn't remember	-	2	-	1	3	-	-	2	-	2
Lack of dexterity	-	-	1	-	1	-	-	1	-	1
Fear, lack of nerve	1	-	-	-	1	-	-	-	1	1
Not reported	-	1	2	-	3	-	-	-	-	-
Injection begun	18	9	31	30	88	17	11	31	29	88
Immediate Reaction After Injection:										
No abnormal reaction	18	9	30	29	86	15	11	30	29	85
Vasomotor instability	-	-	1	-	1	2	-	1	-	3
Not reported	-	-	-	1	1	-	-	-	-	-
No injection	1	3	3	1	8	-	-	3	1	4

the same, the general intellectual level of the college students would, most probably, exceed that of a routine military group. Another important and variable factor is the amount of indoctrination given regarding the proper use of the devices. The study, therefore, should serve as a precursor for a similar but extended and controlled survey on military personnel under varying conditions.

2. One of the more important general impressions gained from the tests is the fact that, in their present form, neither device stands out unequivocally as a completely superior method for the self-administration of atropine. In many areas the ampin and syrette are directly comparable as regards efficiency of self-administration. Small differences are not statistically significant in most cases due to the small size of the group for this type of study. It is noteworthy that the same number of volunteers were able to insert the needle and begin the injection with either type of injector, and that most of the personnel could accomplish this on the first attempt.

The total time required to begin the actual drug injection was approximately equal for both devices. Whereas, the ampin was inserted more quickly, the atropine was ejected from the syrette sooner after insertion into the tissues. Analysis of the reasons for these delays provides us with suggestions for possible improvements in the equipment and/or indoctrination. Three main factors account for the extra time requirement with the use of the syrette: (a) These syrettes did not have instructions on each unit; so, it was necessary to provide them to each student in a cardboard box on which the instructions were printed. Many of the men wasted valuable time in fumbling attempts to remove the syrettes from the box, even though these containers had been opened previously. For field use, and in any future tests, the individual will be given one syrette contained in a single vial with the instructions printed thereon; the total time necessary for self-injection will thus be shortened since removal from the cardboard box will not be a factor. (b) In several cases men attempted to pull off the needle cover. This screws into place on the syrette, but some men took an unusually long time to remember or realize this. (c) A third cause of delay was inability of the men to recognize when they had broken the seal with the wire stylet. A number of them continued the plunging action of the stylet even after the seal was broken.

These three difficulties can be overcome by revisions of the equipment, which will be dealt with under Part A Recommendations.

The reason for the delay between the time of insertion of the ampin and breaking the ampule tip in order to start the injection is more difficult to discern. No actual physical inconvenience can be shown to be responsible here and it is thought that the failure to break the tip quickly was attributable to failure to stress this point during the indoctrination. The value of requiring the men to have used each device previously, at least once, thus becomes evident.

4. In the few cases where complete failure occurred with the use of the syrette, it was due to faulty breaking of the seal on the tube. Personnel remembered to insert the plunger in order to break the seal, but lack of previous experience led them to think they had accomplished this end when actually they had not. They recognized their error after the needle was inserted, but by this time the plunger had been discarded. In the case of the

ampin most of the complete failures were due to faulty manipulation which resulted in breaking the body of the ampule after insertion. This can be attributed to gross carelessness, excitement, poor indoctrination, or any combination thereof.

5. Obtaining only a partial dose of the syrette contents was attributable to two errors in technique. Almost all personnel lost at least a few drops of the solution, and some lost a considerable amount, in inserting the needle through the skin. Most often, the tube was grasped near the top and, in exerting pressure to inject the needle through the skin, some of the drug was squeezed from the tube. A second error which accounted for incomplete dosage was failure to perform multiple squeezings of the tube to empty it completely. However, most students squeezed three-fourths or more of the contents from the tube.

The primary cause for receiving only a partial dose of the drug when using the ampin was faulty tilting during the injection. Most volunteers held the bottom of the ampin straight up or at an obtuse angle, as directed. However, several of them, especially those selecting a medial site for injection, held the needle horizontally, or almost so. Therefore, they received only a partial dose because not all of the solution reaches the neck of the broad-based ampin (used in these tests) when held in the near-horizontal position.

6. All of these factors indicate that both the ampin and the syrette have not reached their final, ideal form. Further improvements should be incorporated into them, especially if they are to be prescribed for intramuscular self-injection in the field. The value of adequate training in the actual use of the devices cannot be overemphasized. Besides lectures, demonstrations, movies, etc., this training should include an opportunity for each man to familiarize himself with the device to be used, or actually use it during his training period.

7. Although not specifically investigated in this study a number of other factors, pertinent to the ultimate use of either device, must also be considered in making a final decision regarding the best injector. These include the fact that the syrette is safer to carry without danger of breakage, and wide experience has shown that trained personnel use it well. However, it is impossible to see the contents in order to detect physical alteration (turbidity, dirt, mold, precipitate, discoloration, etc.) if these exit. The standard syrettes provided for this study were tested for intramuscular injection only. In cases where intravenous injection is desired, this should prove somewhat inaccurate since the tin walls would prevent seeing when the vein was entered. The use of a plastic syrette could eliminate this difficulty. Also, from the psychological point of view, men preferred the automatic injection of the ampin to the one in which it was necessary to squeeze several times in order to inject themselves.

The greatest disadvantage of the ampin is the possibility of breakage resulting from rough handling. This can be prevented by the use of a sturdy cover. However, even during its insertion through the skin, our experience has shown that poorly trained, excited, or clumsy personnel may fracture the glass. The present atropine ampin has been modified into the broad-based shape to allow it to fit into the M5 container. However, by

so-doing a construction has resulted which gives incomplete dosage if the device is not held bottom up or at an obtuse angle. Use of a standard shaped ampule with the rubber tubing and needle bent back upon themselves would improve this situation and still allow the unit to fit the M5.

The problem of gas embolism also comes to mind because of the inert gas in the ampin under 2-1/2 atmospheres pressure. However, during a proper injection, only 2.3 cc. of helium leaves the ampin and, even if all of the medication is left behind, only 2.8 cc. of the gas can enter the tissues. The latter amount of helium in the blood stream should be uniformly harmless.

An additional advantage of the ampin is its ability to function in situations where pressure differentials are altered, such as in an airplane at altitude. Since the device is first inserted through the skin, all of the drug is injected into the tissues when it is opened and pressure equalization occurs. With the syrette, puncturing the seal at altitude results in the immediate ejection of the solution before the needle can be inserted unless the needle is held upright during puncture of the diaphragm.

In the final analysis the decision to use either ampin or syrette for self-injection of atropine must consider the broad spectrum of all of these factors, as well as the important consideration that neither device is yet in its most ideal form. In these tests there were a greater (but not significant) number of failures to begin the injection following insertion of the ampins. Most of these failures resulted from breakage of the body of the ampin rather than the tip, thereby losing the contents.

RECOMMENDATIONS

1. Decisions regarding final selection of the preferred device should await further, more adequately controlled studies.

2. In further studies the following situation should be arranged:

   a. Use of a military population.

   b. Compulsory participation--not voluntary participation.

   c. Each subject must use both devices. It is therefore necessary to have all devices loaded with isotonic physiologically inactive solution, one-half so loaded and one-half with 2 mg. atropine.

3. If military personnel are expected to be able to self-administer drugs by use of either an ampin or a syrette, they should receive careful indoctrination and adequate training in their application. This should include seeing the unit and, under careful monitoring, actually using the selected device for self-injection (or simulating its use). Proper training will obviate many errors in usage, even with the present devices.

4. Neither the ampin nor the syrette shows an unequivocal overall superiority at this time. Furthermore, neither of them should be considered ideal in its present form. The following improvements for each piece of equipment are suggested:

a. Improvements for ampin and its use:

(1). Use of the broad-based ampule should be eliminated since this allows retention of drug with incomplete dosage if the ampin is not held "bottoms up". (See figure 2).

(2). Use of the standard-shaped ampule in the ampin allows for more complete emptying, even if it is used improperly. (See figure 2). By slightly lengthening the rubber connecting piece between ampule and needle, the device bends back on itself, fits into a protective plastic cover and fits into a small area in the standard M5 container.

(3). Inadvertant breakage prior to the time of use is an imminent danger with the ampin. Therefore, greater protection should be sought. It is impossible at present to make a plastic ampule with a breakable glass tip; therefore, more adequate protective plastic covers must remain the goal.

(4). All personnel expected to self-administer drugs with an ampin must be carefully indoctrinated regarding its proper use. This should include an opportunity to actually use the device.

b. Improvements for the Syrettes:

(1). The needle-cover of the syrette should be "pulled off" rather than "unscrewed". In its present form this screw-type cover takes longer to remove and results in time-consuming errors in its use by inexperienced personnel working under conditions of others.

(2). The metal top-portion of the syrette tube should have a metal shoulder for placement of the thumb and index fingers during injection. In its present form, intramuscular injection, especially by non-medical personnel, always results in the loss of several drops of drug-containing fluid, and sometimes sizeable quantities of the total dose are lost because the tube is necessarily squeezed during the injection. Either an extra dose must be put into the tube to compensate for this or a shoulder put on at the head of the tube to prevent it.

(3). The gravest pitfall in the use of the syrette is failure to break the seal of the tube due to incomplete penetration of the wire plunger. This may result from inadequate training, "forgetting" to first push in the plunger before discarding it, or pushing in the plunger to a depth considered correct, but actually not far enough to break the seal. If the man does not know he is supposed to first push in the plunger, or forgets to do so, or does so inadequately, he will not appreciate his error until the needle has been inserted into the muscle and he is unable to express the contents of the tube. By this time he will, in all probability, have discarded the wire stylet. The syrette is then useless and in addition he has wasted valuable time. Use in the dark may result in more cases of inadequate breaking of the syrette seal. Furthermore, pushing in the wire stylet results in frequent contamination of the needle.

ALL of these disadvantages might be overcome by a single improvement in the syrette, namely, if the wire stylet could break the seal when it is pulled out, rather than when it is pushed in. The wire stylet must

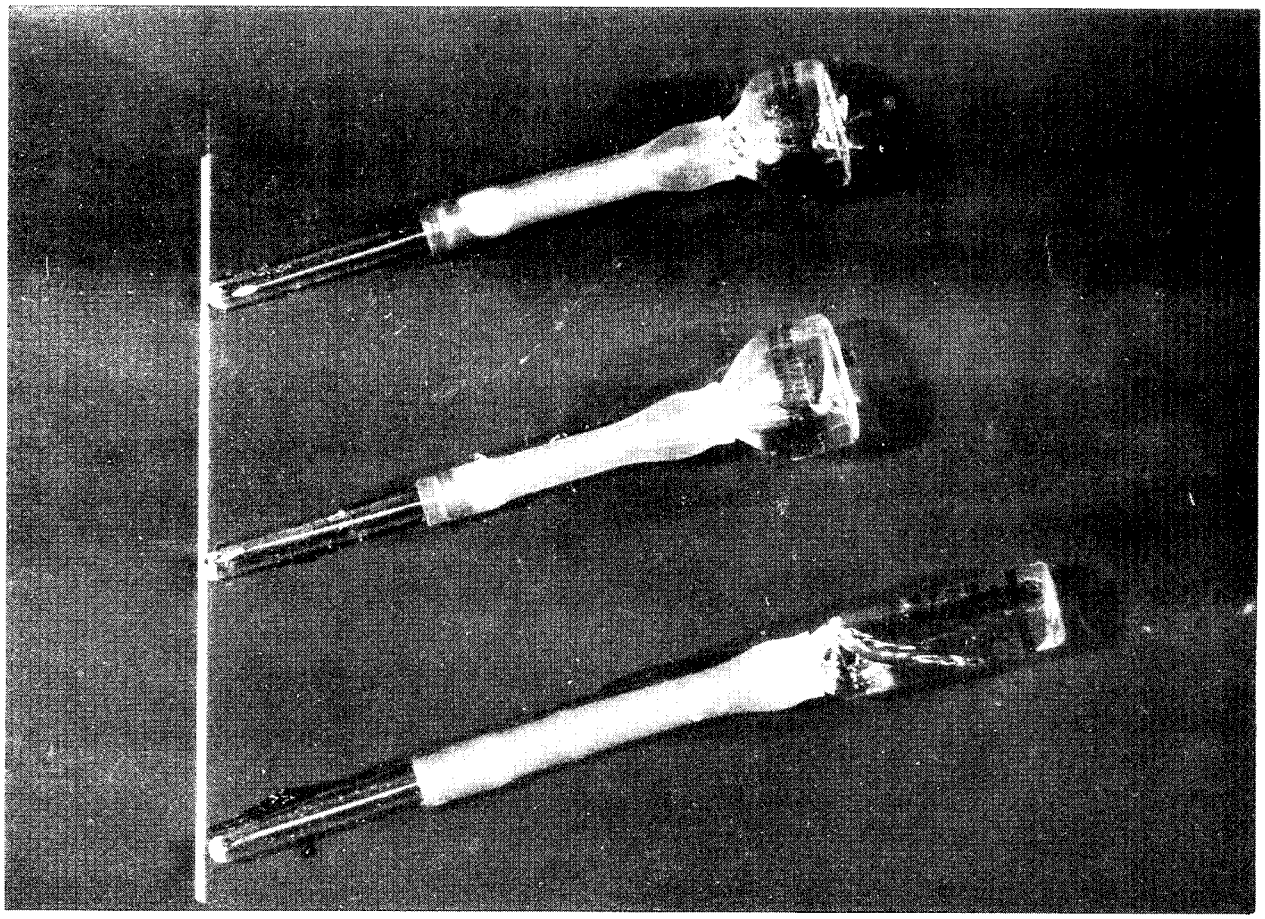

Figure 2 Various Shaped Ampins

Containing 2 mg. atropine sulfate for intramuscular injection, held at approximately 20 degree angle. Note how fluid covers more of neck of conical ampule (middle) than flat ampule (top). Standard ampule (bottom) has greatest amount of solution at neck at this angle, thus providing for greatest volume of dose injected even if this extremely low angle is used.

be constructed so that it breaks the seal when it is pulled out, rather than when pushed in. Since a man cannot inject the needle until he removes the stylet, this modification would automatically preclude failure to puncture the seal, since removal of the wire stylet would automatically break the seal of the tube. Furthermore, this would provide greater assurance of proper use at night. In addition, the incidence of contamination of the needle would be decreased.

The present syrette with "screw" needle cover and "push-in" stylet may be difficult for injured personnel to use. A "pull-out" stylet and "pull-off" needle cover would allow a man to adequately use one hand and his teeth in an emergency.

In the field, and for subsequent tests, syrettes will be provided as single unitsin a plastic vial. This will eliminate the time delay with the use of sealed cardboard containers.

ADVANTAGES AND DISADVANTAGES OF AMPINS

Advantages	Disadvantages
1. Provides accurate, automatic dose, if held properly, or if standard type ampule is used.	1. Ampule may be broken by rough handling.
2. None of dose lost during insertion through skin.	2. May get partial dose only if held in a horizontal or bottom down position during injection. This is especially true if broad-based ampins are used (see figure 2). Should use standard ampule type with rubber tubing doubled back on itself to allow insertion into M5 container.
3. Can be used intravenously if desired, since after insertion of needle into vein, pressure on rubber tubing will draw blood back into sterile tubing, where it can be seen.	3. Helium embolism is a possibility but in quantities used in ampins it can be considered remot.
4. Completely tamper-proof.	
5. Contents can be viewed for inspection of physical condition. Also, if contents freeze, can be hand warmed to a solution in a few minutes. Can see when thawing is complete.	
6. Self-injection easier for some personnel since injection of drug is automatic and does not require multiple squeezings.	

ADVANTAGES AND DISADVANTAGES OF SYRETTES

Advantages	Disadvantages
1. Easily withstands rough handling and wear.	1. Can not see contents or their physical state (amount, deterioration, freezing).
2. Can use partial or full dose of contents.	2. Some of contents lost during insertion due to pressure on tube.
3. Operator can approximately control amount of dose injected, if desired.	3. Breaking seal by pushing in wire stylet may be done inadequately or not done at all. Seal should be automatically broken by pulling out wire stylet.
	4. Carelessness or ignorance may result in incomplete dosage due to faulty squeezing.
	5. Subject to tampering, which allows complete or partial removal of drugs.
	6. Screw-type needle-cover requires time and recognition for removal; cover should be of the pull-off variety.

PART B

SUBJECTIVE FINDINGS RESULTING FROM 2 MG. ATROPINE INTRAMUSCULARLY IN HEALTHY ADULT MALES.

The subjective effects resulting from the unit dose of atropine were essentially as anticipated. There were no serious symptoms and actually less complaint on this score than was expected.

The most commonly reported symptom was dryness of the mouth and lips. This held for both the first report, within two hours after the injection and the final report, which was made within several days. (Tables E and F). The complaint of this and other dryness, usually began within one-half hour after the injection and many men drank large quantities of water in attempts to assuage this symptom. Some men felt that even their skin was dry. A number of the participants who drank water remarked that it seemed to have a peculiar taste. The dryness, need for water, and altered taste perception might be significant considerations for a group in the field.

The second most common symptom reported during the post-injection period was dizziness. In no case did this become so profound as to be incapacitating. However, it was annoying and involved a significant number of the men. The next most common early symptoms were related to the eyes, but these involved less than ten per cent of the classes.

TABLE E

Subjective Symptoms Reported after 2 mg. Atropine Intramuscularly

	Number of Cases Reported by All Classes	
	First* Report	Later** Report
Symptoms reported:		
No symptoms (including those who did not receive injection)	19	14
Dryness of mouth, lips	152	120
Dryness of throat	17	101
Dryness of nose	1	36
Other dryness	18	22
Dizziness	37	41
Tired and sleepy	16	79
Light-headed	16	41
Headacke	16	41
Actually took extra sleep	-	40
Depression or other mood changes	-	15
Lack of physical coordination	1	11
Difficulty focusing eyes	9	24
Smarting of eyes	7	21
Photophobia	3	14
Difficulty reading	1	24
Dilation of pupils	-	23
Double vision	-	1
Other eye or vision symptoms	2	6
Numbness of skin, extremities, etc.	6	9
Face or other skin flushing	6	18
Rapid heart beat, palpitations	5	31
Nausea	4	4
Abdominal cramps	-	5
Pain or tingling of skin, extremities, etc.	-	2
Inability to swallow food	-	58
Difficulty in urinating	-	13
All other symptoms: chills, backache, pressure in throat, etc.	8	13
Symptoms not reported	2	48

*Reported within first two hours.
**Reported within 48 hours following injection.

TABLE F

ALL CLASSES: Onset and Duration of Symptoms Experienced by Twenty or More Men

	Dryness of Mouth	Dryness of Throat	Dryness of Nose	Other Dryness	Dizziness	Tired and Sleepy	Light-headed	Headache	Actually Took Extra Sleep	Difficulty Focusing Eyes	Smarting of Eyes	Difficulty Reading	Dilation of Pupils	Rapid Heart Beat, Palpitations	Inability to Swallow
Onset (in Minutes after Injection)															
15 or less (0-22)	34	21	8	4	8	8	4	8	-	3	3	1	2	11	3
30 (23-27)	43	31	10	4	7	11	6	10	1	5	5	1	2	14	9
45 (38-52)	20	14	3	3	7	-	1	3	-	1	1	2	3	-	2
60 (53-67)	13	25	9	4	10	23	13	11	3	4	2	5	7	4	19
75 (68-82)	2	1	-	-	1	1	1	1	-	1	-	-	-	-	1
90 (83-97)	1	2	2	3	3	7	3	1	3	1	1	3	1	-	6
105 (98-112)	-	-	-	1	-	2	-	-	-	-	-	-	-	-	2
120 (113-127)	3	3	2	1	1	11	5	3	10	6	7	7	4	2	11
over 120	3	2	2	1	4	14	7	3	19	3	2	5	2	-	4
Symptoms present but not reported	1	2	-	1	-	2	1	1	4	-	-	-	2	-	1
Median onset	31.9	36.8	38.0	50.5	49.8	65.7	63.4	48.0	158.0	64.2	64.2	105.0	60.5	27.8	64.4
Duration (in Hours)															
One hour or less	3	1	3	3	6	4	3	9	1	2	5	-	1	17	4
Over 1 to 2 hours	13	15	5	5	10	9	6	6	7	6	4	5	1	9	13
Over 2 to 3 hours	27	23	10	7	9	10	10	8	7	3	3	7	6	2	9
Over 3 to 4 hours	30	25	9	4	5	11	11	4	4	5	3	5	2	1	4
Over 4 to 5 hours	3	1	-	1	3	1	1	-	-	1	-	-	-	-	-
Over 5 to 6 hours	9	4	1	-	2	7	2	3	3	-	-	1	3	-	2
Over 6 to 7 hours	7	4	2	-	-	2	1	-	1	1	1	1	-	-	-
Over 7 hours	24	23	4	1	4	19	6	8	10	5	3	4	7	1	18
Symptom present but duration not reported	4	5	2	1	2	16	1	3	7	1	2	1	3	1	8
Median duration	3.5	3.4	2.9	2.4	2.4	3.8	3.1	2.5	3.1	3.1	2.2	2.9	4.5	0.9	2.9

In the final report, tiredness and sleepiness was the second most commonly reported symptom, and half of those who experienced this actually took extra sleep. About twenty per cent of the men complained of dizziness, light-headedness and headache during the later period, and a slightly smaller per cent experienced rapid heart beat and palpitations. Ocular symptoms only involved between ten and fifteen per cent of the subjects during the period following the initial two hours.

The dryness usually came on as a very early symptom and persisted for three to four hours in the majority of cases. The dizziness, light-headedness, sleepiness and headache came on somewhat later and likewise persisted three to four hours. Those who actually required extra sleep took their rest two hours or more following the injection. Most of them slept from 2 to 4 hours, although a significantly large group reported that they required over seven hours of extra sleep. Those with heart palpitations noticed this symptom within the first half hour, and it passed off by the end of the second hour in most cases.

Although none of these findings could be considered significant in the sense that the men required medical care, or that they were unable to leave by themselves, it does not follow that these symptoms would be as innocuous in the field. No well-controlled psychomotor or performance tests were carried out on the students to test the limiting effects of these symptoms. In a practical field situation, the dryness would probably only be considered annoying. However, the lack of sweating, ocular symptoms, dizziness, headache and tiredness might render some of the men unfit for anything but routine, self-maintenance activities, especially when exposed to elevated temperature, stress or increased exertion. During a military exigency these men might become liabilities. Accordingly, these aspects should be carefully considered in a controlled study carried out under practical field conditions.

VOLUNTEERS' EVALUATION OF AMPIN VERSUS SYRETTE

All of the men were given a lecture-demonstration on both the ampin and the syrette. Later they were given the two devices simultaneously to examine. Despite the fact that they only used one type of injector, they were asked to appraise both (Table G).

It is significant here that most men classified the use of either device as "not so difficult" or "not difficult at all". Three men who used ampins rated them "very" or "rather difficult", while two men who used syrettes rated them in this way. In other words, the users regarded both devices as easy and satisfactory for self-injection. However, an interesting finding in this appraisal is the fact that, although the men generally preferred the unit which they had actually used, men using the ampin considered their unit superior by a far larger number than men using the syrette. If the Not Reported cases are excluded, Section II of Table G reveals a statistically significant difference as regards which unit was harder to use. Of the men using the ampin, over three times as many considered the syrette the harder unit; whereas, the men using the syrette were almost equally divided in appraising which device was harder to use. The exact psychological mechanism here is unknown and can only be conjectured upon. It may well be that the idea of an automatic injection was appealing to most of the personnel.

TABLE G

Evaluation of Ampin Versus Syrette by all Volunteers Regardless of Units Used. All Men Used Only One Unit--Either Ampin or Syrette--but Evaluated Both

	Men Using Ampin					Men Using Syrette				
	Class 1	Class 3	Class 2	Class 4	All Classes	Class 1	Class 3	Class 2	Class 4	All Classes
Difficulty of Using Unit:										
Very difficult	1	-	-	-	1	-	-	1	-	1
Rather difficult	-	2	-	-	2	-	-	-	1	1
Not so difficult	8	4	10	4	26	4	2	11	7	24
Not difficult at all	8	4	19	14	45	11	8	12	7	38
Not reported	2	2	5	13	22	2	1	10	15	28
Unit Harder to Use:										
Ampin harder	4	6	4	-	14	10	6	9	4	29
Syrette harder	12	1	20	16	49	4	1	9	9	23
About the same	1	3	5	2	11	1	3	5	2	11
Not reported	2	2	5	13	22	2	1	11	15	29
Disadvantages of Ampin:										
None	9	3	16	12	40	3	1	9	5	18
Danger of incorrect breakage in use	6	5	7	1	19	2	7	3	3	15
Danger of breakage before use (while carrying, etc.)	2	1	6	3	12	3	1	4	2	10
Danger of breakage while attempting insertion	-	-	1	3	4	1	1	6	1	9
Difficulties of angle of injection	-	-	1	1	2	-	1	-	3	4
Danger of being cut by glass	-	1	1	-	2	1	1	1	-	3
General difficulty of manipulating device	1	-	-	-	1	2	-	-	1	3
Fear of fluid under pressure, fear of device	-	-	-	-	-	1	-	1	-	2
Miscellaneous	1	1	4	1	7	1	-	3	-	4
Not reported	3	2	5	13	23	6	1	10	15	32
Disadvantages of Syrette:										
None	5	6	6	-	17	9	7	7	6	29
Fear of the device; fear of squeezing material into self;etc.	2	2	9	2	15	2	-	1	2	5
Squeezing is awkward difficult, takes too long	2	-	6	7	15	-	-	2	3	5
Difficulty in getting entire injection: failure to empty tube completely	2	-	7	7	16	-	-	-	2	2
Difficulty of breaking seal	-	-	2	2	4	1	-	7	1	9
Danger of loss of some material before ins.	-	-	-	3	3	-	-	2	1	3
General difficulty of manipulating device	3	-	3	1	7	-	-	2	-	2
Miscellaneous	1	-	4	-	5	-	1	3	1	5
Not reported	5	4	7	14	30	5	3	11	15	34
Recommended Unit for Military Adoption:										
Ampin	9	2	21	18	50	1	-	5	7	13
Syrette	5	5	4	-	14	14	10	12	5	41
Either of them	3	3	4	-	10	-	-	7	3	10
Not reported	2	2	5	13	22	2	1	10	16	28

However, since men's approval or rejection of a device is an important consideration in their acceptance and proper use of the equipment, this factor must be considered of some import in the final decision. Despite this reaction in favor of the ampin, when it came to recommending a unit for military adoption, the men using the ampin recommended that unit, while those who had used the syrette preferred their unit.

PART C
OBJECTIVE STUDY OF EFFECTS RESULTING FROM ATROPINE INTRAMUSCULARLY IN HEALTHY ADULT MALES*

The observation of physiologic effects resulting from 2 mg. atropine was essentially a by-product of Parts A and B of this study. Since the men were kept in the area from 1 to 2 hours following the injection in order to elicit subjective reactions and to be sure they were able to continue their routine activities, it was possible to make a few clinical observations. The restricted time available for examination of such a large body of men precluded all but the most general determinations. Control studies were not done before the injection of atropine and it was also impossible to completely standardize the men's activities and the time lapse between drug injection and determination of physiological reactions. (In the determination of skin temperature, measurements were accomplished before and after the injection.)

Accordingly, these results cannot be analyzed according to strict pharmacologic or physiologic criteria. However, from a clinical point of view some responses were of interest and concern. <u>These are noted here merely as uncontrolled pilot observations</u>. They appear to deserve detailed study under controlled field conditions.

Gross neurological changes, such as abnormal reflexes, were not apparent in the first class of students. However, finer coordination was subjectively impaired in some individuals, i.e., one student who appeared normal to gross neurological examination complained that he was unable to walk the edge of a wooden plank, whereas, ordinarily he was a tight-rope walker. Three students complained of marked vertigo and were retained for observation beyond the two hour period. Their "finger to nose" test was impaired and nystagmus was observed in one of them. These few spontaneous complaints suggest the possibility of impairment of finer coordination. As isolated findings they are not significant, but rather indicate the necessity for detailed and controlled testing.

The observation period was limited, so when it became apparent that neurological findings were minimal the major effort was diverted to the observation of cardio-vascular effects. The tests employed included: auscultatory blood pressure, lying and standing; pulse rate, lying and standing; electrocardiograms on individuals with the most marked changes in either pulse rate or blood pressure; and skin temperatures of the hand before and after the injection. All observations were made one-half to one and one-half hours after the subject had received the drug.

*The authors wish to express their appreciation to Dr. Carl C. Pfeiffer, Professor and Head of the Department of Pharmacology, University of Illinois College of Medicine, for valuable assistance in planning this part of the study.

During analysis of the data, a specific relationship was sought between pulse rate alteration and body weight, or amount of dose actually received by Physical Education and Liberal Arts students. However, because of the small number of cases in each final category, no definitive correlation could be made. A search for similar relationships between blood pressure, body weight and drug dose, as well as between skin temperature alteration, body weight and drug dose was not rewarding.

Blood Pressure:

Auscultatory blood pressure in the supine and standing positions were made on 106 students between 30 and 90 minutes following the injection. Eighty-eight of them had had at least three-fourths or more of the unit dose of atropine. The remaining twenty-eight had received one-half or less of the total dose. Statistical analysis of the data shows that a significant number of those who received at least 75 per cent of the unit dose of atropine had a fall in systolic and diastolic pressures with a change in position from the lying to the standing. (Table 1). The changes in systolic pressure were statistically more significant than those in diastolic. There was a fall in pulse pressure but it was not significant.

TABLE 1

Comparison of the amount of dose taken to the alteration in blood pressure with a change from the horizontal to the vertical position

	Amount of Atropine taken		
Systolic Pressure	1.5 mg. or more	1.0 mg. or less	Total
Elevation with standing	17	14	31
Fall with standing	71	4	75
Total	88	18	106

Chi square = 26.8 (significant to 0.1 per cent level)

	Amount of Atropine taken		
Diastolic Pressure	1.5 mg. or more	1.0 mg. or less	Total
Elevation with standing	45	14	59
Fall with standing	43	4	47
Total	88	18	106

Chi square = 4.37 (significant to 5 per cent level)

A comparison was also made between the blood pressure changes in the Physical Education and Liberal Arts students. This was done to determine if the physiological effects were influenced by the status of physical conditioning, since the Physical Education students included athletes who are generally recognized as having better cardio-vascular adaptations to physical stress. The results of this comparison indicate that there was no difference in the blood pressure response of these two groups. (Table 2).

TABLE 2

Comparison of blood pressure change with position change from horizontal to vertical position in trained and non-trained individuals receiving 3/4 or more of 2 mg. dose of atropine.

SYSTOLIC

Blood Pressure	Trained	Non-Trained	Total
Elevation on standing	13	4	17
Fall on standing	55	16	71
Total	68	20	88

Chi square = 0 (not significant)

DIASTOLIC

Blood Pressure	Trained	Non-Trained	Total
Elevation on standing	32	13	45
Fall on standing	36	7	43
Total	68	20	88

Chi square = 2.31 (not significant)

Two observers independently noted while taking blood pressures that in a number of individuals the blood pressure while lying flat was hypertensive or normal but on standing it fell to levels frequently considered "shock-like" in clinical situations. That is, both systolic and diastolic pressures were low, the pulse pressure was very narrow and the sounds were distant. For this reason, the findings for those subjects who demonstrated the most marked changes in blood pressure in the recumbent and standing positions were tabulated. These included twenty-five of the 106 subjects in whom blood pressures were taken. (Table 3). Three general types of blood pressure responses to change in position were noted. Five individuals (Group 1) had a hypertensive blood pressure while lying down and a fall to normal pressure upon standing. Hypertension was defined as a systolic pressure greater than 150 mm. Hg. or a diastolic greater than 90 mm. Hg., or both. Thirteen individuals (Group 2) had a normal blood pressure lying down and a fall on standing, to hypotensive levels clinically considered "shock-like". The criteria for this were arbitrarily set at: (a) a systolic pressure of 90 mm. Hg. or less, or a pulse pressure of 20 mm. Hg. or less. (Two cases with systolic pressures of 96 and 98 were also included here.) There were seven subjects (Group 3) in whom a hypertensive pressure was present while recumbent and a "shock-like" pressure was found on standing.

TABLE 3

Analysis of cases showing most profound changes in cardio-vascular adaptation to 2 mg. dose of atropine*

Group**	Case	Blood Pressure		Pulse		Skin Temperature		Weight (lbs.)	Height (in.)
		Lying Syst/Diast	Standing Syst/Diast	Lying	Standing	Before	After		
1	1	160/110	120/80	--	--	--	--	158	70
1	2	150/118	110/80	112	132	--	--	165	67
1	3	155/110	110/80	120	132	27	27	115	66
1	4	142/92	110/90	120	124	29	33	155	72
1	5	140/102	114/90	90	120	32	33	150	69
2	6	120/88	90/68	84	118	29	28.5	165	73
2	7	112/90	90/80	84	112	31	30	160	72
2	8	100/64	90/72	104	128	--	--	156	65
2	9	120/90	98/70	--	--	--	--	153	68
2	10	100/70	96/88	--	--	--	--	148	66
2	11	92/70	80/60	--	--	--	--	157	74
2	12	128/88	96/68	108	136	28	35	141	69
2	13	120/84	96/78	84	112	30	35	140	71
2	14	122/90	86/78	108	128	26	29	155	72
2	15	100/68	72/54	108	126	29	34	135	69
2	16	116/86	98/88	100	120	29	33	178	71
2	17	110/80	90/80	84	100	32	34.5	142	68
2	18	128/82	92/80	72	104	30	31	145	70
3	19	120/100	92/80	--	--	--	--	158	68
3	20	140/110	98/80	--	--	--	--	130	67
3	21	140/110	80/60	108	124	33	36.5	135	64
3	22	124/96	84/70	100	120	33.5	36.5	160	71
3	23	140/104	90/80	128	140	27.5	26.5	140	74
3	24	130/100	90/70	92	136	34	36	200	69
3	25	150/98	98/88	108	140	30	34	127	71

* All cases received full 2 mg. dose of atropine except case No. 5 who received only 1 mg.

** Group 1 -- Recumbent hypertension with fall to normal pressure upon standing. Hypertension is defined as a systolic pressure greater than 150 mm. Hg. or a diastolic pressure greater than 90 mm. Hg. or both.

Group 2 -- Normal pressure on lying with a fall to "shock-like" levels upon standing.

Group 3 -- Recumbent hypertension with "shock-like" pressure on standing. The arbitrary criteria used here are: (a) systolic pressure of 90 mm. Hg. or less; and (b) or a pulse pressure of 20 mm. Hg. or less. Cases 9 and 12 are included although they do not fall entirely within this range.

Some further information can be obtained from this table:

(1) Twenty-four of the twenty-five subjects who had these abnormal responses received the full 2 mg. dose, while in the total group in which blood pressures were taken, seventy-nine of 106 had all of the dose. This finding is significant. (Table 4)

TABLE 4

Comparison of amount of dose received with blood pressure response to change in position from recumbent to standing.

Amount of Dose	Blood Pressure Response	
	Abnormal Response	Normal Response
Total Dose (2 mg.)	24	55
Less than 2 mg.	1	26
Totals	25	81

Chi square = 7.1 (significant to 1 per cent level)

(2) In the general population, the median weight was 161.5 pounds. Twenty-one of the twenty-five weighed less than the median. This also is significant. (Table 5).

TABLE 5

Relationship of cases having abnormal blood pressure response to median weight of the group (median weight equals 161.5 pounds.)

Relation to median weight	Number with abnormal blood pressure response
Below 161.5	21
Above 161.5	4
Total	25

Chi square = 21.4 (significant to the 0.1 per cent level)

(3) In general, the more abnormal responses were noted in the individuals who weighed less and the impression is gained that the asthenic type was effected more.

Pulse Rate:

Table 3 shows that a definite tachycardia was present in most of the individuals both when lying down and when standing. This tachycardia was

logically more pronounced when the subjects were standing. A compensatory increase in pulse rate on standing occurred in all individuals regardless of the amount of drug injected. (Table 3). Table 6 indicates that in general the increase of the pulse rate was greater in the subjects who received at least 3/4 of the unit dose of atropine, although this was not statistically significant.

TABLE 6

Comparison of pulse rate increase from the horizontal to the standing position as related to the amount of 2 mg. dose of atropine actually taken.

Amount of Atropine	Elevation in Pulse Rate										
	0-9		10-19		20-29		30-39		Over 40		
	No.	%	No.	%	No.	%	No.	%	No.	%	Total
3/4 of dose or more	4	5	21	27	35	44	10	13	9	11	79
1/2 of dose or more	6	37	2	13	6	37	2	13	0	0	16
Totals	10		23		41		12		9		95

Skin Temperature:

The increase in skin temperature following even a minimal dose of atropine was quite apparent. There was no correlation between the amount of drug injected and the degree of skin temperature increase. It should be noted that skin temperatures were taken by the subjects holding an ordinary 0-100° C. laboratory thermometer between the thumb and index finger. This method was crude and allowed wide divergence. However, the overwhelming number showed an increase skin temperature.

Electrocardiograms:

Approximately fifty electrocardiograms were taken, particularly on individuals in whom marked tachycardia or abnormal blood pressure responses were noted. The three standard leads were taken in the sitting position. All electrocardiograms were essentially normal except for sinus arrythmias and sinus tachycardia.

DISCUSSION

It cannot be emphasized too strongly that this was not an ideally controlled study; control readings of pulse and blood pressure were not made prior to the administration of the drug. In addition, it would have been desirable to standardize: the length of the standing period; nature of the change from horizontal to vertical (activity or passivity); character of stance (rigid or relaxed); amount of exercise or rest preceding test; room temperature; and, other incidental considerations. Nevertheless, in the absence of this controlled pharmaco-physiologic situation, these observers were faced with a more strictly clinical situation, which a battalion surgeon might encounter

following use of atropine by troops in the field following suspected presence of nerve gases. The definite clinical impressions gained in this situation appear interesting and significant. Their exact importance, however, must be determined by detailed and controlled studies. These impressions are confined to the disturbance of circulatory compensatory mechanisms, following the relatively large dose of atropine.

The normal circulatory adjustment to a change in position from the horizontal to the vertical consists of an elevation of blood pressure, particularly the systolic, and an increase of pulse rate. The mechanism of this is probably a carotid sinus reflex which causes a relative constriction of certain vessels to dependent areas, thereby preserving the blood volume for distribution to vital areas.

The essential disturbances noted in this study were a significant fall in systolic and diastolic pressures on changing position, together with an increase of skin temperature. In some smaller individuals who received the full dose, the pressure approached remarkably low levels. These observations may be interpreted as resulting from either vasodilatation alone or in combination with inhibition of autonamic reflexes. The well-known atropine flush and the increase in skin temperature indicate a disturbance in the normal vascular responses resulting from use of the drug. On standing, if the blood cannot be diverted from these areas, blood pressure may fall. A contributing factor may also be the initial tachycardia, which is further increased on standing. This may result in very short and inadequate diastolic filling of the ventricles. The mechanism of action must, however, be investigated.

The hypertension noted in individuals in the horizontal position and followed by a decrease to abnormally low levels on standing is puzzling and, at this time no explanation can be given. Further studies involving better controls are needed to verify this observation.

Clinically it is of interest that the observers were more alarmed about the low blood pressures than were the patients. Although some subjects had a barely perceptible blood pressure, they felt well except for moderate vertigo. Only three patients were held for additional observation and these were discharged two and one-half hours after the injection. However, it should be noted that for one to two hours after the injection, the subjects either rested or engaged in routine activities. The ability of these individuals to perform any coordinated acts requiring special skill or physical exertion was not tested. Physical exertion, especially in the smaller individuals and in warm temperatures might lead to a cardiovascular collapse.

SUMMARY

1. The important physiological effects noted here involved a failure of the cardiovascular compensatory mechanisms.

a. A significant number of individuals had marked alterations in blood pressure, as evidenced by depression of systolic and diastolic pressure with change in position from lying to standing.

b. The blood pressure alterations were most marked in the smaller individuals, primarily those who received the full 1.66 mg. dose of atropine base.

2. A significant tachycardia and elevation in skin temperature were also noted.

3. Electrocardiographic tracings on the individuals with the most profound changes in pulse rate and blood pressure revealed them to be essentially normal.

RECOMMENDATIONS

1. A further well-controlled study should be executed with attention directed at cardiovascular alterations resulting from unit doses of atropine, especially as applies to field situations.

2. It should be recognized that postural hypotension, in some instances approaching clinical "shock-like" blood pressure, in the standing position, in personnel who have received 1.66 mg. atropine base does not necessarily signify true shock. However, with exertion, it does not preclude the possibility of impaired cardiovascular function or collapse.

3. Further studies in which atropine is used should include tests of finer coordination, as well as the effects of darkness, battle dress, and other practical circumstances.

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(Copies obtainable from ASTIA-DSC by U.S. Military Organizations only)

Army Chemical Center, Chemical Corps Medical Labs., Md. (Medical Laboratories Special Report No. 10)

Evaluation of Intramuscular Self-Injection of 2 MG. Atropine - Parts A thru C

Gordon, Archer S.; Kalser, Martin H.; Silberberg, Sidney and Others
March'52 31pp. photos, tables

Gases, Poisonous - Antidotes
Atropine

Medicine (19)
Pharmacology (19)

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