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FINAL REPORT

Army Chemical Corps Medical Laboratories

Contract No. DA 18-108-CML-2395
(June 15, 1951 to June 1, 1954)

and

Contract No. DA 18-108-CML-5365
(June 1, 1954 to January 1, 1956)

RESUSCITATION AND ATROPINIZATION in
TREATING ANTICHOLINESTERASE POISONING

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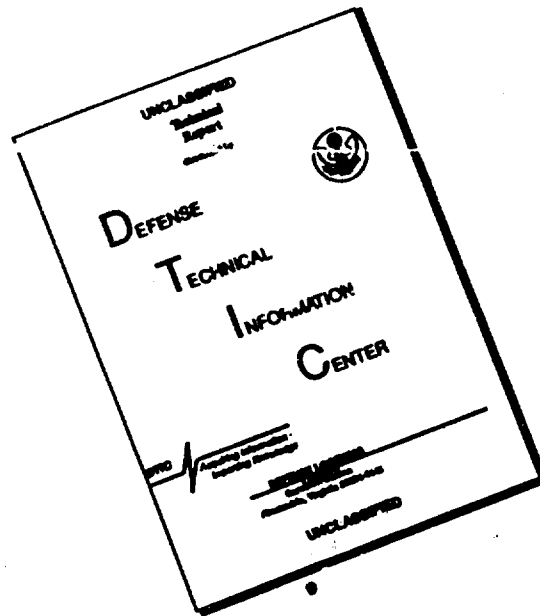
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✓ Poisoning by anticholinesterase agents demands rapid and adequate atropine administration and artificial respiration. These measures have been shown consistently to be the essentials of good treatment. Accordingly, studies under Chemical Corps Medical Laboratories Contract No. DA 18-108-CML 2395 (June 15, 1951 to June 1, 1954) and the first eighteen months of contract No. DA 18-108-CML-5365 (June 1, 1954 to January 1, 1956) have been concerned with various aspects of resuscitation and atropinization. During this time the following investigations have been completed under these contracts:-

Publications and Reports

A. Resuscitation:

I. Manual Artificial Respiration:

1. Critical Survey of Manual Artificial Respiration: Archer S. Gordon, Max S. Sadove, Frank Raymon and A.C. Ivy: J.A.M.A. Vol. 147, pp-1444-1453, Dec. 8, 1951.
2. Artificial Respiration Methods for casualties Wearing Gas Mask: Archer S. Gordon, Charles W. Frye, Robert D. Miller and Gordon Lyant, MLCR No. 45, Army Chemical Center, Maryland, November, 1954.
3. Ibid., U.S. Armed Forces Medical Journal, Vol. 16, No. 6, pp. 781-793, June, 1955.

II. Mechanical Artificial Respiration:

4. Standard Army Equipment for Mass Resuscitation and Artificial Respiration of the Critically Injured: Archer S. Gordon and Charles W. Frye, CCML Contract Report No. 9, Army Chemical Center, Maryland.
5. Performance Characteristics of New Mechanical Resuscitators Archer S. Gordon, CCML Progress Report, Contract DA-18-108-CML-2395, June 1, 1954.
6. Measurement of Pulmonary Edema and the Effect of Negative Pressure Respiration: Charles W. Frye and Archer S. Gordon MLCR No. 44, Army Chemical Center, Maryland, November, 1954.

B. Atropine Sulphate:

I. Atropine Administration:

7. Evaluation of Intramuscular Self-Injection of 2 mg. Atropine: Archer S. Gordon, Martin H. Kalser, Sidney Silberberg and Charles Frye, CCML Special Report No. 10, Army Chemical Center, Maryland, March, 1952.
8. Evaluation of Units for Atropine Self-Injection: Archer S. Gordon, CCML Special Report No. 13, Army Chemical Center, Maryland, August, 1952.
9. Atropine Injection Units: Studies of Comparative Performance with Ace and Ampin: Archer S. Gordon and Martin H. Kalser, MLCR No. 17, Army Chemical Center, Maryland, August, 1953.

II. Atropine Effects:

10. Physiological Tests as Index of Atropine Absorption: Charles W. Frye, Robert D. Miller and Archer S. Gordon, MLCR No. 26, Army Chemical Center, Maryland, March, 1954.
11. Measurement of Atropine-Induced Vascular Pooling: Robert D. Miller, Martin H. Kalser, Charles W. Frye and Archer S. Gordon, MLCR No. 25, Army Chemical Center, Maryland, March, 1954.
12. Ibid., Circulation, Vol. X, No. 3:423-429, September, 1954.
13. Postural Hypotension Induced by Atropine Sulfate: Martin H. Kalser, Charles W. Frye and Archer S. Gordon, Circulation Vol. X, No. 3:413-422, September 1954.
14. Evaluation of Atropinization by Various Routes in Humans, Philip Andrews, Robert D. Miller and Archer S. Gordon, MLCR No. 59, Army Chemical Center, Maryland, July, 1955.
15. Large Doses of Atropine: Low Toxicity and Effectiveness in Anticholinesterase Intoxication: Archer S. Gordon and Charles W. Frye, J.A.M.A. Vol. 159, pp. 1181-1184, Nov. 19, 1955.
16. Atropinization by Intracardiac, Intravenous, Intrapulmonary, Intramuscular and Intraperitoneal Injection Routes: Philip Andrews and Archer S. Gordon, Semi-Annual Progress Report, CCML Contract No. DA-18-108-CML-5365, January, 1956.

Manual Artificial Respiration

Studies on manual artificial respiration completed under previous Department of Defense contracts administered through Army Chemical Center Medical Laboratories have been compiled and summarized under the current contracts.

In addition to extensive investigations regarding the adequacy of pulmonary ventilation, which is the most important consideration in resuscitation, other problems of manual artificial respiration have been studied, including: (a) circulatory phenomena and gas exchange; (b) pneumotachographic studies; (c) energy expenditure of operators; and (d) pedagogical and performance factors.

Ventilatory studies were performed on three types of subjects:

(1) warm, non-rigid corpses immediately after death and before the onset of post-mortem changes; (2) normal adult males, curarized-anesthetized to total apnea; and (3) normal adult males trained to suspend respiration passively. All studies were corroboratory in revealing that those methods which produce an active inspiratory phase and an active expiratory phase, so-called "push-pull methods," are two to three times as effective, as regards pulmonary ventilation, as those methods which have only a single active phase, either inspiratory or expiratory. The push-pull methods include Hip-Lift Back-Pressure, Arm-Lift Back-Pressure and Arm-Lift Chest-Pressure (Silvester). The Schafer Prone Pressure method and the Emerson Hip-Lift method are significantly less effective. The Eve Rocking method (which, strictly speaking, is not a manual method except when applied to infants rocked in the operator's arms) and the Hip-Roll Back-Pressure method are push-pull types but are not as effective as those listed above.

Circulatory studies were also performed on normal adult males, curarized-anesthetized to apnea. These indicated that the mean arterial oxygen saturation is maintained at near normal levels during fifteen minute performance periods with all of the push-pull manual methods. During similar periods of performance of the Schafer prone pressure method, the arterial oxygen saturation fell to a mean of only 67 per cent in a series of 15 cases.

In co-operation with Drs. James L. Whittenberger and John Affeldt of the Harvard School of Public Health, pneumotachographic studies were performed on a further series of curarized-anesthetized normal adult males. These indicated that optimal ventilation is obtained with the push-pull methods by a rate of 12 per minute. Air flow patterns show that this rate results in almost continuous movement of gas in and out of the lungs.

Oxygen consumption per unit of time was used as a measure of energy expenditure by a group of operators performing the various methods on anesthetized patients. Schafer prone pressure was found to be the least taxing, and hip-lift back-pressure required the greatest energy expenditure. The Silvester arm-lift chest-pressure method and the arm-lift back-pressure methods occupy intermediary positions.

Studies carried out on 1000 naval recruits and 200 Waves at Great Lakes Naval Training Center established that, following a ten minute lecture-demonstration on the performance of the various methods, the arm-lift back-pressure method surpasses all variations of the hip methods in accuracy of performance, ease of learning--as measured by the need for an amount of correction--and physical ease of performance.

On the basis of these studies it is possible unequivocally, to

recommend use of the push-pull methods where manual resuscitation is required. Since ventilatory and circulatory effects are essentially the same with all of these methods, the arm-lift back-pressure method is best recommended for general use since it is easier to perform, especially for prolonged periods of time, and is somewhat easier to teach and perform accurately. It is recommended that medical personnel and other trained persons be accomplished in the application of other methods, including hip-lift back-pressure and arm-lift chest-pressure, for use under special conditions which preclude use of the arm-lift back-pressure method.

The necessity for use of the manual methods in field situations where military or civilian personnel may be exposed to anticholinesterase agents raises an additional question. This regards the efficacy of the push-pull methods in accomplishing adequate pulmonary ventilation for casualties wearing gas masks in a contaminated atmosphere. To resolve this issue, a further study was performed on both warm, non-rigid corpses and curarized-anesthetized normal adult males. The various push-pull methods and Eve Rocking method were performed on these subject while they were wearing standard military gas masks and cannisters. Ventilation and intramask pressure were measured. Application of the mask reduces ventilation to approximately 3/4 of the value obtained without the mask. However, with the push-pull methods the amount of ventilation remains at a level 1 1/2 times the normal resting tidal volume of the subjects. The intramask pressure differentials indicate that all of the push-pull methods produce the same expiratory pressure. However, the hip-lift back-pressure results in the greatest intramask inspiratory pressure, and the other two push-pull methods produce slightly less.

It becomes apparent that with a clear airway the push-pull manual methods are able adequately to ventilate casualties wearing military gas masks in a contaminated atmosphere. In case of respiratory obstruction, the hip-lift back-pressure method results in the greatest intramask inspiratory pressure and presumably, would be most efficient in overcoming increased airway resistance.

Mechanical Artificial Respiration

These studies have established that a well-performed push-pull manual method is suitable for adequate and efficient resuscitation. Mechanical devices when available, are useful for supplementing or replacing manual artificial respiration. The principle advantages of automatic units or mechanical devices are:- (1) ease of operation; (2) prolonged resuscitation; (3) supply oxygen; and (4) allow one operator to care for multiple simultaneous casualties.

Consideration of mechanical units requires analysis of both the physiologic and the practical aspects of their use. As regards the former, we have performed comprehensive studies on both animals and humans to evaluate the cardio-respiratory dynamics of controlled respiration in the open and closed chest. This has resulted in the determination of a physiologically ideal airway pressure curve and the testing of a unit which will provide such a curve.* These investigations are being completed under current contract and will be summarized in a semi-annual progress report due July, 1956.

In addition to these overall cardio-respiratory dynamics, we have been

* Unit made available by E & J Manufacturing Co., Burbank, California

concerned with a special problem of pressure breathing. This centers about the controversial issue of whether negative pressure applied to the airway---as in positive-negative pressure resuscitators and controlled respiration units---can lead to the production of pulmonary edema. The evidence supporting the contention that negative airway pressure results in pulmonary edema is rather inferential and embraces such facts as the beneficial effects of intermittent positive pressure breathing in the therapy of pulmonary edema, and increased lymphatic flow in the thoracic duct during negative airway pressure.

In order to further clarify this issue, studies were performed on pulmonary edema and the effect of negative pressure breathing. A controlled series of tests was performed on dogs, using three objective criteria to measure the presence of pulmonary edema. These were: (1) changes in body weight/lung weight ratio; (2) alteration of the pressure-volume diagram of the lungs and thorax; and (3) microscopic examination of post mortem lung specimens.

The study was divided into three phases, in each of which blood pressure and arterial oxygen saturation were measured in addition to the above determinations. In the first phase these data were compiled on a series of normal dogs. The second phase consisted of data collected from animals with experimentally produced pulmonary edema and the third phase from animals who had been subjected to negative pressure breathing on pure oxygen for three hours at a range of 0 to minus 40 cm. water.

On the basis of these criteria it was shown that negative airway pressure per se,---even this large amplitude for a three hour period---does not produce pulmonary edema. Negative pressure breathing results in a shift in

the normal pressure-volume diagram in a direction opposite to that resulting with induced edema. The body weight/lung weight ratio similarly is shifted in the opposite direction from that resulting from induced pulmonary edema. A tendency toward atelectasis, but no pulmonary edema was noted on gross and microscopic examination of the lungs following the negative pressure respiration.

A myriad of mechanical devices has been proposed for resuscitation under various circumstances. These have included electrophronic stimulation, rocking units, bellows manipulated by the hands or feet, bags to be squeezed, mask to mask insufflation, etc. The physiologic aspects resulting from use of these units have been readily resolved by controlled studies. However, the practical considerations of procurement, storage, supply, ruggedness, and suitability for field use, especially by a variety of personnel both medical and non-medical as well as skilled and untrained, are more difficult to assess. Comparative practical evaluation is impossible, and we have not attempted such. However, under these contracts we have evaluated the performance characteristics of several new mechanical resuscitators. These include: (1) Stephenson Modified Minuteman Resuscitator (Military Model); (2) Stanton Handy Resuscitator; and (3) Morch Electronic Resuscitator.

The Stephenson Military Model is a pressure cycling automatic resuscitator for providing intermittent positive pressure or alternating positive-negative pressure breathing. It incorporates a wide range of pressure settings, rate control, manual over ride and extra connections so that several resuscitators can be used simultaneously from the same pressure reducing valve. The unit produces essentially a peaked bi-phasic, straight

line airway pressure curve. The various settings usually result in a high mean mask pressure which is not desirable for routine use. The high mean is primarily related to the excessive duration of the inspiratory phase, which in most instances exceeds 50 per cent of the total respiratory cycle. The multiplicity of settings of the unit is probably ill-advised in a model for field use where relatively unskilled personnel would be required to regulate the machine in a wide variety of respiratory emergencies.

The Stanton Handy Resuscitator is also a pressure cycling automatic resuscitator. It provides positive-negative pressure breathing with mechanisms for rate control and inhalation therapy. It does not feature high peak inspiratory pressures or manual over ride controls for use in non-compliant airway. The pressure curve is bi-phasic with inspiration and expiration of approximately equal duration. Here also, the mean mask pressures are somewhat above the average for this type of unit.

The March Resuscitator is an experimental electronic pressure cycling automatic resuscitator. It consists of an electrically driven air compressor, with solenoid valves and a pressure switch arranged to produce either intermittent positive or positive-negative pressure breathing. It functions by activating the bag of anesthesia machine. It incorporates a wide range of cycling pressures, rates, and ratios of inspiration to expiration, and an attached hand bellows for use in the event of a mechanical failure. The unit has great versatility, but its complexity limits its usefulness to hospital situations where resuscitation or controlled respiration are required. Other limiting factors are its bulk and noise.

There are several situations for which the strictly manual methods of resuscitation do not apply and for which automatic resuscitators may

not be available. These include:

- (1) Field resuscitation of the critically injured, whose wounds will not permit use of the manual maneuvers;
- (2) Mass resuscitation of a large number of casualties simultaneously, as might occur following exposure to the nerve gases; and
- (3) Prolonged resuscitation, for which the manual techniques become too fatiguing.

For these situations a standard Army stretcher can be modified into a portable Eve Rocking Resuscitator. A collapsible rocker is mounted under the stretcher in such a fashion that routine use is not affected. When desired, the rocker can be opened and the stretcher immediately used for rocking resuscitation. Side arms on the stretchers provide a means for connecting several of them in a series so that a single operator can perform multiple resuscitation. In addition to these features, this unit has the advantage of using modified standard military equipment rather than requiring use of new or additional equipment.

Atropine Administration

The necessity for rapid atropinization in the treatment of anticholinesterase intoxication may require self-injection of the drug by troops in the field. Accordingly, a series of "field" tests were performed to evaluate the objective and subjective response to intramuscular self-injection with various devices.

In the initial study, one hundred and eighty-eight normal healthy male Liberal Arts and Physical Education students at the University of Illinois voluntarily participated in a comparison of self-injection with Syrettes (Squibb & Son) and Ampins, (Strong Cobb & Co.) each loaded with 2 mg. of atropine sulfate. Since it was not deemed desirable to have the students receive 4 mg. of atropine, each man used only one device. This was not a completely controlled comparative test but the results indicated a general trend in favor of the Ampin, which was the more automatic device. During the 90 to 120 minutes immediately following the self-injection, no serious physiologic effects were noted in the volunteers. The most common subjective complaints were dryness, tiredness and dizziness.

Subsequently, a controlled study using the Ampin and Syrette was carried out on a military population. Approximately 900 trainees at the Medical Replacement Training Center, Camp Pickett, Virginia, participated in these studies on a nonvolunteer basis as part of their regular training. Following a lecture-demonstration regarding the proper use of the Ampin and the Syrette, each man was required to attempt injection with both. Trained monitors timed and rated the men during their performance and filled out rating sheets recording their ability with the devices. The trainees then filled out a questionnaire which appraised their subjective evaluation of both units. Injection was tested under four circumstances:

(1) self-injection under standard conditions; (2) self-injection while wearing a gas mask; (3) self-injection in the dark; and (4) injection of other trainees.

Despite all attempts at the elimination of biasing factors, several circumstances predisposed the men toward the Syrette. Most of them had previously received a training lecture on the Syrette, and they found the teaching of this unit slightly better than the teaching of the Ampin. They also found the Syrette easier to understand than the Ampin, were surer of how to proceed to use it and found it less difficult to use.

However, the use of the Syrette was not accomplished as well as the use of the Ampin. There were more absolute failures with the Syrette, and there was less complete dose administration with the Syrette. Furthermore, the performance with the Syrette always took longer than with the Ampin.

When questioned, the men felt that the Ampin was faster to use and preferred it for standard self-injection, self-injection in the dark and injection of others. All groups except those who injected others favored use of the Ampin by the Armed Forces; whereas, all groups except those who used a gas mask considered the Syrette more practical for field use.

The most common difficulty with the use of the Ampin was in knowing how and where to break the ampoule. With the Syrette, ^{im-}proper piercing of the seal was the most frequent cause of error. A number of secondary difficulties occurred with the use of either unit.

Since these studies indicated that partially automatic units (Ampin) are used faster and more efficiently for self-injection than non-automatic

units (Syrette), a further series of tests was performed comparing the Ampin with a new automatic unit, the Ace (Potter Aeronautical Co.) These Studies were performed at Medical Replacement Training Center, Camp Pickett, Virginia, using one thousand military recruits during their first two weeks of medical basic training. All men used both units loaded with isotonic physiologically normal saline. They were divided into groups in order to test various conditions. In addition to standard conditions, some of the groups were evaluated for retention of instruction at a subsequent test period; injection through clothing; injection in the dark; and injection with one hand only.

Disregarding mechanical failures, (15.8% of the Ace units were defective and 0.6% of the Ampins were defective) it was found that three-fourths of all men performed adequately or better with both units. Where only one unit was performed adequately, the advantage was in favor of the Ace.

The speed of performance was overwhelmingly in favor of the Ace unit in all groups. The most distinctive advantage was noted in the one-handed group. The superiority of the Ace was slightly less pronounced with the group which performed in the dark. The actual time required for the injection was doubled with use of the Ampin in the darkness and retest group, while it was tripled or more in the standard one-test, clothing and one-handed groups where men were using non-defective units and performed adequately with both units.

The most common errors in performance with the Ace by men who performed adequately were failure to remove the pin on the first try and inadequate pressure to the thigh on the first trial. Numerous errors of several

types were committed by operators who performed adequately with the ampin. These included: failure to insert needle on first try; incorrect insertion of needle; ampoule not broken on first attempt and bottle tilted at wrong angle.

On the basis of their experiences, the overwhelming preference of all men was for the Ace unit. They considered it to be better taught, easier to understand, easier to perform, require less improvement, faster, best for field and all other situations and should be adopted by the Armed Forces.

Atropine Effects

Studies of atropinization require determination of onset, duration and intensity of effects. A chemical blood test would be most valuable for this purpose since it would allow quantitation of the results. To date, direct chemical tests have not been found technically applicable for use with blood or serum. However, it is possible to measure the effects indirectly by use of physiological tests based on atropine-induced changes in vascular tone, skin resistance, pupil size, pulse rate, and sweating. In order to ascertain the most useful physiologic tests for detection of atropine effects we have evaluated the Krasno-Ivy Flicker Fusion Photometer for detection of changes in the retinal vessels; sweat response measured by the starch-iodine skin test; skin resistance measured by use of the Neuro-dermometer; pulse rate changes; and pupillary size.

It was found that variations in the flicker fusion threshold and pupil size do not give results which are consistent and rapid enough in onset. The changes during a 30 minute test period were too small to

be useful with either of these determinations. The remaining tests provide varying degrees of sensitivity for the onset of atropinization. The starch-iodine and skin resistance tests during sweating induced by heat and humidity provide the most sensitive measures of atropine absorption and activity. Since response by an organ distant from the site of injection indicates absorption into the general circulation, the difference in time for the atropine to affect sweat glands and heart must be due to a difference in sensitivity of these receptors to atropine.

In our tests the sweat glands showed the highest degree of sensitivity. The starch-iodine and skin resistance tests gave essentially identical results. Skin resistance measurement probably is more accurate because of greater objectivity and reduction in the personal error. The starch-iodine tests are good, however, because of the ease of performance and lack of special equipment required. Minute to minute monitoring the pulse provides a useful key to atropine onset and effects including the rarely observed slowing of the pulse which precedes the usual tachycardia.

During the initial studies on self-injection of 2 mg. of atropine sulfate, an incidental observation was that hypotension occurred in many individuals while standing. Accordingly an experimental protocol was set up in which 73 normal adult males had blood pressure, pulse and temperature recorded (a) under control conditions; (b) following a placebo injection; and (c) following an intramuscular injection of 2 mg. of atropine sulfate. The subjects exhibited a normal blood pressure and pulse rate response to change in position from supine to erect in control studies and following a placebo of 1 ccs. of an isotonic physiologically inaction solution. This consisted of a slight rise in systolic pressure, with a gradual return

to normal, and a marked rise in pulse rate and diastolic pressure with the elevation being sustained or increasing slightly. Following atropine this normal blood pressure response was altered and was characterized by a profound and sustained fall in systolic pressure with only one-half the previous diastolic rise. A 30 second period of a standard exercise at the time of standing enhanced this fall in systolic pressure and resulted in a simultaneous fall in diastolic pressure.

The most probable explanation for this phenomenon appears to be vascular pooling in dependent muscle masses and/or the splanchnic bed. To evaluate this hypothesis further investigation was undertaken to assess the role of this mechanism in the production of atropine-induced postural hypotension.

For this purpose 30 normal adult males wearing Air Force anti-blackout suits were evaluated following intramuscular injection of 2 mg. of atropine sulfate as compared to a similar injection of isotonic physiologically inactive solution. Their vascular pooling responses were tested with a series of tilts from the horizontal to the vertical position. At each tilt one possible variant was used, including: (1) no inflation of the suit; (2) inflation of the abdominal compartment only; (3) inflation of the lower extremities compartment only; (4) inflation of both the abdominal and lower extremities compartments simultaneously.

These controlled studies corroborated the effect of 2 mg. of atropine sulfate in decreasing vascular tone with resultant pooling in the dependent areas of the body in the erect position. Pooling occurs in both the splanchnic and peripheral vascular beds. Application of external

compression to the abdomen and lower extremities allows easier cardiovascular compensation for the postural changes. Compression of the legs and abdomen is much more effective than compression of either area alone. The exact mechanism for this phenomenon has not been worked out in detail.

A further consideration regarding atropinization is the onset and effects by various routes. Physiologic tests of onset, duration and intensity of atropinization were performed on ten normal adult males comparing the effects of intramuscular and subcutaneous injections of 2 mg. of atropine sulfate in warm and cool atmospheres and the inhalation of 2 and 5 mg. of atropine sulfate powder and vapor.

Results indicated that a 2 mg. dose of atropine sulfate gives almost equal effects with either intramuscular or subcutaneous injection. Minor differences weighing in favor of subcutaneous administration are not statistically significant or occur as late effects of atropinization. Practical considerations favor the use of the intramuscular route.

Inhalation of 5 mg. of the drug gives physiologic effects similar to the injection of 2 mg. The response to 5 mg. of atropine sulfate vapor is more pronounced than the response to 5 mg. of atropine sulfate powder. However, the use of this dose of atropine sulfate produces undesirable symptoms and effects. The use of inhalators for administration of this drug also appear ill-advised on a practical basis.

Subsequently, studies have been performed on twelve mongrel dogs to evaluate the comparative efficacy of atropinization by the intracardiac, intravenous, intrapulmonary, intramuscular and intraperitoneal injection routes. The intracardiac route results in the most rapid onset

of evidences of atropinization. Intravenous injection is almost as rapid, after the needle has been placed. Intrapulmonary injection is more than twice as fast as intramuscular, and intraperitoneal gives the slowest rate of atropinization.

On a practical basis, heart puncture is much more easily and readily accomplished than intravenous (or intra-arterial) injection. The intrapulmonary route is easily performed but, according to the literature and in this small series of dogs, it is associated with a greater hazard.

The recommendation for doses of atropine which appear massive when compared with the usual clinical dosage, led us to investigate the toxicity of atropine reported in the literature as well as the effectiveness of atropine in reported cases of anticholinesterase intoxication. Careful analysis of reported cases of anticholinesterase intoxication clearly indicates that survival depends upon: (1) the speed with which atropine therapy is started, and (2) the amount of atropine which is administered. Review of atropine poisoning cases serves to dispel any serious apprehension regarding the use of large doses of the drug. A survey of 5000 large doses reported in approximately 1000 persons reveals only 11 deaths, of which only three are due to atropine uncomplicated by some other factor. Seven of these were in children and one-half of them were by ocular administration. The relative safety of large doses of atropine is further enhanced by the finding that atropine tolerance is increased many times in the presence of anticholinesterase intoxication.