THE REFLEX ACTION OF VOLATILE IRRITANTS ON THE CIRCULATION *

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Among the measures in common use in combating conditions of threatened or actual circulatory failure, is the subcutaneous or intramuscular injection of volatile substances of a highly irritant nature. Among these so-called circulatory stimulants are ether, alcohol in the form of whisky or brandy, and camphor dissolved in ether, alcohol, or oil. The clinical use of these substances in shock and allied conditions is based, not on exact experimental observation, but on casual bedside impression and tradition.

OBJECT OF THE EXPERIMENTS

As a result both of laboratory observation and clinical experience, we have for some time held the opinion that the effects of the injection of volatile irritants were due, not to a direct stimulation of the circulation, but to a reflex action arising from intense irritation of sensory nerve endings. That intense irritation or stimulation of a sensory nerve may lead to a reflex rise in blood pressure has been known for a long time, but as far as we have been able to ascertain from the literature, this explanation of the action of volatile irritants is not the one ordinarily offered. If this group of substances acts in the manner suggested, the importance of a critical study of measures so universally used by clinicians becomes at once apparent. Any change in the circulation following the employment of these drugs is brought about by excitation of the medullary centers by afferent impulses, initiated at the site of injection. A rise in blood pressure presupposes a vasomotor center which is capable of excitation. These drugs are used almost exclusively in the treatment of shock and collapse—conditions in which the center is believed either to be paralyzed, and therefore incapable of excitation, or to be so active that further stimulation of the center does not bring about any large increase of blood pressure. In either case bombardment of the vasomotor center by afferent stimuli will result in no material increase in blood pressure. Furthermore, the pain at the site of injection may lead to a deepening of the shock or collapse already present.

* Submitted for publication Nov. 14, 1916.

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EXPERIMENTAL STUDY OF ACTION OF VOLATILE IRRITANTS

Technic.—All the experiments were performed on cats, decerebrated under ether, the temperature of the animal being maintained by an electric pad. An interval of at least twenty minutes was allowed to elapse between decerebration and the beginning of the experimental record, so that the ether was completely eliminated and reflex irritability restored. Such an animal is incapable of feeling pain. It breathes spontaneously, but in effect is nothing but a reflex machine.

It is worthy of note that the reflex irritability of an animal is greatly increased by destruction of the cerebral hemispheres. Hence the response to a given stimulus is much more pronounced in decerebrate animals than in normal individuals.

TABLE 1.—DATA OF—

Substance	Abdomen	Chest Wall	Leg (Thigh)	Hand
Ringer's solution.....	I* 2	I 0		II 0
Water.....	I 1	I 0	II 3.5	II 10
Alcohol.....	I 0	I 0	I 0	VII 17.3
Ether.....	I 0		I 0	VIII 17.6
Camphor and ether.....	I 0	II 4	II 4	XI 9.8
Turpentine.....	III 0	II 5	II 0.5	XL 8.1
Camphor and oil.....		II 0	II 0	III 13.7
Total injections.....	VIII	IX	X	LXXIII
Average rise in blood pressure...	0.4	2	1.6	10.3

* Roman numerals indicate the number of injections. Arabic numerals indicate the

For the injections, a glass syringe equipped with a 28-gage needle was used. A needle of such small caliber causes a minimum of local trauma—a factor of importance in estimating the reflex irritant effect of the substance introduced into the tissues through the needle. As a further precaution, the effect on blood pressure of the introduction of the needle alone was observed and an interval of several seconds allowed to elapse between the penetration of the tissues by the needle and the injection of the irritant. In many instances in which the animal was more than ordinarily irritable, the puncture of the skin by the small needle was followed by a rise in blood pressure, or by convulsive movements. These effects were similar to, though less than, those brought about by the irritant injections themselves.

Substances Used.—These were the usual volatile irritants employed in clinical work; ether; camphor, 10 per cent. in ether; camphor, 20 per cent. in oil; "spirits of camphor," (camphor, 10 per cent. in alcohol); whisky; and in addition, oil of turpentine. The latter was chosen because it is an intense irritant without immediate grave toxic effects. Ringer's solution, distilled water and tincture of digitalis also were used.

TABULATED RESULTS

The results are presented in tabular form in order to avoid detailed report of protocols. These tables are arranged to show the effect on blood pressure of: (1) the substance injected; (2) the site of injection (3) the comparative effects of the different volatile irritants.

In compiling these tables from the protocols, it is realized that comparison of quantitative results is not strictly allowable, since the experimental conditions were so variable. However, only those experiments are used in which conditions were usual—the animal having intact reflexes, not having suffered impairment of the central nervous system through asphyxia, faulty technic in decerebration, etc. As the total number of injections was large, the average figures have some value, however inexact.

—AUTHOR'S EXPERIMENTS

Foot	Nose	Dorsum of Foot	Muscle	Arm	Total Injections and Average Rise in Blood Pressure
I 0				I 0	VI 0.5
.....					VI 3.6
II 1					XII 3.6
IX 5	I 28				XX 10.1
XIX 18.5	I 21	I 34			XXXVII 13.0
XXXI 9.9	II 12.5	I 18	I 7		LXXXII 7.6
I 8					VIII 5.3
LXIII	IV	II	I	I	
11.3	18.5	26	7	0	

average rise in blood pressure.

SITES OF INJECTION

Reference to Table 1 shows that irritants were injected under the skin of the following regions: pads of the hands and of the feet, thighs, forearm, abdomen and chest wall. A number of injections were also made into the submucous tissue of the nasal septum. Of these regions the submucosa of the nose seemed to be the most irritable, since the reflex rise in blood pressure was the greatest. That this rise in blood pressure was not due to partial asphyxia as a result of the manipulation, is proved by the fact that after tracheotomy similar increase in blood pressure occurred on injection into the nasal submucosa.

Next in degree of sensibility are the pads of the hands and feet. When injections are made under or into the pads, a prompt and considerable rise in pressure usually occurs. It is interesting to note that the rise in blood pressure following injection into the pads of the feet, is somewhat greater than that following injections of similar doses into the pads of the hands.

The least sensitive areas seem to be the subcutaneous tissue of the

general body surface, for injection into these tissues results in practically no change in blood pressure. In this connection it may be pointed out that decerebrated animals are incapable of appreciating pain, hence changes in blood pressure following the injection of irritant substances are due solely to the reflex action on the vasomotor centers. On the other hand, in intact, unanesthetized animals, such injections are extremely painful and rise in pressure may occur as a result of this disturbance of consciousness.

It may be permissible to conclude from these experiments that the order of sensibility of the various regions injected is as follows: (1) nasal septum; (2) pads of feet; (3) pads of hands; (4) the general body surface. These results are in accord with the observations of von Frey¹ and of Crile² on the comparative sensibility of various parts of the body surface.

RELATIVE IRRITABILITY OF THE VARIOUS SUBSTANCES USED

The irritating character of a substance depends partly on its volatility, partly on osmotic tension, its ability to coagulate protein, and on other inherent and less well defined qualities. Ether, alcohol, and turpentine are volatile substances and seem irritant in proportion to their volatility. The irritant character of ether may be enhanced by having camphor in solution. Oil is by no means a bland substance when brought into direct contact with the sensory nerve-endings in the skin. Camphor in solution doubtless increases the irritant effects of the oil. Water is irritant largely through its alteration of the osmotic relations of the parts injected. Aside from other physical factors, all subcutaneous injections are painful by reason of the local tension brought about. In an injection of a fluid like Ringer's solution, only the last named factor comes into play. Judging from the degree of response, in the way of rise in blood pressure, from subcutaneous injection of the substances used, the order of irritability is as follows: Ringer's solution, practically non-irritant; distilled water, alcohol, equally irritant; camphor in oil, turpentine, ether, camphor in ether. (See Table 1.)

DURATION OF EFFECT

The total duration of the response to the injection was usually less than fifteen minutes. A typical reaction is shown in Figure 1. At the first signal the needle of the hypodermic was plunged through the skin

1. Von Frey: Starling. "Human Physiology," 1915, p. 490.

2. Crile, G. W.: "Surgical Shock," Philadelphia, 1899, p. 122, et seq.

covering the center pad of the right foot. Three seconds later, at the second signal, 1 c.c. of oil of turpentine was injected. A few seconds after the injection was begun blood pressure began to rise. The maximum rise, which was about 16 mm. of mercury, was reached in three seconds and was followed by a *quick* fall of about 10 mm. At this point blood pressure was still 6 or 8 mm. above normal. The pressure now fell more gradually, so that the normal pressure was regained twelve minutes after injection. In a small percentage of the experiments the rise in blood pressure was followed by an abrupt fall to normal, so that the entire reaction lasted less than two minutes. (See Figure 3, A, experiment of Dec. 3, 1915.) The extreme transientness of the complete cycle suggests that the therapeutic use of these substances is very limited.

Fig. 1.—Cat decerebrated under ether. At A, 1 c.c. of oil of turpentine was injected into the center pad of the right foot; nerve supply intact. At B, 1 c.c. of oil of turpentine was injected into the center pad of the left foot; entire central nervous system had been destroyed. In this and the subsequent tracings the lowest line serves as a signal; the next above gives time in five-second intervals, the third line from the bottom corresponds to the zero of blood pressure.

RATE OF INJECTION

The effect on blood pressure seems to be directly proportional to the intensity of the irritation. Figure 2, experiment of Dec. 29, 1915, shows at B the effect of the injection of 1 c.c. of oil of turpentine into the center pad of the right hand. The time occupied by the injection was approximately three seconds. The first part of the tracing at A shows the effect on blood pressure when the same amount of oil was injected into the corresponding pad of the other hand. The only difference in technic is the time required to complete the injection. Injection B occupied approximately three seconds, whereas Injection A required 110 seconds. In one case, irritation is sudden and sharp and is followed by a profound change in blood pressure; in the other, irritation is mild and prolonged and causes no rise in blood pressure.

Fig. 2. Cerebral temperature under ether. A. A 100-volt of temperature was injected into the central part of the left hand; response to complete peripheral 100 seconds. B. A 0.01-volt of temperature was injected into the central part of the right hand; response to complete peripheral 100 seconds.

REPEATED INJECTIONS

In some of the earlier experiments, in which camphor and ether were injected at short intervals, it was found that there was throughout the experiment a gradual and progressive fall of the average blood pressure. At the same time, successive doses of camphor and ether produced relatively smaller and smaller increases in blood pressure. To account for this a number of explanations suggested themselves. In the first place, the effects might be due to the gradual paralysis of the vasomotor center by the progressive accumulation of ether; or they might be the result of exhaustion of the vasomotor center from repeated afferent stimulation; in other words, we might be dealing with a form of traumatic shock; or, finally, the repeated excitation of the same nerve paths might result in their exhaustion. The direct paralytic action of the irritants on nerve-endings was excluded, since no two injections were made into exactly the same site. That the gradual depression of blood pressure was the result of the accumulation of ether was shown by the experiment of Dec. 14, 1915.

Successive doses of 1 c.c. of camphor and ether were injected into different pads of the feet and hands. The first injection was followed by a rise in blood pressure of 12 mm.; the second, five minutes later, resulted in a rise of 10 mm.; the third, five minutes later, gave a rise of 20 mm.; the fourth, after a five-minute interval, gave a rise of 8 mm.; the fifth injection, six minutes later, gave no rise; neither did the sixth, seven minutes later; nor the seventh, five minutes later. In two experiments of Dec. 17, 1915, in which ether 1 c.c. was injected at intervals of ten minutes, thus allowing time for the elimination of ether, the blood-pressure response to the later injections was not lessened.

In other words, if ten minutes be allowed to elapse between injections of 1 to 2 c.c. of ether, no progressive fall in blood pressure occurs. If injections are repeated at two minute intervals, ether accumulates in the organism and prevents reflex blood pressure response.

Because of the danger of ether's depression of the central nervous system and the consequent masking or abolition of reflex effects, recourse was had to oil of turpentine. This volatile oil is highly irritant and causes stimulation of the medulla and spinal cord. Hence, one might expect not a progressive loss, but a progressive increase of irritability, resulting eventually in convulsions. With this substance, repeated injections led to no marked permanent fall in blood pressure, and no marked change in the degree of the vasomotor response to repeated injections until convulsions developed.

SHOCK FROM REPEATED INJECTIONS

The possibility of inducing shock by the repeated traumatism of irritant injections was studied in a few instances. Oil of turpentine was chosen because its toxic effects are comparatively slow in appearing, while the irritant effects are marked and immediate. Collapse could

not be induced before the convulsions of the toxic stage of turpentine action appeared.

In the experiment of Feb. 1, 1916, 23 injections of oil of turpentine, 1 c.c. each, were given in the course of the experiment. Injections 1 to 9, inclusive, were followed by rise in blood pressure varying from 20 to 2 mm. Injections 20 to 23, inclusive, were not followed by any rise in blood pressure. A terminal asphyxial rise of blood pressure showed that the vasomotor center was not paralyzed. Beginning with Injection 15, there were signs of turpentine poisoning, namely, vomiting and convulsive movements. No signs of collapse appeared in this animal.

THE EFFECT OF SUCCESSIVE INJECTIONS INTO THE SAME REGIONS

This phase of the study involves the question of the effect on the nerve-endings of the site of injection, and the reflex arc. A short though variable time, usually not less than two minutes, is required for the recovery of a degree of irritability of the nerve-endings at the site of injection.

TABLE 2.—EXPERIMENT OF DECEMBER 17: INJECTION OF 1 C.C. CAMPHOR 10 PER CENT. IN ETHER

Number of Injection	Time of Injection	Site	Change in Blood Pressure, Mm.
I	2:35	Second pad of right foot.....	+ 20
III	3:15	Second pad of right foot.....	+ 20
II	2:55	Third pad of right foot.....	+ 18
IV	3:30	Third pad of right foot.....	+ 10
V	3:33	Center pad of right foot.....	+ 11
VI	3:35	Center pad of right foot.....	+ 10

It will be noted that in the experiment of December 17 there was exhaustion neither of the nerve endings nor of the reflex arc from successive injections into the same site or sites involving approximately the same reflex arc. The recovery of irritability of nerve endings is shown to be prompt and to take place in less than two minutes (see Injections V and VI).

In several similar experiments with different irritants, corresponding results were obtained.

THE NATURE OF THE RESPONSE

Our original hypothesis was that the reaction to the subcutaneous injection of an irritant is reflex in origin. The impulses arise at the point of injection, pass along the afferent nerves to the central nervous system and excite the vasomotor center. If this assumption is correct, any procedure which interrupts this arc will prevent the development of the reflex rise in blood pressure.

1. *Cutting of the Afferent Nerves.*—Section of sensory nerves prevents the usual rise in blood pressure when an irritant is injected into the denervated area.

In the experiment recorded in Figure 3, at A, 1 c.c. oil of turpentine was injected into a pad of the left foot. There was an immediate rise of blood pressure of 38 mm. A similar injection into the central pad of the right foot also caused a rise of 38 mm. The left sciatic and crural nerves were then cut. Five minutes later at B, Figure 3, 1 c.c. of oil of turpentine was injected into a foot pad of the denervated left leg. Blood pressure remained constant at the previous level.

This experiment shows that when afferent impulses are prevented from reaching the vasomotor center the injection of volatile irritants fails to cause a rise in blood pressure. The fact that the injection into the left leg caused the usual response, indicated that the vasomotor center was active and capable of stimulation. Like results were obtained in a number of experiments.

Fig. 3.—Cat decerebrated under ether. At A, 1 c.c. of camphor and ether (10 per cent.) was injected into a pad of the left foot; nerve supply intact. At B, 1 c.c. of camphor and ether (10 per cent.) was injected into another pad of the left foot; sciatic and anterior crural nerves had been cut.

2. *Depression of the Vasomotor Center.*—In a number of experiments ether was administered by artificial respiration until decerebrate rigidity disappeared. Under these conditions the subcutaneous administration of volatile irritants failed to cause a rise in blood pressure. The same absence of blood-pressure response to injection of irritants occurred when the vasomotor center was injured by a faulty technic in decerebration.

3. *Destruction of the Central Nervous System.*—In three experiments the vasomotor center was destroyed by pithing. In these animals the subcutaneous injection always failed to cause a rise in blood pressure. This is well shown in the experiment of April 5, 1916. The cat was decerebrated under ether as usual. The injection of 1 c.c. of oil of turpentine into the center pad of the right foot caused a rise of blood pressure of 18 mm., from 138 mm. to 156 mm (Fig. 1, A). The medulla was then destroyed. Two minutes later the blood pressure was 27 mm. The injection of oil of turpentine into the center pad of the left foot failed to modify the blood pressure in the slightest degree (Fig. 1, B).

4. *Intravenous Injections.*—Oil of turpentine was injected intravenously in several animals; 1 c.c. of the pure oil caused a prompt fall in blood pressure and usually resulted fatally. Smaller doses almost invariably caused a fall in blood pressure, never a rise. Thus in the experiment of April 3, 1916, 1 c.c. of an official emulsion of oil of turpentine caused the blood pressure to fall from 160 mm. to 80 mm.

That the heart plays little or no part in the rise in blood pressure following the subcutaneous injection of irritants was evident from those experiments in which the heart's movements were recorded by the Cushny myocardiograph. In these experiments neither the systole nor the diastole of the heart was changed; the rate remained practically constant.

EFFECT OF INJECTION OF IRRITANTS IN SEVERE HEMORRHAGE AND COLLAPSE

In just those conditions in which the measures studied are commonly used, they are least effective. In hemorrhage with falling blood pressure the subcutaneous injection of irritants is of little avail in checking the fall.

In the experiment of Dec. 10, 1915, three injections of camphor and ether, 1 c.c. each, into the pads of the feet, increased blood pressure 36, 42 and 42 mm., respectively. The animal was then bled, with resulting fall of blood pressure from 180 mm. to 100 mm. Camphor and ether injected into the pad of the right hand two minutes later gave no response. Three minutes later a similar injection into the pad of the left hand gave no response. The viscera were then manipulated and the pregnant uterus excised. Camphor and ether, 1 c.c., injected into the pad of the left hand gave no rise of blood pressure.

In shock, induced by evisceration, with exposure of the viscera to cold, severe manipulation and traction on the mesentery, nephrectomy, etc., the irritants have little or no influence in checking fall of blood pressure.

In the experiment of Dec. 29, 1915, the abdomen was opened, the viscera exposed, cold water poured on them and the mesentery stretched. Four minutes after this manipulation general blood pressure fell from 190 mm. to 120 mm. One c.c. of oil of turpentine was injected into the center pad of the right foot. The blood pressure rose 20 mm. Later both kidneys were removed, and manipulation of the liver and diaphragm carried out. The blood pressure rose 40 mm. and then fell 40 mm. Oil of turpentine, 1 c.c., was injected into the second pad of the left hand. Blood pressure rose 3 mm., to 95 mm., then gradually fell to 78 mm. Blood pressure continued to fall, and when it reached 40 mm. oil of turpentine was injected into the second pad of the right hand, with no effect. Another injection into the center pad of the left foot also had no effect. Blood pressure continued to fall, and the animal died five minutes later.

Experiment of Dec. 28, 1916: Several injections of irritants into the pads of feet and hands gave the usual rises in blood pressure. The abdomen was opened, the viscera roughly handled and cold water poured into the abdominal cavity. During these procedures blood pressure fell 70 mm., to 120 mm. Oil of turpentine, 1 c.c., injected into the third pad of the left hand, was followed by slight rise in blood pressure, 7 mm. Five minutes later, oil of turpentine, 1 c.c., injected into the third pad of the right hand produced no effect.

DISCUSSION OF RESULTS

In a series of experiments in which the volatile irritants ordinarily used in clinical work and, in addition, oil of turpentine, were injected into decerebrate animals, no direct action on the circulation could be observed other than threatened or actual collapse when the irritants were administered intravenously. Subcutaneous injections caused a rise of blood pressure only when the reflex arc was anatomically and physiologically intact. Gross destruction of the central nervous system or severance of nerve supply of the part injected annuls the circulatory effect of the measures studied. Deep anesthesia (ether), severe hemorrhage, shock and collapse likewise abolish the blood-pressure-raising effect of volatile irritants. In other words, any measure destroying or profoundly depressing the function of any portion of the involved reflex arc robs the subcutaneous injection of volatile irritants of its blood-pressure-raising effect. Other points of interest are that the response is directly proportional to the irritant character of the substance administered and to the sensibility of the area injected.

That the rise in blood pressure following the subcutaneous administration of the volatile irritants is entirely reflex in character is a conclusion that in our opinion cannot be escaped.

The effect on blood pressure of the hypodermic administration of irritants, when the reflex arc is intact, is not great. When one takes into account the fact that the animals were made more than ordinarily irritable by decerebration, the blood pressure changes one might expect in animals with normal reflex irritability are very slight indeed, although in the event of retained sensibility the intense pain of an irritant might well modify the results. The transience of the circulatory effect of the irritant injections is important, the average duration of the rise being seconds. The blood pressure curve following these injections resembles that produced by pinching a sensitive part of the body surface, and is, in our judgment, but a sequel of a not very different local trauma. A series of irritant injections is generally followed by a fall in the average level of blood pressure. It is impossible to know whether or not such a fall is due to repeated bombardment of the central nervous system by painful afferent impulses, or to the toxic action of the substances used, or to other conditions of the experiment. It is impossible to produce traumatic shock by the subcutaneous injection of irritants, because of the early development of systemic toxic effects.

The bearing of the results of this study on the ordinary clinical use of the irritants is obvious. In circulatory deficiencies, the result of traumatic or toxic insult to the central nervous system, an irritant injection may fairly be called an added burden and may well accelerate oncoming shock. It is not claimed that the injection of irritants has no

place in clinical work. In conditions in which cutaneous sensibility is present and reflex irritability preserved, an irritant injection may rouse flagging energies for a momentary emergency. It is, however, a two-edged sword and may also be the final instrument of a collapse. The use of such a measure to stimulate an anesthetized or profoundly prostrated or unconscious patient has no experimental justification.

CONCLUSIONS

The volatile irritants are not direct vasomotor stimulants. They act reflexly through irritation of sensory nerve-endings.

Their effect on blood pressure is both slight and transient.

In conditions of abolished reflex irritability, as anesthesia, shock, etc., the volatile irritants are without effect on the blood pressure.

Their clinical value is questionable.

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