BLOOD-PRESSURE AND GRAPHIC VASOMOTOR CHANGES IN THE PERIPHERY DURING ETHER ANÆSTHESIA*

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In a former paper [1] were set forth the results of a number of experiments on animals to determine and demonstrate graphically the changing conditions of the peripheral vessels during shock brought on by intestinal trauma.

The animals used were anæsthetized with ether, and the question naturally arises as to what depressing, exciting or neutralizing effect the anæsthetic may have had on the vasomotor mechanism.

The great importance of the general physiological effect of ether on the human organism, and the dangers connected with its use, have stimulated scores of physiologists and clinicians to experiment and observe. These investigators have attacked the problem from almost every angle, and as a result we have a great mass of observations, corroborating and disagreeing with each other.

The Question of Blood-Pressure.—As to the state of the blood-pressure during short or long-continued anæsthesia with ether, the consensus of writers seems to be that in the first stage of anæsthesia there is a sharp rise of blood-pressure. Verworn [2], speaking of anæsthetics and the wide-spread relation between excitation and depression, says: "It appears to be a general property of these (anæsthetic) substances that in very small doses or with very brief administration they produce the phenomena of excitation . . . ." The observation that there is a rise of blood-pressure at first also agrees very well with the noted phenomena of the excitement during the first stage of anæsthesia by ether. Patton [3], after summing up the conclusions of other workers, says that a stimulation of the circulation is generally noted by observers. Kemp [4], in his experiments on animals, showed a rise in general arterial pressure. MacWilliam [5], on the other hand, claims there is a general but slight fall in arterial pressure.

Observers also concur in statements that in long-continued ether anæsthesia there is a decided fall in blood-pressure. This phenomenon is well in accord with the observed action of increasing doses of anæsthetics on the individual cells of the organism, as shown by Verworn.[2]

*These experiments were completed in December, 1915.

He says that after the initial phenomena of excitation from small doses, and after brief administration, with increasing action of the anæsthetic, there are phenomena of depression, becoming more and more noticeable, which, apparently, are able to lead to a complete stand-still of life. Lyman [6] says that in consequence of certain factors to be named later, "the vascular pressure in the arteries, which may have exhibited an increase at the outset of inhalation, displays a decided fall. This diminution is much less noticeable when ether is used in place of chloroform." Potter [7] admits that if ether be administered long enough, after the cerebral functions are suspended, the lower centres in the medulla, carrying on the processes of respiration and circulation, are paralyzed. Gwathmey [8] says there is slowing of the pulse and a slight fall of blood-pressure during the later stages of anæsthesia, or when toxic amounts are administered.

While there is general agreement as to the status of the blood-pressure in the later stages of anæsthesia, it is certainly possible, with proper administration of the drug, to maintain deep anæsthesia for certain periods without the usual concomitant phenomenon, *i.e.*, lowering of blood-pressure. Meyer and Gottlieb [9] say that general observations on animals show that "when ether is used the blood-pressure may long remain at normal level." After summing up the conclusions of workers on this subject, an editorial in the *Journal of the American Medical Association* [10] concludes by saying, "It is well known that ether, when administered properly for a moderate length of time, does not lower the blood-pressure." . . . "With ether the blood-pressure may remain constant for several hours . . . ."

Concerning the causes of the lowered blood-pressure in the later stages of ether anæsthesia, all writers are not agreed. There are no investigators who throw the blame on the heart alone. The consensus seems to be that the combined effects of the anæsthetic on both heart and vasomotor mechanism constitute the blood-pressure lowering factors. Of the three great factors in the maintenance and stabilizing of the blood-pressure, the rate, strength and volume of the ventricular contractions and the peripheral resistance, as represented by the arteries of the peripheral and splanchnic circulation, are the principal entities.

Lyman [6] says the blood-pressure is lowered because of a relaxation of the vascular canal, opposed to a heart that beats less energetically. The combination of these two pressure lowering conditions brings about the result noted.

Gwathmey [8] says that ether becomes a cardiac depressant in the later stages of anæsthesia, or when a toxic amount of the drug has been

given. This, with a depressing effect on the vasomotor centre, which brings about a general arterial dilatation, causes the fall of blood-pressure.

Cushny,[11] in commenting on the conditions of the phenomenon, states that "the fall of blood-pressure in prolonged ether anæsthetic is due mainly to the weakness of the heart, along with a dilatation of the peripheral vessels."

Some do not agree that the conditions of both heart and arteries are to blame. Hewitt[12] thinks the fall of blood-pressure, met with under certain anæsthetics, is due to direct vascular dilatation, while Sollman[13] says that the condition is due partly to a direct action of ether on the vasomotor mechanism, but is aided by the asphyxia.

Attacking the problem from the standpoint of anatomical changes in the brain cells of dogs subjected to long-continued ether anæsthesia, Butler[14] in this laboratory demonstrated unvaried cell changes of depression as the end result. The nervous control of both the heart and the vasomotor mechanism would thus more probably be involved, though this does not exclude the direct action on the heart and vessels.

The conclusion of the majority of investigators that the hypostasis under question is conditioned by the combined depressing effects of the anæsthetic on the heart and vasomotor mechanisms is in accord with the conclusions of this laboratory.

The Condition of the Peripheral Arteries.—There seems to be no disagreement as to the dilatation of the peripheral arteries during ether anæsthesia. Weber[15] remarks that after general ether anæsthesia there are evidences of perverted vasomotor functioning, lasting for several days. Lyman[6] says the inhalation of considerable quantities of a powerful anæsthetic results in paralysis, and soon produces relaxation of the vascular canal. Muehlberg and Kramer[16] assign vasomotor paralysis as one of the causes of death under ether. Gwathmey[8] states that there is a general arterial dilatation, agreeing with Cushny[11] and Sollman.[13]

This arterial dilatation is so marked that there is a perceptible increase in hemorrhage from severed arterioles during an operation. Luke[17] states that under ether anæsthesia ". . . incised parts are often very vascular, the surgeon not uncommonly remarking on the free hemorrhage."

Oliver[18] graphically demonstrated the actual increase in size of the radial artery during ether anæsthesia. After many experiments with his clever arteriometer he concluded that ether invariably increases the caliber of the arteries.

The Origin of the Dilatation.—There is not so much agreement concerning the origin of the dilatation. There seems to be a preponderance of evidence that it is conditioned by the action of the anæsthetic on the vasomotor centre.

Chief of those maintaining that the vasodilatation is not due to the action of the anæsthetic on the vasomotor centre, is Cushny[11], who says: "Ether seems to have little or no direct action on the vasomotor centre, but the dilatation of the skin vessels indicates that it excites the vasodilator function." Hewitt[12] specifically states that according to certain researches " fall of blood-pressure, met with under certain anæsthetics, is referable rather to direct vascular dilatation than to dilatation of central nervous origin."

On the other hand, Weber [15] notes that the central vasomotor mechanism is extremely sensitive to injurious influences brought by the blood, and that ether exerts these injurious influences to a degree about midway between that of local anæsthesia and chloroform. Meyer and Gottlieb [9] say that "Large doses of narcotics or other central depressants cause gradual diminution of, and final general paralysis of, the vasomotor centres." Potter [7] agrees with this view.

THE PROBLEM

The purpose of this investigation was to demonstrate graphically the actual changes in the condition of the peripheral circulation and in blood-pressure accompanying long-continued ether anæsthesia, and the relation which the vasomotor changes may have to the blood-pressure. The results will be analyzed along with other understood phenomena, to see what correlation there may be between the sum of the conclusions and any one of the theories of causation cited above. It is also necessary to answer the question as to what neutralizing or other effect the anæsthetic may have in other experimental operations requiring mechanical technic, the trauma from which usually brings about the symptom-complex recognized as shock. This series of experiments should give a fair working hypothesis, therefore, of the relation between shock and depression.

It is proposed, therefore, to show (1) that there are definite changes in the condition of the blood-vessels of the periphery closely following long-continued ether anæsthesia, the term periphery to mean the whole of the legs, and the body musculature with skin; (2) that there are certain definite conditions of blood-pressure during the experiment; (3) and that these changes of vasomotor control and of blood-pressure are

in direct relation to each other. Further, it is proposed (4) to outline the direct relationship between shock and depression, and to show (5) what basis there is for accepting any one of the theories cited in the introduction.

METHODS OF EXPERIMENT

A uniform method of administering ether was necessary, as well as a reliable method of graphically demonstrating the variations of the vasomotor mechanism, and the changes in blood-pressure.

The ether was administered through a tracheal cannula, connected by a rubber tube to a glass ether bottle one liter in capacity. On inspiration the outside air was conducted below the surface of the ether by a glass tube open at both ends and thrust through the cork, and drawn up in bubbles through the ether. By raising or lowering this intake tube, the concentration of ether vapor in the air supplied to the lungs could be very well regulated. Most of the expired air was thrown out through a one-way valve between the trachea and the ether bottle.

In order to avoid the effects of acapnia [10], the rubber tube of large diameter between the ether bottle and the tracheal cannula was lengthened or shortened as required, thus constituting a type of rebreathing apparatus. The animal used was allowed to die at the end of the experiment, and it was not thought necessary to warm the ether vapor.

It is not necessary to repeat the description of the method of graphic demonstration of the vasomotor and blood-pressure changes. The same form of leg plethysmograph, recording through a water system manometer, was used as described in a former paper [1]. The blood-pressure tracing was taken from the carotid artery connected with an ordinary mercury manometer.

DESCRIPTION AND EXPLANATION OF EXPERIMENTS

Dogs weighing from 6 kg. to 10 kg. were used. No drugs such as curare and morphine were used, as in the experiments referred to before. After the dogs were anæsthetized, the dissection in the neck was made the first procedure. One of the hind legs was then shaved from the knee down and the plethysmograph was adjusted. This technic usually required about one hour's time, consequently the record of the changes begins after the dog had been under the anæsthetic for this period; therefore, the first effect of the anæsthetic on the vasomotor mechanism and blood-pressure is not recorded.

For the first hour the drum was allowed to move a little at intervals of five minutes each. At the end of the first hour of the record, the

observations were taken every fifteen to thirty minutes. By close attention for a short time the air intake tube and the rebreathing tube could be adjusted so that the subject would get a steady supply of anæsthetic vapor, heavy enough to maintain the third stage of anæsthesia. The experiments were allowed to run as long as six hours, unless terminated by some untoward incident.

After the death of the animal, the mechanism was calibrated and the records made permanent by fixing in shellac [1].

Of the many records secured, several were discarded because of mechanical errors, but these all showed the typical graphs.

Six of the graphs have been analyzed in the accompanying table.

DISCUSSION OF EXPERIMENTS

The shortest experiment was one hour in length, the longest one, six hours and ten minutes. Three experiments were six hours, or over, in length, and two were over three hours in duration.

The Blood-pressure.—In the three shorter experiments the blood-pressure was from 19 to 70 mm. Hg lower at the end of the experiment than at the beginning. In the three longer experiments the blood-pressure was from 12 to 21 mm. Hg higher than at the beginning. In four cases out of six there was a slight fall of blood-pressure at the end of the first half hour. Two of these showing such a fall (Experiments 10 and 12) had a continuous fall to death, while Experiments 3 and 8 showed a slight gradual rise to death. Experiment 9 showed 16 mm. Hg rise at the end of the first half hour, but ended finally in a 19-mm. fall. Experiment 11 showed a 16-mm. rise at the end of the first half hour and ended in a total rise. In all cases there was a relative slowing of the heart, progressing towards the end of the experiment. Time records were not kept. Also there was a marked increase in amplitude of individual beat which seemed to vary with the slowing of the rate.

The Vasomotor Reactions as Indicated by the Leg Volume.—In five to forty minutes after the adjustment of the plethysmograph a change in leg volume was noted, three cases showing a vasodilatation, and three showing a vasoconstriction. At the end of the first half hour there was a general vasodilatation shown except in one case. At the end of the first hour (the second hour of anæsthesia) all cases showed a marked vasodilatation, which condition slowly increased, with occasional periods of vasomotor recovery, until at death there was a total increase of leg volume of 2 cu. cm. to 18 cu. cm.

TABLE I

DATA OF EXPERIMENTS

Number of experiment	Length of experiment in hours	Time in minutes elapsing before change of leg volume	Character of volume change			Total increase of leg volume at end of experiment in cubic centimetres	Blood-pressure in mm. Hg				Total fall of blood-pressure	Total rise of blood-pressure	Periods of recovery of volume
			Five-minute intervals		Remainder of experiment		At end of		At start of experiment	At end of experiment			
			First half hour	Second half hour			First half hour	Second half hour					
3	61/12	40 rise	No change	2½ c.c. increase	Irregular increase	8.5	104	112	108	122	...	14 mm.	.5 c.c. at end of 2 hours. Rapid recovery. .5 c.c. at end of 2½ hours. Recovery in 10 minutes. .5 c.c. at end of 3 hours. Recovery rapid.
8	61/6	5 rise	2.5 increase	3.5 increase	Irregular increase	14.5	96	96	103	124	...	21	.5 c.c. at end of 40 min. 1.5 c.c. at end of first hour. .5 c.c. during second hour. 3. c.c. during fifth hour. 1. c.c. during sixth hour.
9	31/4	10 slight fall	1.5 increase	2.5 increase	Slow, regular increase	7.5	98	108	82	63	19	...	1 c.c. fall below 0 in 10 minutes. 1.5 c.c. at end of first hour.
10	1	5 fall	1 increase	2 increase	Slow, regular increase	2	140	78	148	78	70	...	1.5 c.c. fall below 0 in 5 minutes. Slight recovery at end of first half hour.
11	6	10 fall	4.5 increase	8 increase	Irregular increase	18	78	62	62	74	...	12	.5 c.c. fall in 10 minutes Rapid increase for 25 minutes. 1 c.c. recovery at end of 2 hours. No increase last 1½ hours.
12	4	5 rise	4 increase	7 increase	Slow, regular increase	12	140	120	148	85	63	...	

All cases but one showed a steady progressive increase of the vasodilatation up to the very last half hour of the experiment. Experiment 11, which ran six hours, showed the limit of vasodilatation in four and one-half hours, with no recovery during the last one and one-half hours.

GENERAL DISCUSSION AND CONCLUSIONS

Ordinary third-stage ether anæsthesia, prolonged beyond one hour, always results in more or less marked vasodilatation in the periphery. This is a progressive change, more or less regular in character, increasing directly in proportion to the lengthening time of administration. In most cases the limit of vasodilatation is not reached within seven hours after the beginning of the anæsthetic, but occasionally the extreme of the condition may be reached after a shorter administration of the drug.

If the endeavor be made to explain the response of the vasomotor mechanism as being conditioned by the local action of the ether on the peripheral vasomotor mechanism, it is necessary to assume that the results are to be explained by the variation of the normal degree of vasoconstriction-dilatation present in the periphery at the inception of the experiment. It is well known that there is a more or less constant tonic activity of the peripheral vasomotor function in the normal animal. It is conceivable that there may be times when the peripheral arterioles are dilated or contracted to such an extent that any further dilatation or constriction would be impossible; but normally there is a tonic balance of function, the variation being noticeable only within the narrow limits set by the requirements of the mechanics of circulation.

Granting that the degree of dilatation or constriction of the peripheral arteries at the beginning of the experiment varies with different individuals, it can be safely said that the variation is not great enough to be considered as limiting or conditioning the present graphic result.

If an explanation is based on the hypothesis that the vasomotor centre is the variable factor in bringing about the vasomotor change, one may say that the variation of response is directly dependent upon the anatomical-functional changes in the nerve cells of the vasomotor centre produced by ether. This centre cannot escape such changes as are demonstrated by Butler[14] as the general effect of ether, as hereafter explained.

In half the cases cited there is a decided fall in blood-pressure. It is noted also that the time length of the experiment was in these instances much shorter than others showing different net end results. The

three tabulated experiments, running six hours or more, showed the blood-pressure to be slightly more than maintained. There is then a disturbance of the normal physiologico-mechanical relation between two of the three great blood-pressure controlling factors, *i. e.*, the rate and strength of the heart, and the peripheral resistance in the arteries. This disturbed relation is shown by the behavior of the blood-pressure in three of the cases. There is a fall of blood-pressure as an end result in these three cases. This, of course, is what would be expected in the presence of such great vasodilatation.

The normal tone and resistance in the arteries have been altogether or partly destroyed in all cases, and the blood-pressure lowering effect of this one factor, obtaining throughout all of the periphery, must be tremendous. Why, then, is there in half the cases a decided and fatal fall in blood-pressure, and in the other half a decided maintenance of the tension? It is evident that the question must be answered by considering the normal compensatory reaction to the blood-pressure lowering tendency of the peripheral dilatation on the heart. While the heart did not increase in rate in any instance, there was a decided increase of ventricular output, an increase great enough to overcome the hypostatic effect of the peripheral dilatation: the blood-pressure was maintained and even raised a little. It is evident that if the heart fails to show this compensatory reaction, because of organic disease, or too early response of the nervous centre to the effect of the anæsthetic, the blood-pressure must fall, as it did in the three cases noted.

In considering the three cases showing the failure of cardiac compensation, it is permissible to argue that any means of preventing or overcoming the peripheral vasodilatation would have resulted in maintenance of blood-pressure.

In a former paper[1] it was clearly shown that trauma to the exposed intestines brings about a certain vasomotor response in the blood-vessels of the periphery, and this response is a reflex vasoconstriction. Interesting to note also is the fact that in seven experiments, from 45 to 165 minutes in length, the blood-pressure was either nearly exactly maintained, as in two cases, or was higher at the end of the experiment than at the beginning, as in three cases. Only two cases showed a fall of pressure at the end, and these results were obtained from dogs living less than an hour after the beginning of the trauma, the leg volume tracing in both cases showing little or no vasoconstriction to offset the heart failure.

In the light of what we have learned from all experiments it is safe to say that in the ordinary major operation, with ether as the

anæsthetic, a moderate amount of excitation from handling is a helpful factor. There can be no question that there are occasions at times, with the patient on the verge of syncope from ether depression, when a vigorous cutaneous or visceral irritation would restore the vasomotor tonus, resulting in a beneficial reflex rise in pressure. Bearing on this generalization, we repeat the notes of Experiment January 31 in a former paper referred to above[1]: "In one experiment (January 31) the handling of the intestine immediately brought about a slight fall in the volume of the leg with at first a fall then a rise in blood-pressure. When the handling ceased for two minutes the leg volume went up, the blood-pressure remaining about normal. When the manipulation was taken up again there was a fall in volume. These transitory changes in leg volume and blood-pressure went on through the whole experiment (52 min.), the general trend of the volume being downward, so that at the end of the experiment there was a permanent fall of 5 cu. cm." This case, on the experimental side, shows the sensitiveness of the vasomotor mechanism to reflex stimulation, and it is clear how such a reflex stimulation, in proper time and moderation, may very well become a remedial measure in impending ether death. Weber[15] recognizes this principle when he treats by alternate hot and cold douches the disturbances of the vasomotor mechanism after general anæsthetics.

It is interesting, indeed, to read of Kirstein's four cases[20], the report of one of which has been abstracted[21]. One case of cessation of the manipulation of the peritoneum during a laparotomy arrested the respiration and heart beat. He theorizes that the amount of anæsthetic required depends on the intensity of the irritation from the operative procedures, a certain amount of anæsthetic balancing a certain amount of irritation. If this irritation stops suddenly, the anæsthetic then makes its influence felt more on the general system, so that anæsthesia slides into the danger phase. The narcosis-asphyxia came on suddenly when the operator had finished with his investigation and manipulation of the peritoneum.

In the case just cited it is evident that the sensory stimulation from the manipulation of the peritoneum was the prop which supported the function of the centres of respiration and circulation. The stability of function of the vital centres in the medulla under such conditions is, therefore, more apparent than real.

Reasoning from the same facts toward the same end, namely, the safety of the patient, Oliver[18] says, "Inasmuch as I have shown that operative procedures are apt to throw an increased strain on the heart

and great vessels by causing extensive contraction of the middle and smaller sized arteries, it would seem to follow that those anæsthetics will be the safest that maintain the heart's action and the fullness of the arteries."

As being of interest on this topic, one of Henderson's conclusions is here given: "Morphine and complete anæsthesia counteract the development of shock by quieting the respiration" [22].

So we come naturally to the fundamental question of excitation versus depression. Verworn early defined these as "quantitative opposites, activity being an increase, depression a decrease in the intensity of vital phenomena." Anatomically, so far as concerns the analysis of the function of the nerve cell, this is supported by actual volumetric comparison (Dolley [23]).

These processes depend upon the fundamental property of irritability of protoplasm. To show the scope of this property, there are only two other fundamental ones concerned in dynamic reactions, reproduction (division of cells) and nutrition. Function of the nerve cell is deduced as the manifestation of its irritability which has been determined by specialization, anatomic differentiation (Dolley [25]). The stimulus to the irritability, as Verworn defines it, is "Every alteration in the external vital conditions." Stimuli, therefore, are either excitant or depressant. In respect to irritability, nervous phenomena can be only referable primarily to excitation or depression, or both.

Excitant stimuli produce function in the usual sense. Looking now only at end results, if excitant stimuli are excessive, there results a using up of substance faster than it can be replaced, which in the earlier stages is an organic fatigue, and which leads to eventual organic exhaustion. Depressant stimuli produce depression, the lowering or blocking of function, its diametric opposite. In moderate degrees depression corresponds to fatigue of another sort, such for example as occurs in the accumulation of waste products, or the blocking of function may be complete.

There are then two kinds of fatigue, from excitation and depression. Both may lead to an absolute condition, either complete exhaustion or depression. But, though the end result is reached by entirely different processes, its effect is identical in a complete functional incapacity. An exhausted cell is just as incapable of function as is a depressed cell.

To understand the effect of ether, therefore, one must keep in mind its relation as a stimulus. It belongs to that more common group which are only different in that they combine excitation and depres-

sion, first exciting, then depressing. The depression is its essential effect.

To understand the primary effect of an operation, it must be kept in mind that the primary stimuli are excitant only, being mechanical. Their effect then is wholly excitory, leading to overactivity, and, if long enough continued, to more or less of fatigue, and possibly to exhaustion. So the primary effect of shock is overfunction, though it is to be noted that this effect is only displayed outwardly according to the body mechanism which permits its display. Anatomically it is a general phenomenon for the nervous system.

It is evident that when sensory stimuli and the anæsthetic are exhibited together as in any ordinary surgical operation there is one period when the excitation from the surgical technic and the depression from the drug are pitted against each other, to the good of the patient. There is a later period when the two antagonists become allies in effect, and total functional incapacity and death come about quicker than when only one agent has been at work.

It has been concluded, therefore, that the symptom-complex known as post-operative shock is a combination of the effects of excitation and depression and varies directly with the algebraic sum of these two factors (Dolley [25]).

Proof that the phenomenon of vasodilatation rests entirely on the extent of dilation or constriction in the arteries at the inception of the experiment rather than on the central reaction, demands a graphic demonstration of the absolute vasomotor changes taking place during the first hour of anæsthesia. To proceed to base conclusions on the changes noted *after* the first hour of anæsthesia is unsound practice. There is every reason to believe that when the inhalation of ether is begun there is a condition of increased tonicity of the vasomotor system. The extreme excitement accompanied by the heightened blood-pressure are sufficient grounds for assuming that there is a heightened activity of the vasoconstrictor function. It is probable, therefore, that in the ordinary ether anæsthesia, conducted into the third stage, the vasomotor response runs through phases of excitation into depression. Granting, however, that some part of the result is peripheral in origin, against which there is no objection, the essential effect must be central, simply from the difference in degree of irritability in one against the other, the smooth muscle cell against the nerve cell.

"Ether anæsthesia produces certain definite anatomical changes in nerve cells of dogs. The changes are first those of mild activity and later there are superimposed changes of depression depending in se-

verity upon the duration of the anæsthesia. The changes first make their appearance microscopically in one and one-half to two hours. Anæsthesia of two to six hours produces a moderate depression, one up to eight hours a marked depression, and one of more than eight hours a profound depression, with the beginning of necrobiosis.

"The severity of the anatomical changes in the nerve cell appears to be in direct relation to the length of the anæsthesia, allowances being made for individual variations.

"The changes vary in degree in animals of the same species kept under the same form of anæsthesia for the same length of time." (Butler.[14])

It is true that no one has ever studied the anatomical changes in the cells of the vasomotor centre in the medulla after prolonged overstimulation, or after ether anæsthesia. Indeed, it is impossible even to locate these individual functionally specialized cells with any degree of accuracy.

We may base our argument on Dolley's [24] conclusion: All nerve cells go through the same quantitative sequence of changes in their function, exhibiting therein a unity of mechanism. Because of this unity of mechanism deductions from any single type of cell which relate to the fundamental quantitative principle may be applied to all.

SUMMARY

1.—Ordinary third-stage ether anæsthesia prolonged beyond one hour results in more or less marked vasodilation in the periphery. This is a progressive change, more or less regular in character, increasing directly in proportion to the lengthening time of administration. In most cases the limit of vasodilatation is not reached seven hours after the beginning of the anæsthetic, but occasionally the extreme of the condition may be reached after a shorter administration of ether.

2.—There is a direct relationship between the condition of the vasomotor control and the blood-pressure.

3.—The end result of ether depression is loss of function. The symptom-complex, known as post-operative shock, is a combination of the effects of excitation and depression, and varies directly with the algebraic sum of these two factors.

4.—The vasomotor centre is the variable factor in bringing about the vasomotor change; the variation of response is directly dependent upon the changes in the vasomotor centre produced by ether.

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