JCI The Journal of Clinical Investigation

# THE RÔLE OF THE VENOUS SYSTEM IN CIRCULATORY COLLAPSE INDUCED BY SODIUM NITRITE

Robert W. Wilkins, … , Florence W. Haynes, Soma Weiss

*J Clin Invest.* 1937;16(1):85-91. https://doi.org/10.1172/JCI100841.

Research Article



# THE RÔLE OF THE VENOUS SYSTEM IN CIRCULATORY COLLAPSE INDUCED BY SODIUM NITRITE [1]

By ROBERT W. WILKINS, FLORENCE W. HAYNES, AND SOMA WEISS

*(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston)*

(Received for publication September 2, 1936)

An experimental study of the vasomotor collapse induced by sodium nitrite in normal subjects in the upright position has revealed that the state of collapse is accompanied by a fall in venous pressure and an inadequate return of venous blood to the heart from the lower half of the body (1). As long as the subject remains in the prone position, a small dose of sodium nitrite will produce no symptoms and only slight, if any, measurable circulatory changes in terms of blood pressure, heart rate, arterial blood flow or venous pressure. When the subject is raised from the horizontal to the upright position after the same dose of nitrite, however, he soon develops signs and symptoms of collapse. After nitrite has been given, the peripheral circulation is unable to adjust itself to the strain of the orthostatic position.

Our purpose in the present work was further to clarify the mechanism of the nitrite collapse. On rising to the upright position, the greatest relative change in the circulation is on the venous side of the vascular system in the lower half of the body. Here the venous pressure is normally raised from an average prone value of 5 cm. of water to about 100 cm. of water in the feet and 50 cm. in the abdomen. This consideration, as well as the fact that previous studies revealed no appreciable dilatation of the arterioles or change in the cardiac output after nitrite (2), turned our attention to the venous side of the circulation as possibly one of the most important sites of action of sodium nitrite. We therefore undertook to test the effect of nitrite on the distensibility of the peripheral vascular beds under increases in venous pressure. We were particularly interested to know whether the effect of nitrite on the venous system is generalized or limited to certain vascular areas, such as the splanchnics.

In the present study, the hands of normal subjects were placed under known increases in venous pressure, and the corresponding increases in hand volume were measured both before and after the administration of nitrite. The subject remained in the prone position and in this way other factors, such as changes in arterial blood pressure, pulse or blood flow, were eliminated. Capps, working in this laboratory, developed this method as a means of measuring the tone or "resistance to stretch" of the capillaries, venules and veins of the hands in both normal and diseased states (3). We have used this procedure, with minor modifications, with satisfactory results.

## METHOD

The subject rested in a comfortable horizontal position for at least 45 minutes after all apparatus had been adjusted before any observations were begun, and remained in this position throughout an experiment. Arterial blood pressure was determined in the arm by the usual auscultatory method, using a mercury manometer. The heart rate was counted by arterial palpation or from the plethysmographic tracings. The rate of blood flow was determined by Freeman's modification of the plethysmographic method of Hewlett and Van Zwaluwenburg (4). The averages of from 5 to 10 separate tests were used for each measurement of the blood flow.

After the blood flow had become constant, the tone of capillaries, venules and veins was determined by measuring the increases in volume of the hand when subjected to increases of venous pressure in amounts of 10 mm. Hg up to 50 mm. Hg. This was done by inflating a pressure cuff around the wrist at these pressures. To avoid the possible objections that the resultant changes in volume are due in part to reactive hyperemia, edema formation or spontaneous changes in hand volume, each pressure was done separately, so that the time during which the pressure was applied was only a few seconds and any change in the base line was immediately apparent.

In determining the increments in volume, the hand volume at 10 mm. Hg venous pressure was used as the base, by subtracting the increase due to 10 mm. Hg from that due to 20, 30, 40 or 50 mm. Hg, respectively. This procedure eliminates the effect of any possible spontaneous variation in systemic venous pressure, and also makes all the increments in volume due to equal increments in

[1] This investigation was aided in part by a grant from the Josiah Macy, Jr., Foundation.

venous pressure (10 mm. Hg). The total hand volume was determined by measuring the displacement volume of water in the plethysmograph. From this the volume changes were calculated per liter of hand volume.

The responses of these various functions to the following experimental conditions were determined on each of 6 normal subjects on separate days: (*1*) Both hands were kept at a temperature of 32° C. (normal hand temperature). After several normal control values had been obtained, the effect of an oral dose of 0.12 to 0.18 gram (2 to 3 grains) of sodium nitrite was measured. (*2*) Both hands were kept at 37.5° C. (body temperature). After establishing normal values, the effect of the same dose of sodium nitrite was determined. (*3*) One hand was kept at 32° C., and the other maximally dilated at 45° C. This heat not only caused local dilatation in the hot hand, but also produced reflex vasodilatation with maintained vasomotor reactivity in the cool hand. After constant values had been established, the effect of the same dose of sodium nitrite was measured.

## RESULTS

Figure 1 shows the tracings obtained from a typical subject, S. M. Both hands, at 32° C., were subjected to increases in venous pressure, which caused corresponding increases in hand volume. These increases in volume were remarkably constant on repeated tests under the same conditions. After 0.12 gram (2 grains) of sodium nitrite had been given, however, there was a marked increase in the volume changes produced by the same venous pressures. It is important to note that after nitrite, although there was a definite decrease in the resistance of the "venous" vessels to stretch, as measured by the height to which the curves rise, there was simul-

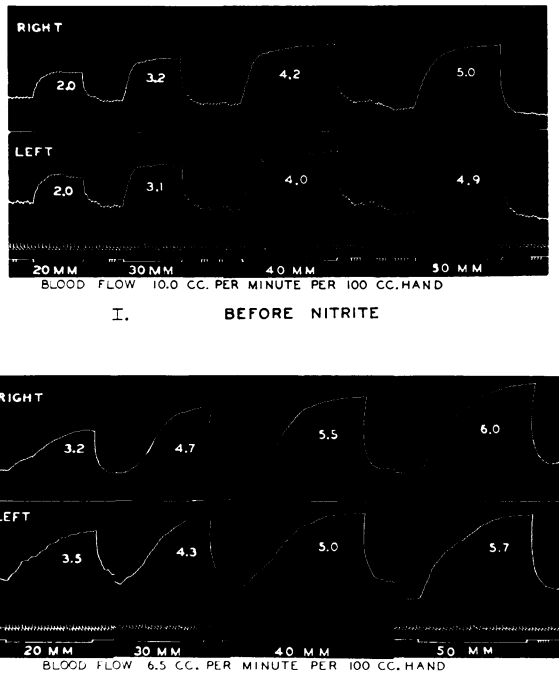


FIG. 1. SUBJECT S. M. PLETHYSMOGRAPHIC RECORDS OF THE VOLUME INCREASES CAUSED BY INCREASES IN VENOUS PRESSURE IN BOTH HANDS AT 32° C., BEFORE AND AFTER THE ADMINISTRATION OF 0.12 GRAM OF SODIUM NITRITE.

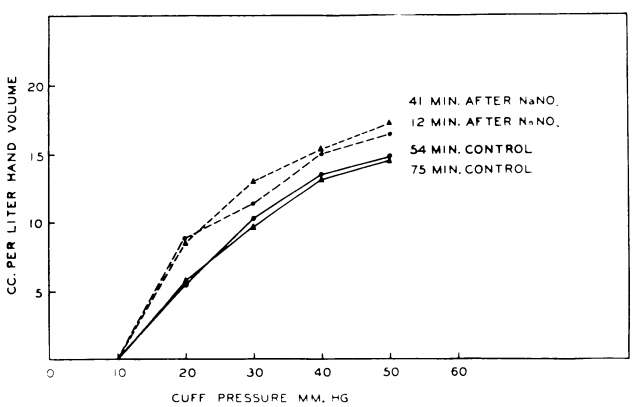


FIG. 2. SUBJECT S. M. VOLUME INCREASES CAUSED BY INCREASES IN VENOUS PRESSURE IN ONE HAND AT 32° C. BEFORE AND AFTER THE ADMINISTRATION OF 0.12 GRAM OF SODIUM NITRITE.

The hand volume at 10 mm. Hg venous pressure was used as a base.

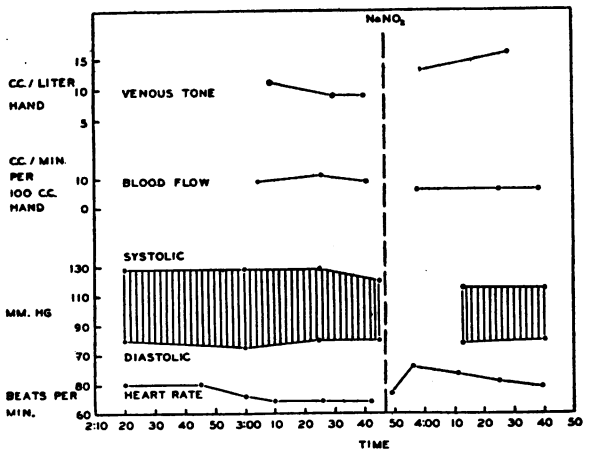


FIG. 3. SUBJECT S. M. EFFECT OF 0.12 GRAM OF SODIUM NITRITE ON THE VENOUS TONE AND THE BLOOD FLOW IN ONE HAND AT 32° C., ON THE ARTERIAL BLOOD PRESSURE AND ON THE HEART RATE.

The venous tone is measured by the increase in hand volume per liter of hand produced by increasing the venous pressure from 10 to 30 mm. Hg.

taneously an increase in the resistance offered by the arterioles to the flow of blood, indicated by the steepness with which the curves rise. Hence, after the administration of nitrite there was within the same vascular area both a decrease in venous tone and at the same time an increase in arteriolar tone. The arteriolar constriction shown in this instance we believe is a response to and not a result of the nitrite, as it did not occur in every case. An arteriolar dilatation was never demonstrated after nitrite, however; there was either no change or, as in this case, a slight constriction. Therefore, we conclude that the changes produced directly by nitrite must involve elements of the vascular bed peripheral to the arterioles, i.e., capillaries, venules and veins. This is in agreement with Capps' conclusions (3) that his method actually measures the tone of those vessels peripheral to the arterioles, mainly the venules and the veins.

In this subject, therefore, the capillaries, venules and veins of the hand were distended by the same venous pressures from 20 to 30 per cent more after nitrite than before. Figure 2 is a graph of the volume increases caused by increases in venous pressure, before and after the administration of nitrite to the same subject (S. M.).

Figure 3 is a chart of the whole experiment, showing the changes in pulse, blood pressure, blood flow and "venous" tone. For the latter values the increment in hand volume produced by the increment of venous pressure from 10 to 30 mm. Hg has been calculated for each liter of hand volume. This gives a single figure representative of the changes as graphed in Figure 2.

Figure 4 shows the effect of 0.18 gram (3

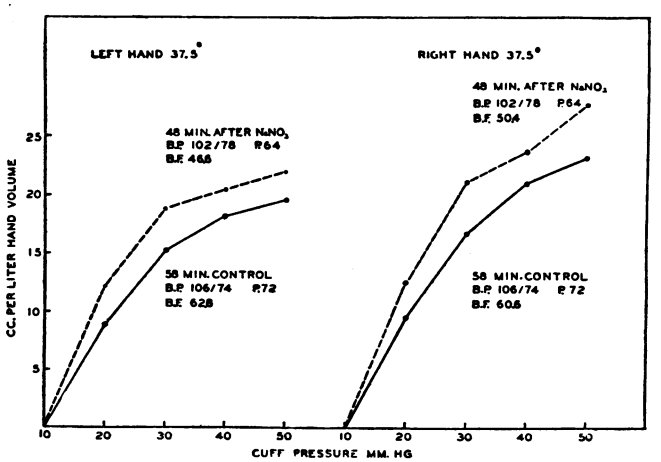


FIG. 4. SUBJECT R. W. VOLUME INCREASES CAUSED BY INCREASES IN THE VENOUS PRESSURE OF THE TWO HANDS AT 37.5° C. BEFORE AND AFTER THE ADMINISTRATION OF 0.18 GRAM OF SODIUM NITRITE.

The hand volume at 10 mm. Hg venous pressure was used as a base.

grains) of sodium nitrite on the tone of the capillaries, venules and veins of the hands of Subject R. W. Both hands were at 37.5° C. It should be noted that although there was a decided decrease in the tone of these vessels (i.e., a "dilatation") after the nitrite, there was little or no change in blood pressure, pulse or blood flow. There were no symptoms. It is of interest that these changes in venous tone were not apparent under the normal low venous pressures of the prone position. The hand volume increased only slightly, if at all, after the administration of nitrite.

After small doses of nitrite, some subjects showed slight or no change in the venous tone of the hand, especially at the lower temperatures, which cause local vasoconstriction. When the hands were already moderately dilated, however, as at body temperature (37.5° C.), or reflexly dilated by immersing the opposite hand in hot water (45° C.), the effect of nitrite on the venous tone became more apparent.

Of 6 subjects tested with both hands at 32° C., only 2 showed a definite decrease in venous tone after nitrite, 2 showed a slight decrease and 2 showed no change. Of 5 subjects tested at 37.5° C., 4 showed a definite decrease in tone and 1 showed a slight decrease. Of 6 subjects tested with one hand at 32° C., reflexly dilated by having the other hand at 45° C., 5 showed a definite loss of tone after nitrite, while 1 showed no change.

Figure 5 is a graph of the changes in tone after the administration of nitrite in Subject T. L. at various temperatures and shows the trend of the results of the whole group. There was no change after nitrite with both hands at 32° C.; a definite decrease in tone after nitrite with both hands at 37.5° C.; and a decrease also with the hand at 32° C. reflexly dilated by keeping the opposite hand at 45° C.

We have found that at local temperatures above 40° C. this method for measuring the tone of the capillaries, venules and veins in the hand is impractical. At these temperatures there is either no effect or an apparently reverse effect after nitrite. Likewise, at such high temperatures we have found that other procedures, such as elevation of the body to an upright position, which we know should increase the tone of these vessels, apparently result in an increase in distensibility. Measures which cause dilatation, on the other hand, as returning the subject to a horizontal from an upright position, apparently cause a decrease

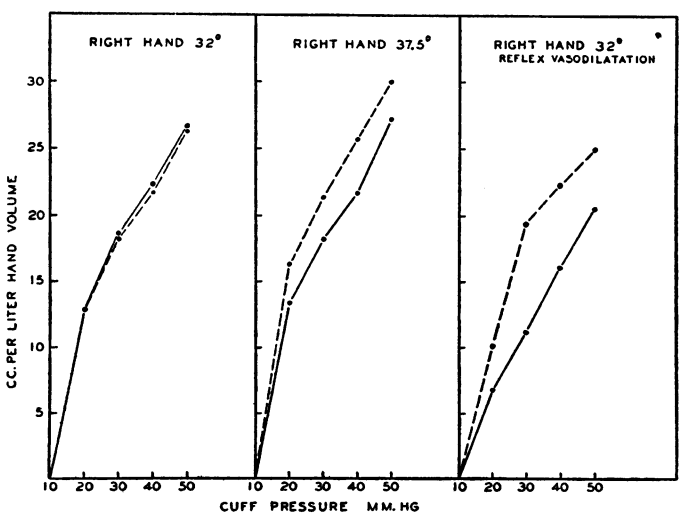


FIG. 5. SUBJECT T. L. VOLUME INCREASES CAUSED BY INCREASES IN THE VENOUS PRESSURE OF THE RIGHT HAND AT 32° C., AT 37.5° C. AND AT 32° C. REFLEXLY DILATED BY HAVING THE LEFT HAND AT 45° C. BEFORE (SOLID LINE) AND AFTER (BROKEN LINE) THE ADMINISTRATION OF 0.18 GRAM OF SODIUM NITRITE.

in distensibility. This effect is possibly due to the fact that at this high temperature the vascular bed of the hand is already fully dilated and therefore distended against the integument and fascia of the hand. Any further distention is actually against the skin and fascia, and not of the vessels alone. The more completely the vessels are already dilated, the less the hand can be further distended by any means, because of the limiting effect of the inelastic integument. Since the method used depends upon the ability of the vessels to distend freely under increases in venous pressure, it obviously cannot be used in the hand when the vessels are already completely or almost completely dilated by local heat. Except for this objection, the method has given uniformly satisfactory results.

*Vasomotor responses after administration of the nitrites.* It has been shown that the changes in venous tone produced by sodium nitrite are independent of the existing state of the arterioles. It was of interest to ascertain whether under such conditions the responses of the arterioles, as well as of the venules and veins, are influenced by nitrites. We have therefore analyzed the vasomotor effects of two types of stimuli, namely, those of pinch and of increased respiratory movements. The effect of pinch on the vascular system of the normal hand has recently been studied by Capps (5). He has shown that this noxious stimulus produces a sudden and transient decrease in the blood flow due to reflex arteriolar constriction, and, in addition, a reflex contraction of the venous vessels. The changes in these two types of vessels do not necessarily parallel each other. The arteriolar changes are more regular and more intense. Uhlenbruck (6) and Stürup, Bolton, Williams and Carmichael (7) have also demonstrated a reflex decrease in volume of the human arm and finger after deep inspiration, as well as after pain and other stimuli.

Our observations have confirmed the findings of these workers. We also found that these reflex vascular changes caused by pinch and respiration remain qualitatively and apparently quantitatively the same after nitrite as before. The increase in blood flow in response to an elevation of the local temperature, which depends upon the relaxation of the arterioles, is also the same after nitrite as under normal control conditions. These observations indicate that in spite of the changes in the venous tone following nitrite the vasomotor reactivity of the vessels was essentially maintained.

## DISCUSSION

The results of the previous experimental study of collapse produced by sodium nitrite suggested that in this type of collapse the essential change is in the peripheral circulation (1). After even small doses of nitrite there is a loss of tone of the peripheral vascular beds so that under the increased venous pressures of the upright position they dilate in the lower half of the body until they hold a considerable portion of the total blood volume. As a result, there develops a disproportion between the total volume of blood and the total volume of the vascular beds, which we believe is the fundamental mechanism of collapse. Large doses of nitrite alone may produce this state without the additional stress of the upright position.

Whatever essential primary action sodium nitrite has on the peripheral circulation must be independent of the position of the subject and should also be present in the prone position. In this study we have demonstrated a specific effect of nitrite on the peripheral "veins" by measuring the increase in volume of the hand due to known increases in venous pressure. We have shown that the hands are distended by the same venous pressures from 20 to 40 per cent more after nitrite than before.

Capps has previously shown that the method measures the tone of the capillaries, venules and veins of the hand. Our results confirm his contention that this test does not measure the tone of the arterioles. Furthermore, we have shown that small doses of nitrite do not essentially affect the tone of the arterioles or their reflex or local vasomotor responses to various types of stimuli. Thus, in the presence of decreased venous tone the reactivity of the arteriolar system is maintained. The fact that arteriolar constriction and "venous" dilatation have been observed simultaneously within such a small localized area as the hand, while the other bodily functions remained in the control state, suggests that simultaneous constriction of the arterioles and dilatation of the venous vessels may occur in collapse

clinically and can develop without the presence of increased epinephrine secretion. The marked arteriolar constriction (as indicated by a very low blood flow) present at the height of the circulatory collapse which we produced experimentally, as well as that which occurs clinically, can be explained as a secondary response to and not the primary essential pathological physiology of collapse. This sharp arteriolar constriction, on the other hand, coupled with the small arterial pressure, may result in such a low blood flow to the tissues that a dangerous degree of anoxemia is produced. When this anoxemia involves the vital centers, such damage may be done to them that a " vicious circle " is established, and the patient goes deeper into collapse and dies.

The demonstration of decreased venous tone in the hand indicates that the venous system of the splanchnic area is not the sole site of the pooling of blood and is not a specific area for a " venous depot " in collapse. In the upright position the arms and hands become such blood depots, as well as the feet, legs and abdominal viscera. In the horizontal position, likewise, all the dependent portions of the body play such a rôle, if the venous tone is decreased. This is borne out amply by clinical observations on patients in collapse.

That the rôle of the spleen and of the splanchnic area as representing " blood depots " has been overestimated is supported by observations on animals. Dale and Richards (8) have noted that the vasodepressor effect of histamine is maintained after animals have been eviscerated. Frey and Kraut (9) have concluded that the vasodepressor effect of certain organic substances depends on vasodilatation in the skin and muscles. Weiss, Robb and Ellis (10) and Wollheim (11) indicated that the subpapillary venous plexuses of the skin under certain conditions represent important blood reservoirs. Hochrein and Keller (12) attributed such a function to the pulmonary veins. Lindgren (13) has attributed an important rôle to vascular changes within the muscles in collapse.

As far as we know, the data here presented represent the first direct evidence that a chemical substance, namely, sodium nitrite, may lead to circulatory collapse by acting primarily on the venous side of the circulation, reducing the tone of the capillaries, venules and veins. Presumably other vasodilating drugs and toxins may act in a similar way. Histamine has been shown to have a dilator effect on the human venous vessels, and when given in small doses this may be its only action on the vascular system (10). By showing that a loss of venous tone is accompanied by a tendency to collapse, we have established the value of tests which measure the tone of the capillaries, venules and veins in the study of collapse. Postural adaptation tests, since they indirectly measure the " venous tone " in the lower half of the body, are of value (14). The test of venous tone in the hand offers a method likely to prove valuable to clinical investigators. Investigation of the venous side of the circulation will prove fruitful in solving the problems of peripheral circulatory collapse.

## SUMMARY

1. The vascular tone and vasomotor reactions in the hands of normal subjects have been studied by plethysmographic methods before and after the administration of from 0.12 to 0.18 gram of sodium nitrite.

2. Sodium nitrite decreases the tone of the veins of the hand, as indicated by the decrease in resistance of these vessels to graded pressure. The volume of the hand remains essentially unchanged at a normal level of venous pressure, but it becomes increased from 20 to 40 per cent more after nitrite than before, at elevated venous pressures. The decrease in tone of the veins after nitrite is less at a local temperature of 32° C. than at 37.5° C., or at 32° C. with reflex dilatation.

3. The tone of the arterioles, as indicated by the blood flow, remains normal even in the presence of a pronounced decrease of venous tone.

4. The vasomotor responses of the arterioles and veins to certain local and reflex stimuli are maintained in the presence of decreased venous tone.

5. On the basis of the observations described in this and in the preceding study, it is concluded that the primary action of sodium nitrite is on the venous side of the circulation. This action, under elevated pressure, results in a disproportionate increase in the volume of the venous system, causing peripheral pooling of venous blood and hence collapse.

6. The observations reported represent additional evidence demonstrating that the splanchnic area is not the sole or the specific vascular area functioning as a blood reservoir (depot) in collapse.

7. The studies demonstrate the active rôle of the venous system and gravity in certain types of collapse.

This investigation was carried out with the technical assistance of Miss Josephine M. McIntire.

## BIBLIOGRAPHY

1. Weiss, Soma, Wilkins, R. W., and Haynes, F. W., The nature of circulatory collapse induced by sodium nitrite. J. Clin. Invest., 1937, **16**, 73.
2. Weiss, Soma, and Ellis, L. B., Influence of sodium nitrite on the cardiovascular system and on renal activity in health, in arterial hypertension and in renal disease. Arch. Int. Med., 1933, **52**, 105.
3. Capps, R. B., A method for measuring tone and reflex constriction of the capillaries, venules and veins of the human hand with the results in normal and diseased states. J. Clin. Invest., 1936, **15**, 229.
4. Freeman, N. E., The effect of temperature on the rate of blood flow in the normal and in the sympathectomized hand. Am. J. Physiol., 1935, **113**, 384.
5. Capps, R. B., The reflex effect of a noxious stimulus on the blood flow in the hand. (In press.)
6. Uhlenbruck, P., Plethysmographische Untersuchungen am Menschen. I. Über die Wirkung der Sinnesnerven der Haut auf den Tonus der Gefässe. Ztschr. f. Biol., 1924, **80**, 35.
   II. Die Spontanschwankungen des Extremitätenvolumens und der Einfluss der Atmung auf dasselbe. Idem, p. 317.
7. Stürup, G., Bolton, B., Williams, D. J., and Carmichael, E. A., Vasomotor responses in hemiplegic patients. Brain, 1935, **58**, 456.
8. Dale, H. H., and Richards, A. N., The vasodilator action of histamine and of some other substances. J. Physiol., 1918–19, **52**, 110.
9. Frey, E. K., and Kraut, H., Ein neues Kreislaufhormon und seine Wirkung. III. Arch. f. exper. Path., u. Pharmakol., 1928, **133**, 1.
10. Weiss, Soma, Robb, G. P., and Ellis, L. B., The systemic effects of histamine in man with special reference to the responses of the cardiovascular system. Arch. Int. Med., 1932, **49**, 360.
11. Wollheim, E., Die Blutreservoire des Menschen. Klin. Wchnschr., 1933, **12**, 12.
12. Hochrein, M., and Keller, C. J., Beitrage zur Blutzirkulation im kleinen Kreislauf. I. Der einfluss mechanischer Vorgänge auf die mittlere Durchblutung und die Depotfunktion der Lunge. Arch. f. exper. Path. u. Pharmakol., 1932, **164**, 529.
13. Lindgren, A. G. H., Kapillarstudien bei Schockzuständen. Arch. f. exper. Path. u. Pharmakol., 1934, **176**, 96.
14. Irwin, J. H., The Crampton test and surgical shock. J. M. Soc. New Jersey, 1935, **32**, 416.