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principles of the exchange of fluid and dissolved crystalloids between blood and tissues. Capillary walls in general are regarded as having the properties of an inert membrane, which is freely permeable to the passage, in either direction, of water and crystalloid or gaseous solutes, but impermeable, or only to the slightest extent, to the blood colloids, notably proteins. Certain notable exceptions to this general rule exist.



OEDEMA RESULTING FROM ARTIFICIAL ELEVATION
OF THE VENOUS PRESSURE.

The introduction of a satisfactory method of determining the cardiac output in man, the existence of methods for determining circulation velocity and blood volume, and increasing knowledge of respiratory function in disease, have rendered an accurate study of the phenomena of circulatory failure a practical possibility.

My interest has been centred chiefly in the problem of cardiac oedema. This essay is an account of experiments directed to the artificial production of oedema, mostly in normal subjects, together with a consideration of the results obtained by previous investigators in the same field.

There is today fairly general agreement regarding the regulation of the exchange of fluid and dissolved crystalloids and gases between blood and tissues. Capillary walls in general are regarded as having the properties of an inert membrane, which is freely permeable to the passage, in either direction, of water and crystalloid or gaseous solutes, but impermeable, or only to the slightest extent, to the blood colloids, notably protein. Certain notable exceptions to this general rule exist, e.g. /

e.g. the cutaneous capillaries in the frog which, according to Landis and others, are freely permeable to protein, while various noxious influences may render the walls of any capillaries, permeable to protein. In virtue of the impermeability of the capillary walls to proteins, the latter are enabled to exert an osmotic pressure, which in the case of human blood amounts, in vitro, to about 35 cm. of water.

Normally a balance exists, whereby the average capillary blood pressure, which tends to filter out fluid and crystalloids, is offset, and indeed exceeded by this colloid osmotic pressure, which attracts fluid into the capillaries from the surrounding tissues. Owing, however, to the gradient of hydrostatic pressure within the capillaries, filtration proceeds at the arterial end where, according to the direct measurements of Landis, in the capillaries of human skin the pressure is of the order of 43 cm. of water; at the venous end, absorption proceeds, as the pressure there, according to the same authority, is about 16 cm. of water, 19 cm. less than the colloid osmotic pressure. It is believed that this mechanism of filtration and absorption, subject to local variations in blood flow, surface of exchange and accumulation of metabolites, to mention a few of the factors involved, maintains a more or less constant condition in respect of the tissue fluid content.

A factor counteracting filtration, is the pressure within the tissues. The precise part which this plays is obscure; probably it exerts little influence over fluid exchange in normal amounts, but it is believed that its influence in controlling abnormal filtration and assisting in the removal of excess tissue fluid, has hitherto been underestimated. That it is a factor of considerable significance, is suggested by the results of this investigation.

According to the above conceptions, tissue fluid normally resembles an almost protein free ultra-filtrate of blood plasma, isotonic therewith. Alteration in either of the major factors mentioned, viz. capillary blood-pressure and plasma colloid osmotic pressure, will upset the balance between filtration and absorption, e.g. elevation of the capillary pressure, such as occurs naturally during hyperaemia, active or passive, and artificially, as under the conditions of the experiments to be discussed, will increase filtration, while a reduction of the colloid osmotic pressure such as occurs when the blood proteins are unduly lowered, as in copious albuminuria, or when, for some reason, the capillary wall becomes permeable to protein, will result in diminished absorption. This, of course, is equivalent to an increase in "effective" filtration pressure. Under these circumstances, fluid will accumulate in the tissues.

No mention in this discussion has been made of "increased permeability" of the capillaries as a factor leading to increased filtration, except in so far as permeability to protein is concerned. It seems obvious on theoretical consideration, that an increased permeability of the capillary walls to water and crystalloids alone, cannot, of itself, give rise to oedema. Such an increased permeability will merely facilitate fluid exchange in either direction. Absorption will increase as much as filtration. When, however, an account of an upset of the balance in the fundamental factors, a predominance of filtration or of absorption has been established, they will proceed at a greater rate, the greater the permeability of the capillary wall, as defined in this section.

A number of quantitative studies have been made, regarding the relation between elevated venous pressure and the consequent excess of filtration over absorption. The principles have been essentially the same - viz. the elevation of the venous pressure in a limb by the application of a pneumatic cuff inflated to the desired pressure, the rate of swelling of the limb being then measured by various means, of which only the plethysmographic need be considered.

Drury and Jones (1927) constructed a water plethysmograph
in /

in which the subject's leg was immersed in a vertical position. The temperature of the water was kept constant by surrounding the plethysmograph by a water bath warmed by a gas flame, and could be regulated to any desired level. The initial volume of the limb was determined by the volume of water it displaced from the plethysmograph, and graphic records of the change in volume were obtained by means of a float recorder.

They applied pressures of 20, 40, and 60 mm.Hg. to the thigh, by means of a pneumatic cuff, and showed that, during the time of their observation, which lasted for 30 minutes, the increase in limb volume bore a linear relationship to the constricting pressure in any individual subject. The rate of swelling was also increased by increase in temperature of the water surrounding the limb, but the relationship in this case was less direct. In each subject the rate of tissue fluid accumulation, measured at 16°C, 26°C, and 36°C, showed a much greater increase between 26°C and 36°C than between 16°C and 26°C.

At similar temperatures and constricting pressures they found considerable variation in the rate of swelling, measured from the 10th to the 20th minute of congestion, the range being from 0.090 c.cs./100 c.cs. of limb/ min. to 0.097/ 100/ min., and the average 0.093. Five subjects were used, the temperature being /

being 36°C., and the pressure in the cuff 60 mm.Hg. The rate in the same individual, however, under the same conditions, remained practically constant in each of several observations.

The period of the 10th - 30th minutes was chosen, as during this time they believed that swelling of the limb was due solely to the accumulation of tissue fluid, while during the first ten minutes of the experiment the increase in limb volume was due chiefly to vascular filling following the application of the constricting pressure. They demonstrated that this was complete within 10 minutes.

They observed that the rate of oedema formation from the 10th to the 20 minutes, in all the subjects, was considerably greater than from the 20th to the 30th minute, the average values for these periods being, respectively, 0.080 c.cs./100c.cs. of limb/ minute and 0.063/100/ min., at 36°C. and 60 mm.Hg. cuff pressure. Under the same conditions, rates were observed in one subject, whose limb was subjected to congestion for 220 minutes falling from 0.066 during the 10 - 20 minute period to 0.022 during the 210 - 220 minute period.

In the present series of experiments, in which the upper limb was used, a similar, but much less marked, diminution in rate of swelling was observed in some of the subjects.

Drury and Jones also observed that after 8% of the limb's volume /

volume of oedema fluid had collected, pitting on pressure was detectable. This has not been confirmed in the present series of experiments, in which the arm has been used.

A comparison of the present results with those just summarised, is hardly feasible. In our cases the experimental congestion was maintained for a much longer period than the 30 minutes generally employed by Drury and Jones, and the limb was allowed to swell at room temperature, as against a temperature of $36^{\circ}\text{C}.$, well above the normal skin temperature, as used by Drury and Jones. Lastly, the upper limb was used, as being more easily measured, and not normally liable to tissue fluid accumulation, as the leg is, the venous pressure in the feet rising to the order of 75 mm.Hg. in a normal subject in the erect posture. There is also evidence that part of the mechanism controlling excess filtration is more effective in the lower, than in the upper limbs (vide infra). Drury and Jones, too, have overlooked the fact that the increased hydrostatic pressure within the veins engendered by the dependent position of the limb, is almost entirely cancelled when it is immersed in water. Their estimation of average venous pressure within the immersed limb is accordingly too high in every case; it is, in fact, scarcely higher than that exerted by the pneumatic cuff. Allowing for this, the rate of swelling they observed /

observed at 26°C. and 60 mm.Hg. pressure ~~temperature~~ on the average, 0.048 c.cs./100c.cs. of limb/ minute, from the 10th - 20th minutes, does not differ greatly from the figures obtained in the present series, in the upper limb at room temperature, with a congesting pressure of the same order.

Their method, of course, does not permit an exact determination of how much of the swelling is due to true tissue fluid accumulation, apart from the blood present in the vessels at the time of the observation.

Krogh, Landis and Turner (1934) endeavoured to obtain figures of "reduced arm volume", i.e. of the arm volume, less the volume of blood contained in the larger vessels.

Their method of producing excess filtration was the same, viz. constriction of a limb by a pneumatic cuff. The upper limb was used, a segment of the forearm being enclosed in an ingenious, but cumbrous device, named a "Pressure Plethysmograph". The plethysmograph contained water, which was maintained at a constant temperature, throughout the short duration of their experiments, by wrapping the plethysmograph in cotton wool.

A burette was connected to the plethysmograph, and the movement of the water level in it indicated the change in volume in the forearm. The open end of the burette was connected to

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a compressed air supply, exerting a pressure of 55 cm. of water.

To obtain a base line, several readings were made, as follows:-

A high pressure was suddenly thrown into a pneumatic cuff, placed as high as possible on the arm. This immediately cut off all circulation through the limb. The compressed air supply to the burette was then turned on, and was transmitted, via the water in the burette-plethysmograph system, to the enclosed segment of the limb. This pressure forced blood out of the vessels into the parts of the limb outside the plethysmograph, and a figure for reduced arm volume was obtained. After several such readings were in agreement, the limb was congested by means of another cuff around the middle of the arm, various pressures being exerted in the different experiments. At the end of half an hour, another determination of reduced arm volume was made, from which the increase in limb volume could be obtained.

At the end of the experiment, the plethysmograph was removed and the volume of the enclosed limb was calculated, on the assumption that the enclosed segment was a truncated cone.

In a number of experiments, the rate of removal of the accumulated tissue fluid was determined after release of the congesting cuff.

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The conclusions drawn by Krogh, Landis and Turner from these experiments, were briefly as follows:-

1. Fluid accumulates in the tissues at venous pressures above 15 - 20 cm. of water.
2. Above an average venous pressure of 17 cm. of water, fluid accumulates at the rate of .0023 ccs./100 c.cs. of limb/minute for unit rise (1 cm. of water) of venous pressure.
3. The rate at which fluid is removed from the tissues depends upon the amount which has accumulated. When less than 0.6 c.cs. per 100 c.cs. of limb is present, its removal is prevented by elevating the venous pressure to 20 cm. of water. This they regard as evidence that such amounts are removed by absorption into the blood. When more than this amount has collected, the same venous pressure does not prevent its removal. This they regard as indicating that larger accumulations are removed by lymphatic drainage. They discount "tissue turgor" as a factor facilitating removal.

The above measurements were all made with the subject reclining, with the limb at heart level. With the subject standing, the limb again being at heart level, the rate of fluid accumulation was in all cases considerably less than that occurring in the reclining /

reclining position.

They regard this as being due chiefly to the elevation in the colloid osmotic pressure of the blood, which occurs in a standing subject, due to blood concentration on account of excess filtration occurring in the lower limbs. They determined the colloid osmotic pressures under these conditions, and concluded that unit rise (1 cm. of water) of the colloid osmotic pressure of the blood, reduces filtration by an amount ranging from .0027 to .0045 c.cs. per 100 c.cs. of limb per minute.

Regarding the above experiments and conclusions, one makes the following observations.

The method, as mentioned, is ingenious but too clumsy for ordinary use. The figures obtained for reduced arm volume are probably accurate, but the pressure required to empty the vessels will also empty the lymphatics, a point which does not escape Krogh, Landis, and Turner. They appear, however, to have overlooked the fact that, as the contents of the lymphatics are derived from the tissues around them, the fluid thus expressed must have come from the same source. In consequence, their measurement of filtration takes no account of that part of the filtered fluid which has found its way into the lymphatics.

The rate of swelling in the present series of experiments, in /

in which a congesting pressure of 60 mm. of Hg. was employed should, according to the figures given by Krogh, Landis and Turner, have amounted to .1473 c.cs./100 c.cs. of limb/minute, in the initial stages. In fact, it amounted to far less than this in all the normal subjects.

The observations regarding the removal of accumulated fluid, are capable of a different interpretation to that given. That absorption is prevented by raising the venous pressure to 20 cm. of water, when the accumulation amounts to less than 0.6 c.cs./100 c.cs. of limb, is probable. If such be the case, the capillary hydrostatic pressure must be greater than the combined absorptive effect exerted by the colloid osmotic pressure of the blood, and whatever pressure may be exerted by the tissues upon the extravascular fluid. Having regard to the method of raising the venous pressure, viz., a pneumatic cuff, encircling the whole arm, the lymphatics will be subjected to the same pressure. Unless the biological properties of the lymph capillary endothelium differ markedly from those of blood capillary endothelium, it seems obvious that the pressure of the contained lymph can never be higher than that outside the lymphatics, in other words, the pressure within the tissues themselves. Under the circumstances mentioned, we have seen that the "tissue pressure" must be considerably less than that exerted by the constricting /

constricting cuff (20cm.H₂O). The lymphatic pressure, therefore, must also be less than 20 cm. of water. Under these circumstances, then, neither is fluid absorbed by the blood, nor can it escape via the lymphatics, so that the attempt to separate absorption from lymphatic drainage fails.

When larger accumulations of fluid are present, it was observed that elevating the venous pressure by means of the cuff, to 20 cm. of water, did not prevent fluid removal. In this case, obviously, the pressure driving fluid out of the tissues, either by absorption or by lymphatic drainage, must have exceeded 20 cm. of water. If the escape were occurring as is suggested by Krogh, Landis and Turner, via the lymphatics, then the intralymphatic pressure must have exceeded 20 cm. of water, and in this case, the pressure within the tissues must have been higher still. By the same token, a tissue pressure of this order, plus the colloid osmotic effect, must have resulted in a greater absorptive force so far as the blood capillaries are concerned. This force may have been great enough to cause absorption even in the presence of a venous pressure as high as 20 cm. of water.

It is apparent, from the foregoing theoretical considerations, that both absorption into the blood and lymphatic drainage may be operative, irrespective of the size of the tissue fluid accumulation. The significant factor determining whether fluid will be removed or not is evidently the amount of fluid present, and /

and one submits that the evidence points strongly to "tissue turgor" being, far from the negligible quantity which Krogh, Landis and Turner account it, a highly significant factor governing the exchange of fluid between blood tissues.

4. The attempt to calculate the anti-filtering force exerted by unit rise in colloid osmotic pressure is clearly bound to fail under the circumstances mentioned. Krogh, Landis and Turner themselves recognise that the only methods available for producing an elevation of the colloid osmotic pressure of the blood (e.g. the erect posture or diversion of blood to the lower limbs by means of pneumatic cuffs around the thighs) produce simultaneously gross alterations in the circulatory conditions. No reliance, therefore, can be placed on the figures quoted, viz., reduction in filtration rate of .0027 to .0045 c.cs. per 100 c.cs. of limb/ minute per rise of 1 cm. of water in the colloid osmotic pressure of the blood.

Both the preceding series of observations suffer from the defect that they were continued over short periods of time. As will be seen, if the congestion be maintained for a sufficient length of time, results of material interest are obtained.

Smirk, in a recent paper, describes a simple method of plethysmography /

plethysmography applicable to the upper limb, and a modification of this method has been employed in the present series of observations.

The hand and forearm are placed vertically in a cylindrical glass jar, and marks are made on the skin at the level of the rim of the jar. These marks are then rendered ineffaceable by the application of strips of sticking plaster, the upper edges of which coincide with the marks. The jar is now filled with water, the temperature of which is immaterial, so long as the same temperature is employed in subsequent observations. In the present series, a standard temperature of 37°C. has been employed.

The limb is now sunk in the jar until the marks are level with the rim, which is greased to prevent overflowing water adhering to it, and obstructing the observer's view of the marks. The limb is then withdrawn, and the volume of the limb immersed is measured by the volume of water required to refill the jar. Duplicate measurements are made at each observation.

The congesting pressure is applied by means of a sphygmomanometer cuff placed round the arm, the pressure being raised as desired. The level is maintained by means of a compressed air supply, which is connected to the cuff, with a mercury manometer in parallel.

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In all but one of our observations, a pressure of 60 mm.Hg. was employed.

The limb is disposed comfortably in a horizontal position, on a level with the heart, the subject's posture being recumbent or erect as may be required.

When subsequent measurements of limb volume are to be made, the inlet and outlet tubes of the cuff are clamped, and the air supply is disconnected. The subject can then walk to the measuring jar, the pressure in the cuff falling little owing to leakage during the short time necessary for the measurement. Measurements at intervals indicate the change in volume which the limb undergoes, duplicate observations being made on each occasion.

Compared with those described above, this method appears crude in the extreme, and no steps are taken to ensure a constant temperature in the immediate environment of the limb. It has, however, considerable advantages in respect of simplicity of apparatus and ease of application, and occasions little inconvenience to the subjects (one of whom reclined uncomplainingly for a period of over 7 hours). Under indoor conditions, the temperature of the air remains practically constant, and within the physiological range of external temperature. One regards, as its greatest advantage, the fact that by its use, the observations may be continued for a well-nigh indefinite period, without /

without the necessity for unusually patient, well-trained subjects.

In the attached table, the figures obtained in a series of 6 subjects are shown. In each case, the observations were made with the subject reclining, the pressure in the pneumatic cuff being maintained at 60 mm.Hg. The colloid osmotic pressure of the plasma was determined in 5 of the 6 subjects by means of a capillary osmometer of the type described by Krogh, potassium oxalate being used as an anti-coagulant.

Against the time in minutes from the commencement of the observation, the change in limb volume has been recorded as a percentage of the initial volume. The results have also been expressed graphically, the percentage increase in limb volume being plotted as ordinate against the time as abscissa, and curves have been constructed on or near which the plotted points lie. The rate of swelling per 100 c.cs. of the initial limb volume per minute during the earlier part of each observation, has been calculated.

Five of the subjects were healthy young men, with normal blood pressures. The 6th, L., was a somewhat anaemic individual (Hb. = 80%, Haldane) who had recently been confined to bed with a febrile illness of obscure aetiology.

It is at once apparent that there is little agreement in detail between the individual subjects, either in respect of the /

Subject

Congesting Pressure = 60 mm Hg in all cases. All reclining.

G. J.

Initial limb vol. = 840 c.c.; Coll. Osmotic Pres. = 23.8 mm Hg.

Time (mins)	0	6	9	40	134	195	234	Cuff released	290	340	430
Vols. % +	0	2.6	5.5	7.85	10.25	13.35	15		10.7	4.74	6.55

Remarks - Pitting on pressure not observed at any time.
Rate of Swelling - 9th - 40th minute = .0385 cc./100 cc./minute.

H. D.

Initial limb vol. = 964 c.c.s.; C.O.P. = 24.6 mm. Hg.

Time	0	20	53	88	128	151	148	208	235	266
Vols % +	0	2.5	3	5.2	6.8	8.8	9.95	10.85	11.5	12.9

Remarks - Pitting on pressure not observed.
Rate of Swelling - 20th - 88th minute = .0304 cc./100 cc./minute.

L.

Initial limb vol. = 1052 c.c.s.

Time	0	13	23	80	112	146	180	Cuff released	184	198
Vols. % +	0	6.4	7.1	10.65	11.5	14	17.05		12.6	11.6

Remarks - Pitting on pressure not observed.
Rate of Swelling - 13th - 80th minute = .0590 cc./100 cc./minute.

J. W.

Initial limb vol. = 1058 c.c.s.; C.O.P. = 23.4 mm. Hg.

Time	0	5	14	35	60	86	116	146	188	Cuff released	199
Vols % +	0	3.65	5.25	5.2	7.9	9.55	11.25	11.45	11.45		4.6

Remarks - Pitting on pressure not observed
Rate of Swelling - 14th - 86th minute = .0597 cc./100 cc./minute.

K. W.

Initial limb vol. = 1061 c.c.s.; C.O.P. = 21 mm. Hg.

Time	0	6	20	36	60	96	123	147	161	165
Vols % +	0	3.3	4	4.8	5.6	7.6	7.6	7.8	Cuff released	5.5

Remarks - Pitting on pressure not observed
Rate of Swelling - 20th - 96th minutes = .0475 cc./100 cc./minute

A. S.

Initial limb vol. = 1075 c.c.s.; C.O.P. = 22.2 mm. Hg.

Time	0	9	14	28	60	90	110	116	121
Vols % +	0	1.95	3.2	3.8	6.5	8.8	9.5	Cuff released	4.2

Remarks - Pitting on pressure not observed
Rate of Swelling 17th - 90th minute = .0467 cc./100 cc./minute

the rate of swelling in the earlier period, or in the total amount of swelling present when the experiments were discontinued. The former varied from 0.0307 - 0.0767 c.cs./ 100 c.cs. initial limb volume/ minute, with an average of 0.0520 c.cs./ 100 c.cs. /minute, and the latter from 7.8% - 17.05%. As the experiments were discontinued at different times, the latter figures, of course, are not directly comparable.

It will be noted, however, that the results all show certain features in common, more readily appreciated on a study of the graphs. In all cases, there is a sharp initial rise in limb volume. This varies in its magnitude from one subject to another, but is of the order of from 2% - 4%, occupying, on the average, about 10 minutes or less. This sharp rise, of course, is the expression of the vascular filling which occurs immediately following the application of the constricting pressure. It corresponds closely with that observed by Drury and Jones (vide supra), and ceases when the vascular filling has raised the venous pressure to the level of that exerted by the constricting cuff, at which point blood once more escapes from the limb via the veins. It has been assumed, in common with Drury and Jones, that the subsequent increase in the volume of the limb is due solely to the accumulation of fluid filtered from the capillaries. Fluid, of course, must be accumulating during the early "vascular" phase, /

phase, but the present method does not permit of the determination of the part played by filtration during the time of vascular filling.

When the veins have filled, a pronounced shoulder appears on the curves, and thereafter the limb continues to increase in volume at a steady, but much slower rate, the curve at this stage being scarcely distinguishable from a straight line. The steepness of the slope, however, varies from one subject to another.

When the observations have been continued for several hours, a phenomenon appears which separates the results into two distinct groups. It will be observed that in the case of the first three subjects, G.I., H.D., and L., the swelling showed no sign of approaching a limit, whereas in the remaining three, J.M., K.M., and A.S., the swelling had either ceased altogether, or had slowed down markedly, a second shoulder appearing on the curves obtained from these individuals.

In some of the records, the abrupt decrease in limb volume, following release of the congesting cuff, is shown. This, of course, is the expression of the vascular emptying which occurs, and is the opposite of the sharp initial rise. A quantitative correlation between the initial rise and the final fall has not as yet been sought, owing to the difficulty of obtaining measurements /

measurements at exactly comparable times.

At first sight, the foregoing results appear to be so haphazard that no conclusions can be drawn therefrom. The rate of swelling differs considerably from one case to another, despite the application of a constant congesting pressure of 60 mm.Hg. The difference between this pressure and the colloid osmotic pressure of the blood, in the cases in which it has been determined, does not vary sufficiently to account for this.

It might be said, therefore, that either, (1) the accuracy of the observations is questionable, or (2) the conditions, apart from venous pressure and colloid osmotic pressure, have varied so much from one experiment to another, that the results show no correspondence.

Regarding the first of these possibilities, one may say that were the observations notably inaccurate, one would hardly expect the observed alterations in limb volume to fit so well the curves constructed. As against the second possibility, it can be stated that in the case of two of the subjects, repeated experiments carried out on different days, without any attempt to maintain conditions (apart from congesting pressure and posture) absolutely constant, yielded results which were substantially in agreement. This observation also supports the contention that the accuracy of the measurements is not seriously in question. It /

It is reasonable, therefore, to postulate that the results indicate that in normal subjects, under similar conditions, the rate of filtration varies considerably from one to another, but remains practically constant in the same individual. This corresponds exactly with the previous findings of Drury and Jones (vide supra).

An interesting problem is presented by the observation that in some of the subjects swelling ceases after about two hours, whereas in the others it continues.

In the former instances a new balance has evidently been attained between the forces favouring filtration and those counteracting it. There would appear to be three means by which such a balance may result.

1. A decrease in the filtering force -
 - (a) By a fall in the capillary hydrostatic pressure
or
 - (b) By a reduction in the available filtration area, the hydrostatic pressure remaining constant.
2. The elevation of the anti-filtering force to equality with the filtering force -
 - (a) By a rise in the colloid osmotic pressure of the blood, with or without.
 - (b) A rise in the pressure of the fluid present in the tissue spaces.
3. Escape of tissue fluid via the lymphatics as rapidly as it accumulates from filtration.

Regarding /

Regarding 1(a), it is hardly likely that any fall in the capillary pressure will occur so long as the arterial blood pressure and the artificially elevated venous pressure remain constant.

The contingency 1(b) might arise if closure of some part of the capillary bed were to occur. In order that the hydrostatic pressure in the capillaries still patent might remain constant, this would necessitate a diminution in the volume of blood present in the arm, which would in turn necessitate a reduction in the inflow of blood. That such will occur so long as arterial and venous pressure remains constant, does not appear probable.

In the case of either of the above contingencies, short of complete stoppage of the circulation, the hydrostatic pressure in any capillaries in which blood flow is occurring, must still remain somewhat above the venous pressure of 60 mm.Hg., and filtration from these capillaries will continue, though at a slower rate than formerly.

Factor 1, therefore, while it may account for a slowing, cannot account for a cessation of filtration. A gradual diminution in the volume of blood passing through the arm in unit time might account for a curve such as that exhibited in the case of subject W.B. (attached).

That the second factor, viz. an increase in the anti-filtering forces /

forces, produces in time a cessation of filtration, seems highly probable. It is known that the colloid osmotic pressure of the blood leaving a region in which excess filtration is occurring, is considerably elevated. Youmans et al.(1934) found that the colloid osmotic pressure of venous blood in the feet of standing subjects increased, on an average, by 42.7% of its value when the subjects were reclining. This corresponded with a 27.2% rise in the plasma proteins, and is the expression of blood concentration, resulting from filtration of fluid into the tissues of the dependent limbs.

Haemocrit determinations provided confirmatory evidence of blood concentration. An increase of the colloid osmotic pressure of this order, however, is insufficient to prevent accumulation of fluid when the venous pressure is as high as 60 mm.Hg. Some other agency is required, to supplement the "anti-filtration" effect of the rise in colloid osmotic pressure.

It is believed by the writer that this agency is factor 2(b), viz., a rise in the pressure of the fluid within the tissue spaces, the expression of a refusal of the tissues to be further distorted by the accumulation of fluid within their spaces.

It is surprising to what extent this factor has been overlooked or discounted. Two possible reasons for this are that in the first place, in researches directed to the study of fundamental /

fundamental causes of oedema, tissue tension is not a feature which attracts attention, as a reduction in tissue tension obviously cannot cause oedema, so long as the capillary hydrostatic and colloid osmotic pressures retain their normal relationship. In the second place, as noted above, previous experiments have been of such short duration, that the fluid accumulation has been of insufficient magnitude to occasion a tissue tension capable of preventing further filtration. The possibility, in fact, of there being any limit to the amount of experimentally produced oedema, has apparently been largely overlooked, whereas it is obvious that sooner or later a limit must be reached, or rupture of the soft tissues will occur. Youmans et al., however, were forced to the same conclusion when they observed that the swelling of an erect subject's leg reached a maximum, beyond which further swelling did not occur.

One cannot express any opinion as to the nature of this tissue force; it must vary from one subject to another, as witness the fact that some of the subjects in the present series, had not attained equilibrium after an increase in limb volume much greater than that at which the others had ceased to show any further swelling. That it is a force of considerable importance is shown by the fact that it was sufficient, in these normal subjects, to limit the oedema to an extent short of that at which pitting on /

on pressure appears. The same observation was made by Youmans et al. The appearance of the congested limb when the swelling had reached its maximum, bore a striking resemblance to that which one has seen in patients with pathological elevations of venous pressure in such conditions as venous thrombosis and occlusion of large veins by tumours. In such cases the affected limb is often swollen, dusky and tense, yet exhibits no pitting on pressure despite the fact that at times the cause of the high venous pressure persists indefinitely.

The third possible reason for the cessation of swelling, viz. escape of fluid via the lymphatics, is unlikely to have been operative under the conditions of the present experiments. Unless the endothelium of the lymph capillaries has the power of secreting fluid into them from the tissue spaces, the pressure within the lymphatics cannot be greater than that of the fluid in the tissue spaces. As has been seen, owing to the diminution of effective filtration pressure by the colloid osmotic pressure, filtration will cease considerably before the tissue fluid pressure has risen as high as the filtration pressure, and the lymphatic pressure will therefore be materially less than the capillary hydrostatic pressure, and will probably be less than that exerted by the pneumatic cuff. Lymph, therefore, cannot force its way past this obstruction. When no cuff is present, however, /

however, ^{/or} if the pressure in it be low (as in the experiments of Krogh, Landis and Turner already quoted), lymphatic drainage doubtless plays a notable part in the removal of tissue fluid. It is likely that the absence of lymphatic obstruction is partly responsible for the non-appearance of pitting on pressure in cases of pathological high venous pressure of the type mentioned above.

Why some of the subjects used, continued to swell for so long, it is impossible to say. One would hazard the opinion that had the observations been continued for long enough in these cases, an equilibrium would eventually have been struck. In this connection, attention is directed to the curve obtained from subject G.I., in the standing position. In this case, swelling proceeded considerably more rapidly than in the reclining position, reached a higher level, and fairly abruptly slowed down, ~~and~~ the general shape of the curve obtained being like that exhibited by those subjects who normally ceased swelling during the period of the experiment, when reclining. A possible inference from such a result is that, owing to the more rapid rate of filtration, equilibrium was attained earlier, and consequently came within the period of observation.

It appears that the capacity of the tissues to accommodate excess tissue fluid varies in different individuals. In some
it /

it is small, and filtration ceases comparatively early. In others it is considerable, and filtration is correspondingly prolonged. It is stressed, however, that in none of the subjects under review did pitting oedema ever become apparent, even in the case of L., whose limb volume showed an increase (including, of course, that due to accumulated blood) of 17%. That the tissue capacity may vary in the same individual, under differing circumstances, is a possibility which has not been excluded, and its investigation is contemplated.

In conclusion, brief reference must be made to a series of experiments undertaken to ascertain the effect of posture upon the rate of swelling. In the course of determinations of the cardiac output in normal individuals, by Grollman's acetylene method, it was observed that the cardiac output during quiet standing fell considerably below that of the same individual in the reclining posture. This fall in output is accounted for by the diminished return of venous blood, to the heart, which occurs in the erect posture, when a considerable volume of blood accumulates in the lower limbs under the influence of gravity.

It was thought that this might influence the rate of filtration in the arm, and the rate of swelling was accordingly determined in four subjects when standing, the arm, as before, being /

being maintained horizontal at heart level. The congesting pressure, as in the previous experiments, was 60 mm.Hg.

The results obtained were surprising. In every case the rate of swelling was considerably greater in the erect than in the recumbent posture, as will be appreciated from a study of the curves obtained. The rates of swelling, expressed as c.cs./100 c.cs. of limb/minute, calculated from these curves were, in the four subjects used, as follows:-

<u>Subject</u>	<u>Reclining</u>	<u>Standing</u>
G.I.	0.048	0.111
L.	0.060	0.125
J.M.	0.0575	0.100
K.M.	0.0450	0.105
Average	0.0527	0.110

As will be seen, there is a remarkably close correspondence between the results obtained, as in each case, the rate of swelling when standing, is about twice that when reclining.

No explanation of this result can be given. On theoretical grounds, there is good reason to expect exactly the opposite. A reduction in cardiac output presumably means a reduction in the blood flow through the arm, and the standing posture is known to be associated with a rise in the colloid osmotic pressure of the blood (vide supra). Both of these factors will counteract filtration, and should, other conditions remaining constant, result in a slower rate of swelling in the erect posture. In the /

the light of previous experimental findings, too, this result is anomalous. Krogh, Landis and Turner report a diminished rate of swelling in the erect posture.

It is possible that some undetected vascular phenomenon, of the nature of a gradual capillary dilatation, with a progressive accumulation of blood in the limb, may account for this finding, though one can think of no theoretical grounds for supposing that such will occur. Even if it does take place, it is difficult to imagine why it should appear only, or to a greater extent, in the standing position.

It was thought that the explanation might be found in an increased permeability of the capillary walls on account of a diminution in their oxygen supply, resulting from the diminished blood flow. An attempt to obtain support for this supposition was made, by producing a degree of anoxaemia in subjects G.I. and J.M. These individuals breathed low concentrations of oxygen, in one case with the addition of 5% CO₂ for considerable periods; J.M. also breathed 5% CO₂ alone in one experiment. As will be seen, however, from the accompanying curves, no material alteration in the rate of swelling resulted.

The increased rate of swelling, therefore, observed to occur in the erect posture, requires further investigation.

SUMMARY

1. A method of measuring the change in limb volume produced by elevation of the venous pressure is described.
 2. The experimental use of this method indicates that marked individual variation occurs in the swelling resulting from an elevation of the venous pressure to 60 mm.Hg., but that in the same individual, the rate of swelling is virtually constant.
 3. Evidence is adduced in support of the contention that tissue tension plays a significant part in limiting oedema formation.
 4. Changes in the rate of swelling in relation to posture are discussed, and the failure of partial anoxaemia to affect the rate of swelling is noted.
 5. A brief survey of previous observations in the same field is given. Certain criticisms of these observations and the conclusions drawn therefrom are offered.
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References.

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Landis, E.M.; Physiol.Rev., 14;3(1934),404.

Krogh, A., Landis, E.M., and Turner, A.H.; Jnl.Clin.Invest.,
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Jnl.Clin.Invest., X111(1934), 447.

The accompanying graphs are arranged in the order in which they are referred to in the text.

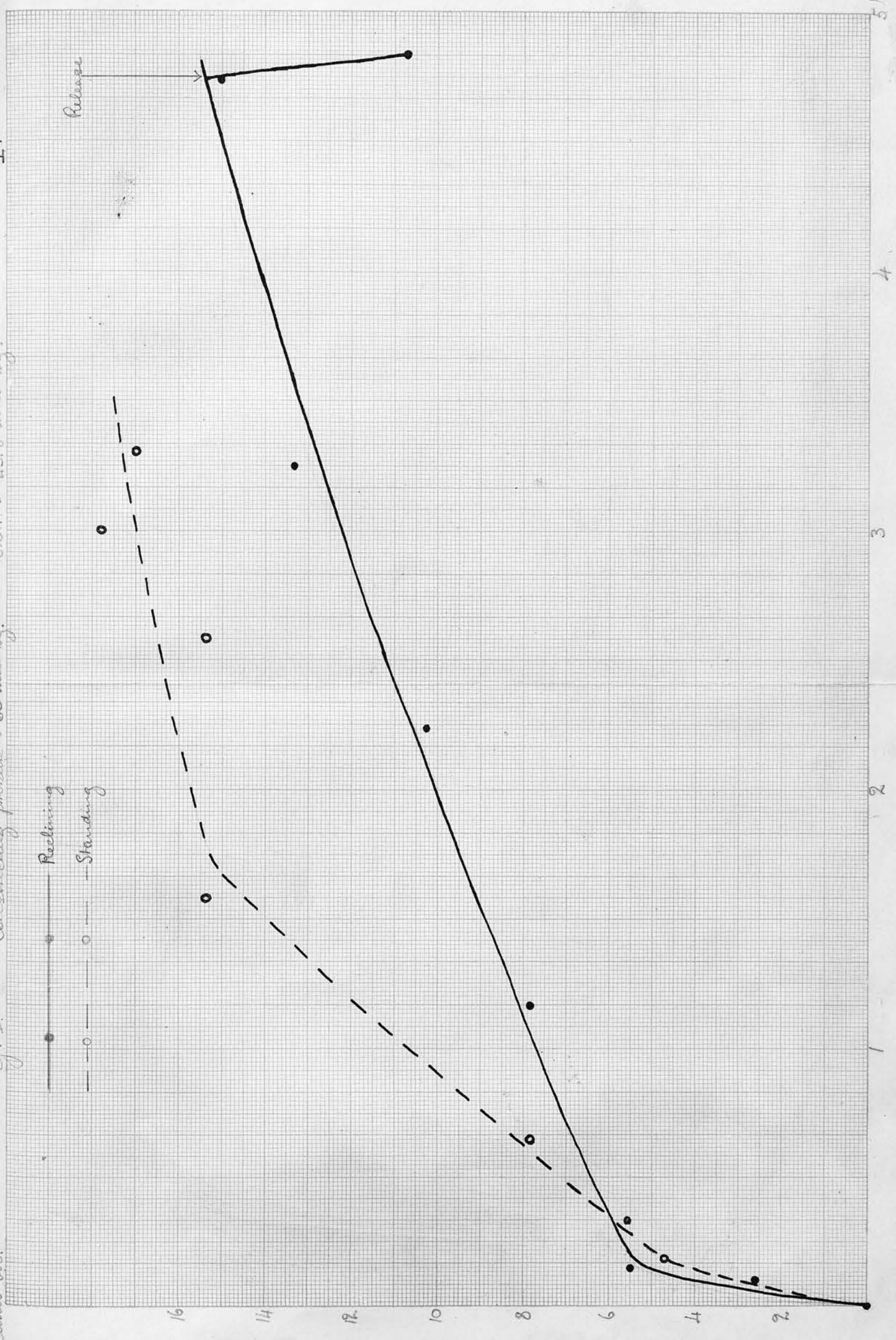
The percentage increase in limb volume is plotted against the time. In certain instances, duplicate measurements are plotted at the same time.

% increase
in limb vol.

G. I.

Constricting pressure = 60 mm Hg. C.O.P. = 23.8 mm Hg.

I.

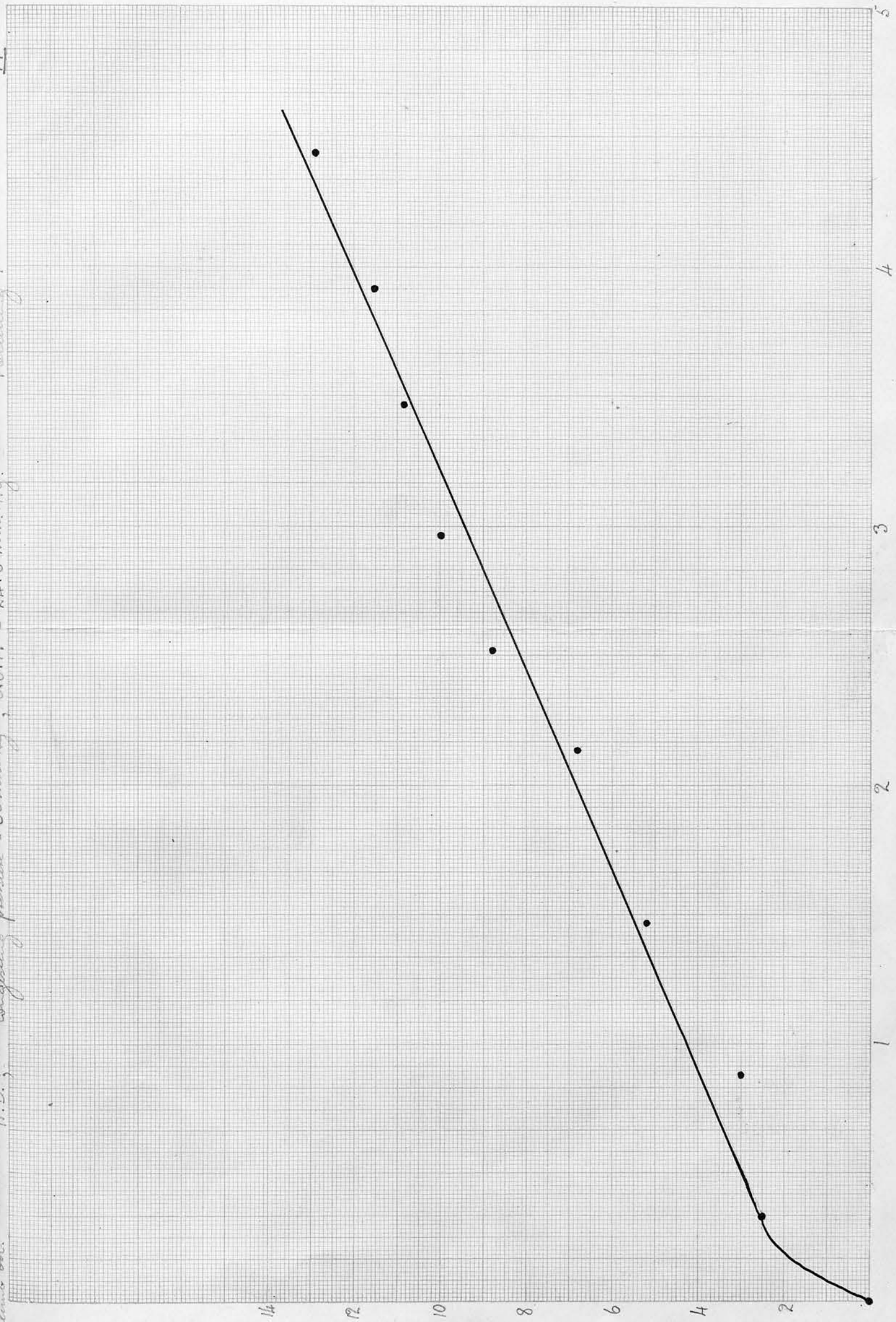


5 Hours

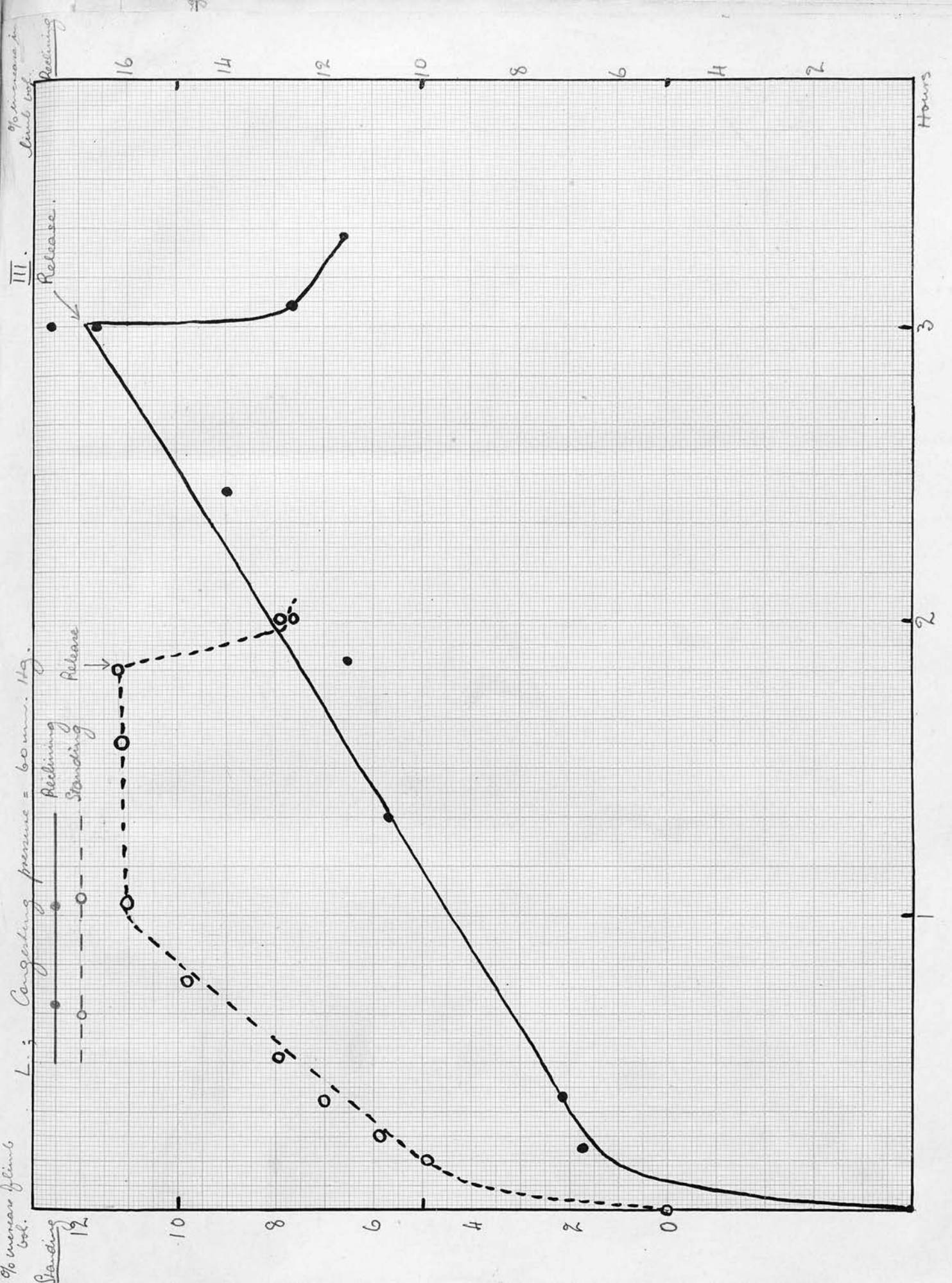
90 minutes
in limb & vol.

H.D.; Congesting pressure = 60 mm Hg; C.O.P. = 24.6 mm. Hg. *Reclining.*

II.



5 Hours

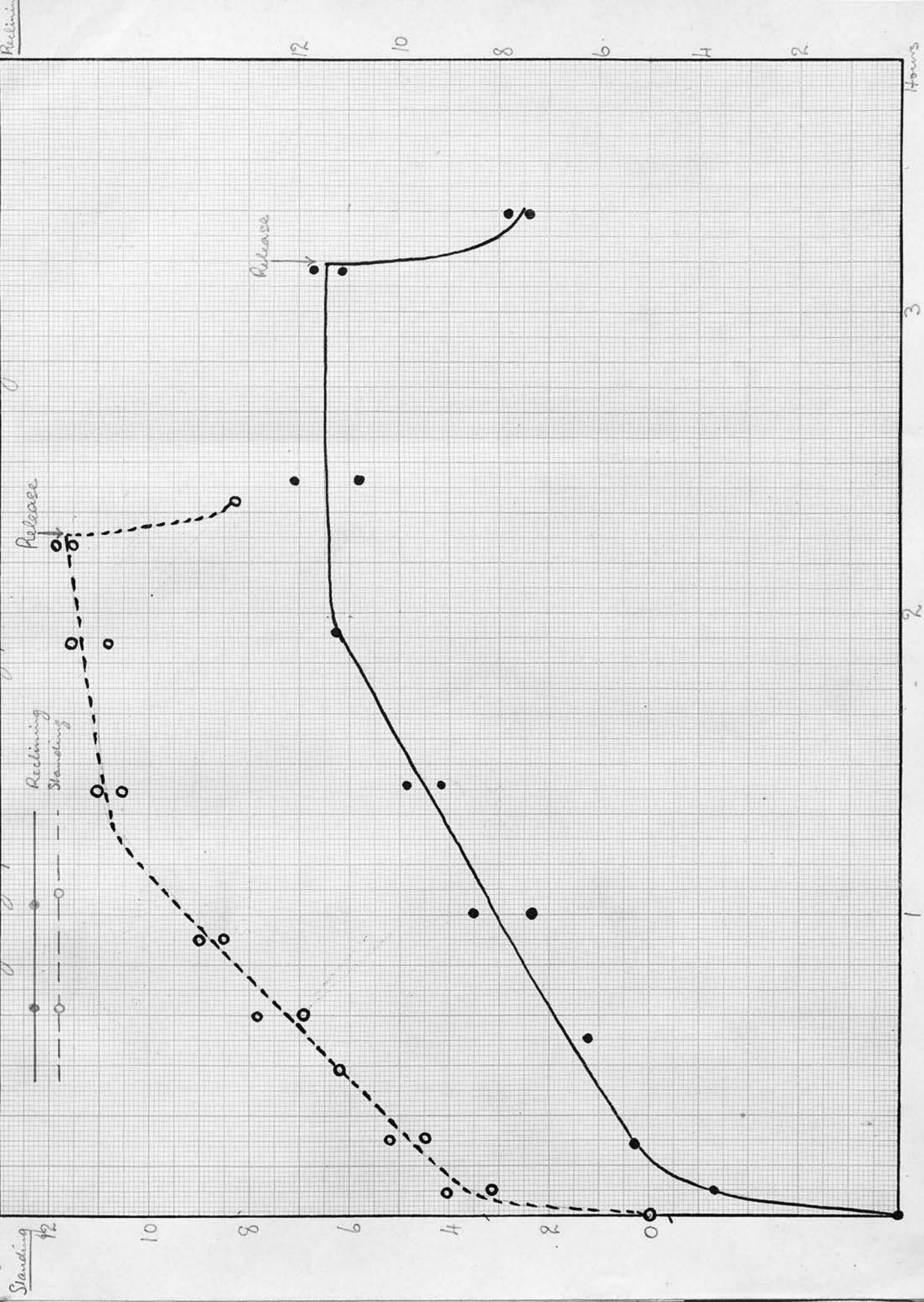


% increase in limb vol. Reclining

IV.

J.M. Congesting pressure = 60 mm Hg.; C.O.P. = 23.4 mm. Hg.

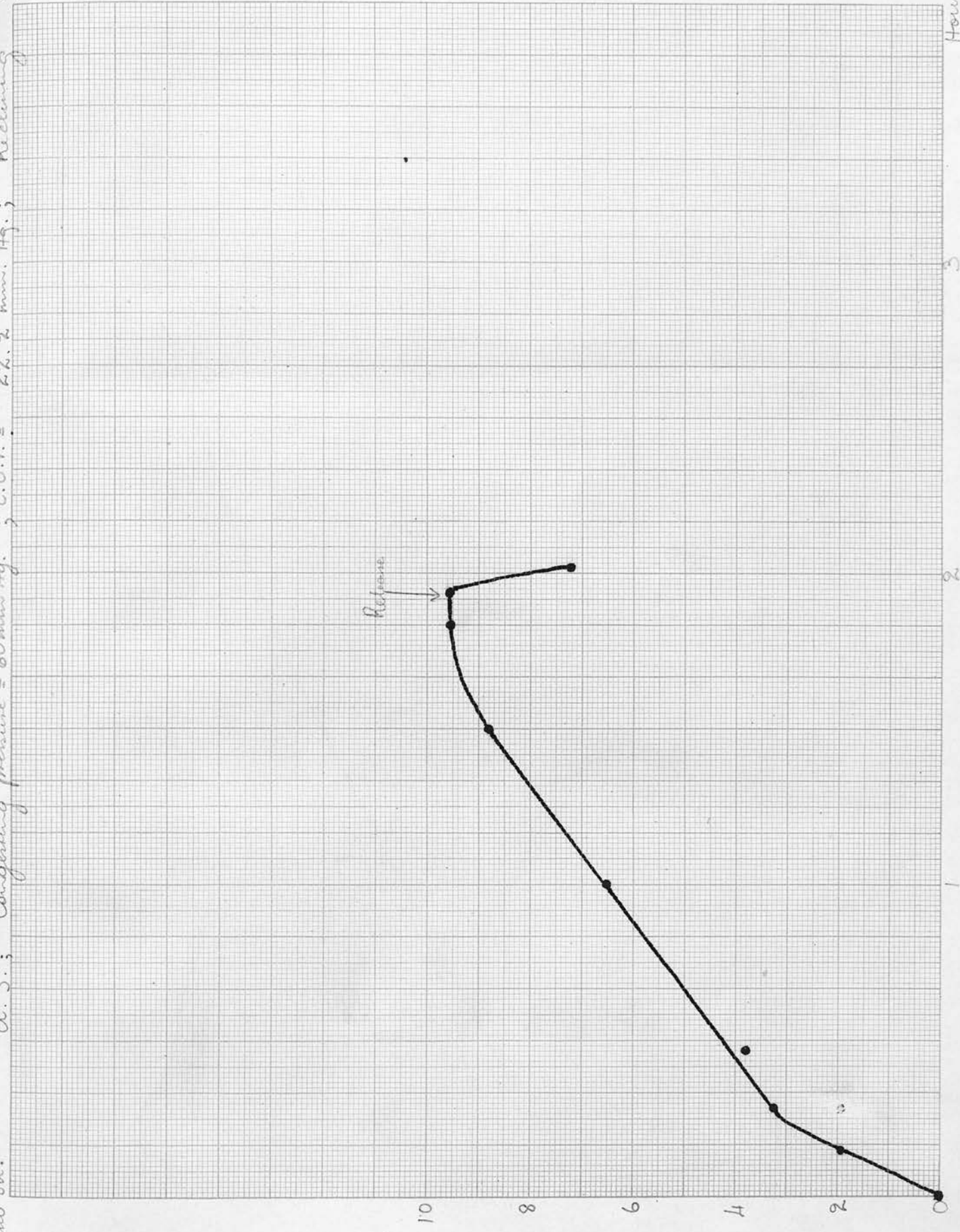
% increase in limb vol. Standing



% increase in
limb vol.

A. S.; Congesting pressure = 60 mm Hg.; C.O.F. = 22.2 mm. Hg.; Reclining

VI.



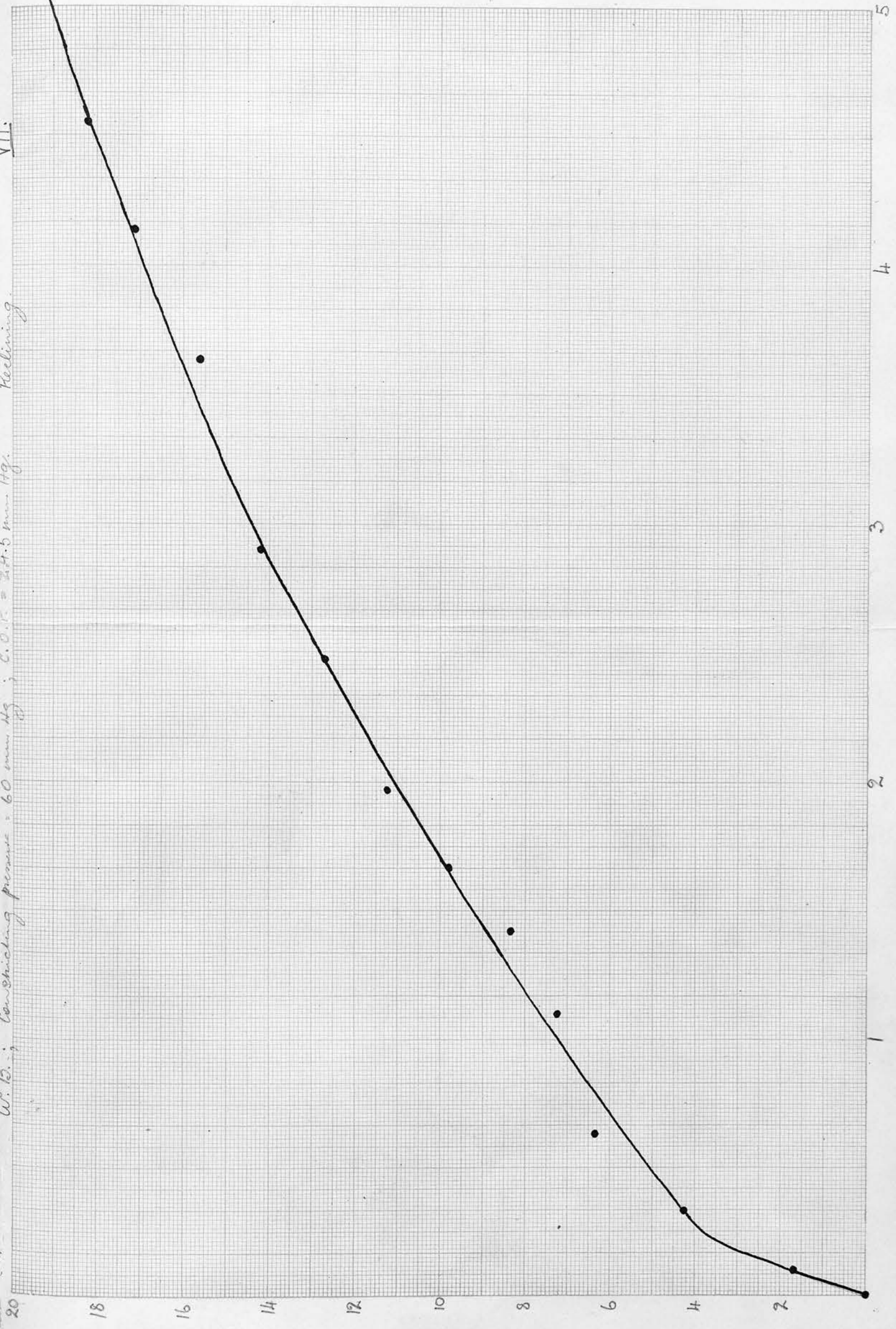
Hours.

To increase
in the end

W.B.; Constricting pressure = 60 mm Hg; C.O.P. = 24.5 mm Hg.

Reclining.

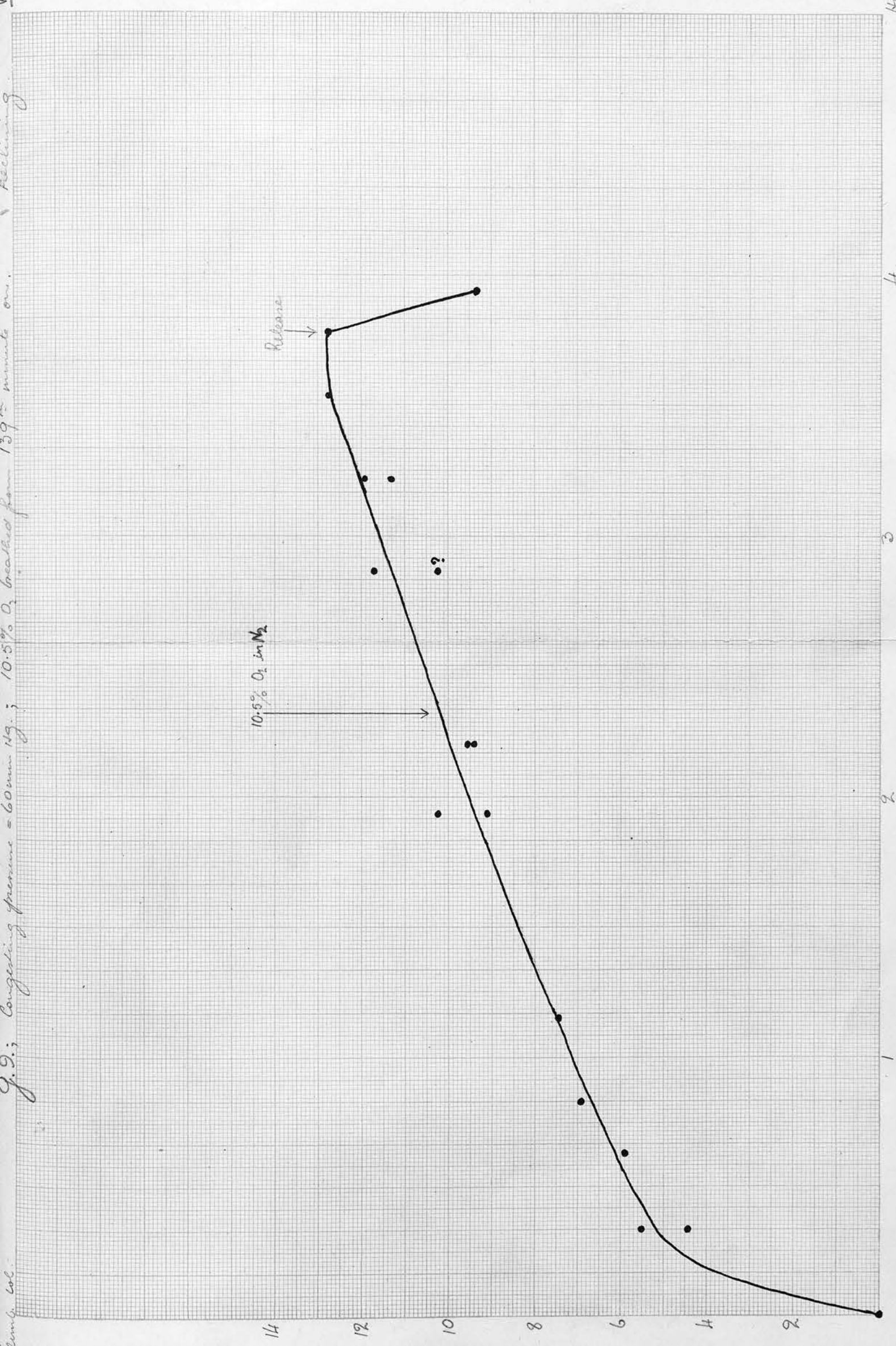
VII.



5 Hours

J. 9.; Congesting pressure = 60 mm Hg.; 10.5% O₂ breathed from 139th minute on. Reclining

50 increase in double vol.



J.M.; Congestion. pressure = 60 mm. Hg; Reclining
 ••• - CO₂ 5%; O₂ 10.5% in N₂ from 11th minute on.
 ••• - CO₂ 5% in air from 22nd minute on.

