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The Pathology of the Oedema Which Accompanies Passive Congestion

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XVII. *The Pathology of the Œdema which accompanies Passive Congestion.*

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SECTION I.—INTRODUCTORY.

THE experiments detailed in the following pages refer solely to the so-called passive œdema, the active, hydræmic, chlorotic, and cachectic varieties not being taken into consideration. The view usually held at the present day is that the œdema in question results from an obstacle to the return of blood by the veins to the heart, or to the flow of lymph through the lymphatics, or to both combined; in other words that it is of mechanical origin.

SECTION II.—AUTHORITIES.

The literature of the subject of œdema begins so far as I can learn with RICHARD LOWER,* who in his 'Tractatus de Corde,' in 1680, stated the view that the œdema of cardiac disease depends upon venous obstruction. This view was not universally accepted, but in 1823, BOUILLARD† by his work strongly supported LOWER. In 1829, ANDRAL‡ came to the conclusion that the obstruction of many veins is necessary, the free anastomosis of the veins readily allowing the blood to proceed towards the heart after the obliteration of one—even if that be the main trunk of the limb. In 1869, RANVIER§ repeated LOWER'S experiments, but failed to obtain any œdema; he afterwards modified LOWER'S method of ligaturing the inferior vena cava, by adding thereto section of the sciatic nerve on one side. On this side œdema appeared, the other limb remained free from it. The first evidence of œdema was visible around the tendo achillis, and came on about an hour after section of the nerve.

* LOWER, 'Tractatus de Corde,' &c., 1680, p. 81.

† BOUILLARD, "De l'oblitération des veines," 'Arch. génér. de Méd.,' 1823, vol. 2, p. 188.

‡ ANDRAL, 'Path. Anat.,' cited by PERLS, 'Lehrb. d. Allge. Path.,' &c., p. 53.

§ RANVIER, 'Comptes Rendus,' 1869, vol. 69, No. 25.

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BOUILLARD, who was present at the reading of the paper before the French Academy, regarded this as another variety of œdema, but in no way as contradicting the occurrence of passive œdema from obliteration of veins which he had himself produced experimentally in several cases, and had seen clinically produced hundreds of times. COHNHEIM,* who did more work on the whole subject of œdema than any previous investigator, regarded the cardiac or passive variety as "the result of two pressures, venous obstruction, and arterial pressure, which, acting against one another, cause an outpouring of fluid through the walls of the thinnest vessels, the capillaries, and probably also the smallest veins." RANVIER's results he regarded not as showing the importance of the vaso-motor nerves, as their author insisted, but he explained the œdema by pointing out that "the congestion resulting from section of the nerve very unfavourably modifies the inequality between inflow and outflow." In 1875, VULPIAN† gave the account of an experiment in which he tied the inferior vena cava a little below the kidneys. The animal only lived twenty hours, but before death "a very evident commencement of œdematous infiltration of the two limbs had been noticed." In 1879, SOTNITSCHEWSKY,‡ working in COHNHEIM's laboratory, produced œdema by obliteration of the vein and its collateral branches with an injection containing plaster of paris. In 1881, CORNIL and RANVIER§ stated that "if in an animal in which one has tied a vein, the vaso-motor nerves be cut, the arteries being dilated, a larger amount of blood reaches the part and the tension becomes sufficient to lead to transudation of serum. This increased tension is the true cause of dropsy, if this tension be sufficient, independently of obliteration of the veins, œdema will occur. All kinds of œdema, except, perhaps, the œdema of cachexia, may be referred to the same cause." In 1889, WOOLDRIDGE‖ wrote, "If a solution of fibrinogen be injected into the circulation through the jugular vein and the femoral vein be then ligatured, the effect is most pronounced, and is as follows: either the most extensive and rapidly developing simple œdema of the leg occurs, or an enormous hæmorrhage" per diapedesin "takes place throughout the tissues of the limb; or the two are combined—there is hæmorrhage and œdema." Since that time the chief work that bears upon the subject of œdema is that by WAYMOUTH REID,¶ by which he showed that the absorption of fluid by the frog's skin and by the intestine is not osmotic but depends upon some process which he calls "vital secretory." So far as his work goes, though he has not turned his attention to œdema as a separate question, it is the basis of that view of œdema which is held by Sir GEORGE

* COHNHEIM, 'Allge. Path.,' Berlin, 1877, vol. 1, p. 121.

† VULPIAN, 'Leçons sur l'Appareil vaso-moteur,' Paris, 1875, vol. 2, p. 591.

‡ SOTNITSCHEWSKY, "Ueber Stauungsœdem," 'Virch. Arch.,' 1879, vol. 77, p. 85.

§ CORNIL and RANVIER, 'Histologie Pathologique,' 2nd ed., Paris, 1881, vol. 1, p. 491.

‖ WOOLDRIDGE, "On Auto-infection in Cardiac Disease," 'Roy. Soc. Proc.,' 1889, vol. 45, p. 309.

¶ WAYMOUTH REID, 'Brit. Med. Journ.,' 1890, vol. 1, p. 165; *ibid.*, 1892, vol. 1, Feb. 13th and May 28th 'Journ. of Phys.,' vol. 11, p. 312.

JOHNSON,* and which regards the outpouring of œdema fluid as the result of a vital secretory action of the smaller blood-vessels.

To sum up, passive œdema has been regarded as :

I. Mechanical.
   (*a.*) The result of venous obstruction.
   (*b.*) The result of inequality between inflow and outflow (COHNHEIM).
   (*c.*) The result of increased tension dependent upon vaso-motor dilatation (CORNIL and RANVIER).
   (*d*) The result of venous and lymphatic obstruction.

II. Vital secretory (JOHNSON).

III. The result of auto-infection by tissue-fibrinogen (WOOLDRIDGE).

SECTION III.—METHODS.

1. *Of obtaining Venous Congestion.*

In all cases this was done by means of a ligature placed round the limb of a dog,† but the experiments are divided into two classes. The first and largest class is those in which a simple piece of indiarubber tubing was tied round the limb and *included* the femoral artery. The second class is those in which a piece of tubing was tied round the limb *excluding* the femoral artery, which was raised from its bed in order that the ligature might be passed beneath it. When the artery is included in the ligature the blood-pressure is diminished on the distal side, by the friction to which the blood is exposed in the constricted portion : this is avoided by exclusion of the artery, but the advantage so gained is probably counterbalanced by the interference with the flow that the necessary stretching of the artery over the ligature occasions. The friction in the first class too, is in most cases not great, for the blood flows apparently with undiminished force from a cut artery on the distal side of the ligature. For this reason, and also because as little injury as possible was necessary in view of later investigations, the artery was as a rule included in the ligature, nevertheless care was always taken that the pulse was perceptible in the lower part of the limb. It is a ligature of this description insufficient to obliterate the pulse below that is designated in the subsequent figures and text as "Medium Ligature."

2. *Of measuring the pressure in the Femoral Vein.*

This was done *directly* and *indirectly*. For the direct measurement a vein was

* JOHNSON, 'Proc. Roy. Med. and Chir. Soc., Lond.,' 3rd series, vol. 4, p. 115 (Discussion on a Paper, by W. HOWSHIP DICKINSON, "On Renal Dropsy").

† Dogs were the animals used throughout the whole investigation, except in sub-section 8, on the method of estimating the absorption of fluid by muscle after stimulation. Frogs were here used. The anæsthetic was either ether or ACE mixture : in no case was curare administered.

laid bare close to its "embouchement" into the femoral vein. Into this inferior vein a cannula was tied which was connected with a mercury manometer. From the thinness of the walls of the veins it is quite easy to invaginate the small vein and push the end of the cannula beyond the valve at the entrance into the femoral vein, and so estimate the pressure from that vein directly ; when the pressure had been registered the cannula was withdrawn from the femoral vein into the small vein, the valve again closed the entrance and the flow went on in the main trunk without the presence of any foreign body. This method is much easier of performance and much less open to objection than the use of a T-shaped cannula inserted into the main vein. There was then placed round the limb an elastic ligature the tightness of which was regulated as was thought fit. When sufficient pressure had been produced in the vein, as shown by the manometer, the ligature was made fast and the only precaution necessary was to take the pressure from the main vein as above shown from time to time.

The indirect method was by means of a piece of intestinal tube, which, after preparation by drying, removal of fat and soaking in glycerine and water, was tied at each end on the two arms of a T-piece. This formed a ring which could be made to press with varying degree of force upon the limb, by filling it more or less with air or some other fluid. The upright of the T-piece was connected with a manometer. It was found however after repeated trial that the difficulties in the employment of this method were very great. In the first place the pressure inside the gut required to be high, and very frequently caused rupture, and in the second place—apart from leakage—the pressure in the veins registered by the manometer diminished. Apparently this was due to the fact that the ligature expelled the blood and lymph from the superficial parts of the limb, which therefore yielded and consequently diminished the pressure on the limb. This method was given up therefore and an elastic ligature with direct measurement of the venous blood-pressure was adoped as the usual method of procedure. The actual blood-pressure was only measured in a certain number of cases in which it was necessary. In the greater number of the experiments the ligature was regulated to such a degree of tightness as would correspond to about 25 or 30 millims. of venous pressure. In these cases it was more important that the arterial flow should not be stopped than that the venous obstruction should be very great, and therefore the pulse, as above stated, was taken as a guide. Enough pressure, however, was always applied to make saphenous vein tense.

3. *Of obtaining evidence as to Increased Transudation from the Blood-vessels.*

Inasmuch as the evidence of œdema given by eyesight, measurement, and pitting on pressure, are not sufficiently trustworthy, and in the case of a small amount of œdema may be completely overlooked, numerical values obtained from observations on the specific gravity of the blood, of the blood-plasma, of muscle and of skin, were taken as the evidence of œdema. The specific gravity of the blood was taken by

Roy's method, and arterial and venous blood were considered separately, the respective kinds of blood being taken from an artery and from one of its venæ comites. The specific gravity of the blood-plasma, also taken separately in the case of the artery and of the vein, was obtained after the addition of potassium oxalate and centrifugalising. A known amount of oxalate solution of known specific gravity being added in each case, the true specific gravity of the plasma was a simple matter of calculation.

The specific gravity of muscle was arrived at in the following way :—

A muscle being exposed, a piece, about 1 centim. square, was removed with the greatest possible rapidity and the least possible injury. This piece was placed on filter-paper to remove any traces of blood or serum and the remaining part of the estimation was done by a modification of Roy's method for obtaining the specific gravity of the blood which was suggested to me by Professor Roy himself. Small portions of the piece of muscle removed were gently dropped into solutions of different specific gravity previously arranged in tubes on the table. That fluid in which the piece of muscle neither floated nor sank was taken as the correct one, and a perfectly fresh piece of an, as yet, untouched part of the same muscle was taken and used as a control. The method is simple, and gives good results after a little practice, but there are several points concerning its employment to which attention must be paid.

In the first place, the muscle must not be roughly handled, and the time occupied by the investigation must be as short as possible, for the changes undergone by dying muscle may possibly,* and drying from exposure to air will certainly, introduce serious error. It is for this reason that a fresh piece has always been taken from some part of the muscle at a distance from the original injury, in order to control the first result. This, the second point of importance, takes but a small fraction of the time necessary for the first determination. Thirdly, it is necessary to pay attention only to the first few seconds after the immersion of the piece of muscle; it so rapidly absorbs glycerine (with which the solutions are made up) that it invariably sinks after the lapse of a very short time, even though it may have floated at first. Fourthly, no bubbles of air must be allowed to remain in contact with the piece of muscle when it is immersed in the solution, as they infallibly vitiate the result. They are sometimes a source of great annoyance; I have found it best to take portions cut in the long axis of the muscle, as the air-bubbles attach themselves principally to the cut transverse surfaces, and consequently the smaller this is the better may this difficulty be avoided. In connection with this point, it must also be added that the muscle-sheath should be cleared away as well as possible before removal of the piece of muscle from the body: the air-bubbles are particularly prone to become entangled in this fascia. The use of boiled solutions has also been tried, and this obviates the difficulty to some extent. Lastly, for purposes of comparison, corresponding muscles

* If evaporation be prevented the specific gravity of muscle rises about three degrees during the first half-hour after removal from the body, *i.e.*, during death; the specific gravity undergoes no further modification during the subsequent twenty-four hours. Sept. 29, 1894.

must be used in each limb, as there is frequently a considerable difference in specific gravity among the various muscles of a limb.

Estimation of the specific gravity in the case of the skin is a much more difficult operation than in the case of muscle. In the first place, the skin of the lower animals must be shaved, and there is always a possibility that some of the superior layers of the epidermis, which are the most compressed and therefore have the highest specific gravity, may be removed on one side and not on the other. Secondly, in one specimen a larger amount of the loose sub-epidermal fibrous tissue may be taken up in the piece for examination. Thirdly, the difficulty arising from air-bubbles is much greater than in the case of muscle. Consequently, though the greatest pains have been taken to obtain accurate results, I regard the specific gravities of the muscle in the subsequent account of my experiments as more nearly correct than those for the skin. Inasmuch, however, as corresponding parts of the limbs were used in all cases, the numbers obtained for the skin are fairly capable of comparison among themselves.

4. *Of obtaining Evidence as to the Amount of Lymph Secreted.*

This was done by measuring the quantity that flowed from an opened lymphatic vessel in a known time. The saphenous vein having been dissected out and the lymphatics that run in its sheath being laid bare, a cannula was tied into one of them, and all the others that were visible were securely ligatured. The limb was kept in a state of rest during the observations, but immediately before the end of each observation it was raised and rapidly and firmly pressed from the paw upwards, so as to expel any fluid that might be in the lymph channels. They were thus left empty at the very beginning and the very end of an observation, so that the amount of lymph collected represented as accurately as possible the amount secreted.* Inasmuch, however, as the general tendency for the lymph is to find out for itself anastomotic channels, after an experiment has lasted for some hours, the final results are always below the mark. If, therefore, the amount registered at the end of an experiment be equal to that registered at the beginning, it is certain that the actual amount secreted at the end must have exceeded the amount secreted at the beginning. This is a point which must always be borne in mind when considering investigations into the amount of a lymph secretion. The period of time for each observation was one hour, unless anything to the contrary be expressly said.

* The word "secretion" is used here and elsewhere in accordance with HEIDENHAIN'S work ("Versuche u. Fragen z. Lehre von d. Lymphbildung," PFLÜGER'S 'Arch.,' vol. 49, p. 209). That the lymph formation is absolutely comparable with the secretion of saliva is not proven, and, indeed, there are facts incompatible with such a view. The word is to be taken only in the sense of being different from purely "mechanical."

5. *Hæmostasis.*

This term will be frequently used in the following pages, and it refers to a condition of the limb obtained in the following way. A piece of india-rubber tubing was tied tightly round the limb, as high up as possible, in order to stop completely not only the venous but also the arterial flow through the limb. The limb was subjected in no way to previous treatment and was simply cut off from the rest of the circulation with whatever blood it might contain for a certain period of time. As a rule, to which but few exceptions were made, this period was one hour. At the end of that time the "hæmostatic" ligature was removed and the limb was again put into connection with the general circulation. In some cases after hæmostasis the pressure to which the vessels was subjected was that exerted by the otherwise unaltered circulation; in others the venous pressure was raised by means of a "medium ligature," as described in Sub-section 1 of this section. On no occasion was the blood in the limb so treated found to have coagulated.

6. *Anæmia.*

This term in the following pages will be used in two senses, either as comparative anæmia or as absolute anæmia. The context will easily show which of the two is meant in any individual case. Absolute anæmia was obtained by bandaging the limb from the paw upwards as tightly as possible. Over this bandage, which was an ordinary linen one, an ESMARCH's elastic bandage was tightly wound and was firmly secured above, so that no blood could possibly enter the limb. The period during which the limb was thus kept anæmic was from two-and-a-half to three hours. After the removal of the bandages the limb was either left untouched or the venous pressure was raised by a "medium ligature," as was necessary in the case of any individual experiment. It is obvious that by this method not only is the limb rendered absolutely anæmic, but also during the process of bandaging much of the lymph is driven out of it.

7. *Of performing* RANVIER's *Experiment.*

The only difference instituted was that the inferior vena cava was tied through an incision in the abdomen, instead of from behind, as was RANVIER's practice. One point, however, was regarded as essential. The ligature of the inferior vena cava and the section of the sciatic nerve on one side, were carried out as nearly simultaneously as possible. The ligature was passed beneath the vessel in readiness for tying, and the nerve was dissected out and a director passed beneath it, and, when both these parts of the experiment had been done, the ligature was drawn tight and the nerve divided, the two operations not taking together more than a few seconds. RANVIER gives no indication as to his actual method of procedure in his original paper, but it is imperatively necessary that no long interval of time should take place between the two operations. In fact, the general absence of any information as to time is very evident throughout the whole literature of œdema. And yet, in physiological matters, time cannot be neglected; in fact, during a neglected period, some events may have taken place—and, indeed, in the case of œdema they can be shown to take place—which afford the key-note of the whole question, while, if time be ignored, the conclusions derived from otherwise accurately observed facts are extremely likely to be erroneous in whole or in part.

8. *Of estimating the Absorption of Fluid by Muscle after Stimulation.*

This was also done by the specific gravity method, to which reference has already been made. The two gastrocnemii of a frog were taken with a length of nerve attached. Immediately after removal from the body, they were slightly dried on filter paper and placed under oil. One muscle was then stimulated by an interrupted current of increasing strength, until the strongest current produced a barely perceptible contraction. Both muscles were taken out from the oil simultaneously, the oil rapidly removed with blotting paper, and were then placed in normal saline solution. After a varying period, they were again simultaneously removed from the saline solution, rapidly dried, and the specific gravities taken in the ordinary way. By taking portions from the muscles alternately, the differences from drying, &c., were made as nearly constant as possible, while there was no danger of comparing different parts of the muscles, such, for example, as a piece taken from the belly of one with a piece taken from near the tendon of the other.

As has already been shown by a reference to the literature of passive œdema, the general tendency is to explain it upon purely mechanical grounds. If this explanation be true, it is obvious that increased exudation must follow *immediately* upon increase of venous pressure. It is not sufficient to find after a varying but long period, reckoned by hours, that there is an increase of exudation. Upon a mechanical explanation, the exudation ought to appear in the tissues without any interval. For the determination of this point experiments were done, and they had reference to the following questions, viz.:—

a. Does an increase in the specific gravity of the blood as a whole, and of the plasma, coincident with a diminution in specific gravity of the muscle and of the skin, occur immediately after the blood-pressure in the veins has been raised?*

b. Is an increase in venous pressure accompanied by a corresponding increase in the amount of lymph flow per unit of time?

* It must be remembered that the method used for increasing the venous pressure in the veins also obstructed the flow of lymph. The effect of an obstruction to the flow of lymph is discussed in Section V.

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The latter question was obviously necessary, even though the former might be answered in the negative, since it was quite possible that any excess of exudation, instead of showing itself by any modifications in specific gravity in the blood, muscle, &c., might be carried off by the lymphatic vessels, an increased rate of flow acting in a compensatory manner.

These two questions will now be considered in detail.

Section IV.—The Effect of Increase of Venous Pressure in a Limb.

1. *On the General Blood-pressure.*

Beyond an initial fall which accompanies, or very soon follows upon the application of the ligature used to increase the venous pressure, and which is very constant, the effects on the aortic blood-pressure are somewhat uncertain. The mercury in the manometer usually recovers its former position in a few minutes after the application of the ligature, but then its tendency is to fall again. The excursions are not, however, great, rarely exceeding 10 millims. of mercury.

2. *On the Specific Gravity of the Arterial Blood.*

If the venous pressure in a dog's hind limb, which is usually less than 5 millims. of mercury, be raised to a considerable degree, care being taken that it be not raised to within some sensible difference from the pressure in the femoral artery, the flow of blood through the limb is impeded, but not completely stopped. Under such conditions, the mechanical explanation of œdema requiring that fluid should pass out of the blood-vessels which is of lower specific gravity than the blood, the blood of the system, as a whole, must of necessity be raised. Experiment shows that this is not by any means the case. Thus the venous pressure was raised in various experiments to 50–75 millims. of mercury, the pressure in the carotid being over 100 millims. of mercury in each case. In some cases the specific gravity of the blood as a whole remained absolutely constant, in others, a very small rise or fall occurred, sufficiently small, however, to come almost within the range of experimental error. It must also be remembered that apart from any interference the specific gravity of the blood may rise or fall slightly. Had a small rise been constant, it would have been significant as showing that the constant drain from the vessels was able to raise the specific gravity of the whole blood in the body to a certain small extent; but inasmuch as a small fall is as common as a rise, this explanation cannot hold good.

I therefore conclude that increase of the venous pressure in a limb for one hour does not in any way affect the specific gravity of the arterial blood of the body as a whole.

3. *On the Specific Gravity of the Arterial Blood-plasma.*

Partly because the normal specific gravity of the plasma is so much lower than that of the blood as a whole and differs but little from the specific gravity of the lymph, and partly because the plasma forms so considerable a portion of the volume of the blood, variations in the specific gravity of the plasma are rarely so considerable as those of the blood as a whole. Inasmuch as the specific gravity of the plasma could only be taken conveniently after the addition of potassium oxalate and centrifugalising, and as its estimation involved several operations which need some nicety, the liability to experimental error was greater than in the case of the blood. Inasmuch, however, as the rise or fall in any individual case was less than ·5°, and in most cases the specific gravity remained absolutely constant, *I conclude that even enormous increase of venous pressure in a limb for one hour has no influence upon the specific gravity of the arterial blood-plasma.*

4. *On the Specific Gravity of the Venous Blood.*

It is obvious that the conditions in the case of the venous blood are widely different from those in the case of the arterial blood. The quality of the blood reaching the two limbs, whether obstructed or not, must be the same. In fact, since the blood that enters the femoral artery on either side is, to all intents and purposes, the same as when it was mixed in the aorta, the arterial blood has, for the necessary purposes, always been taken from the side on which no experiment was being done. The object of this was to interfere as little as possible with the blood-supply of the limb that was specially under observation. In the case of the veins, however, the case is very different. In the limb in which the venous return is impeded, the blood remains for a longer time than it does in its fellow, and hence—the tissues requiring their nutriment, whether there be obstruction to the blood-flow or no—each volume of the blood on the obstructed side has to give up a larger portion of the contents of its plasma than is the case on the unobstructed side. It is, therefore, only to be expected that the effect of increase of venous pressure in a limb should vary according to whether the obstructed area or parts other than the obstructed area, are considered. In the former case the alterations are very small, not exceeding 1° in specific gravity. The alteration too may be either in direction of a rise or of a fall. In the latter case a rise in specific gravity *invariably* takes place, in some experiments amounting to over 6°.

It follows, therefore, that increase of venous pressure in a limb for one hour differs in its effect upon the specific gravity of the venous blood according as whether the obstructed area, or parts other than the obstructed area, are under consideration. In the former case there is invariably a rise in specific gravity; in the latter case the specific gravity remains unaltered.

5. *On the Specific Gravity of the Venous Blood-plasma.*

The same remarks which have been made in Sub-section 4, as to the difference between the effect of an increase of the venous pressure in a limb upon the venous blood in that limb, and the venous blood in other parts, also holds good in the case of the venous blood-plasma; the venous blood-plasma of the system, as a whole, remains constant in specific gravity, that of the obstructed limb rises in some cases as much as 5°. The rise in specific gravity of the plasma of venous blood proves that the watery part of the plasma has been chiefly removed during the passage through the limb. This occurs in the normal state, so that the blood does not lose plasma as such during its passage from an artery to a vein, but something less than plasma. At the first glance this rise suggests that, since water has left the plasma, the limb must have become œdematous. Such, however, is not necessarily the case, and, in fact, the constancy of the plasma in other parts of the body shows that the total amount that left the vessels for the supply of the needs of the tissue was not excessive though each volume of plasma in the veins of the obstructed part, owing to its prolonged sojourn in the limb, lost a larger quantity of water than an equal volume in any other part where the sojourn was shorter.*

I conclude, therefore, that the effect of increase of venous pressure in a limb for one hour, is to raise the specific gravity of the venous blood-plasma in the limb itself, but as far as the venous blood-plasma of other parts is concerned, it is without effect.

6. *On the Specific Gravity of Voluntary Muscle.*

Inasmuch as any fluid which passes out of the blood vessels must present itself, at any rate for a time, in the muscles as part of the tissues surrounding the blood-vessels, evidence was sought here as to the effect of venous pressure in a limb. As it was inadvisable to injure the limb which was destined afterwards to bear the ligature, the preliminary estimation of the specific gravity of the muscle was always made upon the control limb. It was assumed—and previous investigations had warranted the assumption—that the specific gravity of corresponding muscles in the normal state is identical on the two sides. At the end of the experiment the specific gravity of another as yet untouched portion of the same muscle upon the unligatured limb was taken, while this was compared with the corresponding muscle upon the ligatured limb. Not only, therefore, was it determined whether the muscle on the ligatured limb underwent an alteration in specific gravity, but also whether the muscle of a part other than the ligatured limb underwent alteration. In all cases where the specific gravity of muscle is being taken, the divergence or parallelism of the

* In some experiments the specific gravity of the whole blood fell, though that of the plasma rose; in others, the converse took place. This suggests that the amount of water in the blood-corpuscles varies under different circumstances, and within fairly wide limits, for the number of blood-corpuscles cannot vary to any very important extent during the period of the experiment.

lines drawn from the common starting point is of much greater importance than any consideration from data given by one side alone. If, for example, the muscle on the ligatured side be found at the end of an experiment of lower specific gravity than that which obtained in the muscle of the unligatured side, we might assume that the muscle on the ligatured side had taken up water as the result of increased venous pressure; but if on examination we find that the muscle on the unligatured side has also fallen in specific gravity, we are certain that the access of water on the ligatured side is *not* due intrinsically to the increased venous pressure.

All experiments on this point show clearly that an increase of venous pressure is unaccompanied by any change in the specific gravity of the muscle, either in the ligatured or in the unligatured limb. That an access of fluid *does* cause a diminution of the specific gravity of the muscle, and *vice versâ*, will be shown in a later section.

I therefore conclude that increase of venous pressure in a limb for one hour has no effect upon the specific gravity of muscle either in the limb itself or in parts other than the limb.

7. *On the Specific Gravity of Skin.*

The curve given by the initial and final specific gravity of skin is absolutely identical with that of muscle, excepting as regards the actual figures, and these are sometimes higher, sometimes lower than that of muscle. The remarks made when dealing with muscle concerning the essential importance of divergence or parallelism, and the comparative unimportance of actual numbers, are equally true in the case of skin. That the specific gravity of skin is an indication of the amount of water which it holds, and that it may vary considerably will be shown in a later section. It is here sufficient to state as my conclusion that *increase of venous pressure in a limb for one hour has no effect upon the specific gravity of the skin, either of that limb or of other parts.*

8. *On the amount of Lymph-flow.*

If a cannula be inserted into one of the lymphatic vessels of the hind limb of a dog and all other lymphatics be ligatured, the amount of lymph collected gives the amount secreted under normal conditions. If the amount thus collected for a certain length of time (in the actual experiments, one hour) be registered, and then a "medium" ligature be applied above the part investigated, and the amount of lymph under these altered conditions be again collected for the same length of time, an indication is given of the effect of an increase in venous pressure on the lymph-flow. This was done, and it was seen that the amount secreted with an increase of venous pressure was either identical with or slightly less than the amount secreted when the venous pressure was normal: in no case was it greater. It was evident, moreover, that the increase of venous pressure had no after-effects upon the lymph-flow, as the amount collected during the hour after removal of the "medium" ligature was, in all cases, the same as that collected during the hour previous to its application.

The conclusion to which I am led, therefore, is that an increase in venous pressure in a limb for one hour is not accompanied by an increase in the amount of lymph-flow.

9. *On the Circumference of the Limb and its Appearance as concerns Œdema.*

During the actual period when the ligature is around the limb the blood-vessels are unusually full of blood, and hence the circumference of the limb, measured over a marked line a little above the paw, is greater than that of its fellow measured in the corresponding position. To draw a fair comparison, it is necessary first to remove the ligature, and allow the limb to empty itself of its excessive amount of blood. This takes but a very few seconds, and if now the limb be measured it is found to be of exactly the same circumferential size as at the beginning of the experiment. As far as the ordinary appearances of œdema are concerned, they are completely wanting.*

I therefore conclude that an increase of venous pressure in a limb for one hour is not followed either by an increase of circumference of the limb or by any of the ordinary appearances of œdema.

Section V.—The Effects of Obstruction to the Lymph-flow in a Limb.

Inasmuch as the elastic ligature which was used to produce venous obstruction in the experiments described in Section IV. was placed round the whole limb, it is obvious that the lymphatic vessels, together with other parts, were placed under the same conditions as the veins. Though, therefore, the pressure in the lymphatics was not measured, as it was in the case of the veins, there can be no doubt that there was obstruction to the lymph-flow. Indeed, in several instances this was seen by the naked eye to be the case, as, on dissection, they were found to be dilated, sometimes almost to the size of a crow-quill. The results given in Section IV. are consequently true, if increase of "lymphatic" pressure be substituted for increase of "venous" pressure.

I therefore conclude that increase of lymphatic pressure in a limb for one hour is unaccompanied by any alteration in the specific gravity of the blood or blood-plasma, arterial and venous, of muscle or of skin, and also that it does not lead to any alteration in the circumference of the limb or any of the ordinary appearances of œdema.

* It is necessary again to draw attention to the fact that the conclusions stated are true only for the period during which the increase in venous pressure lasted, viz., one hour. Such an increase in venous pressure as was experimentally produced could obviously not exist for an indefinite period without introducing some modification other than venous obstruction.

SECTION VI.—THE EFFECT OF VENOUS OBSTRUCTION IN CONJUNCTION WITH LYMPHATIC OBSTRUCTION IN A LIMB.

It follows as a corollary to Sections IV. and V. that increase of venous pressure, in conjunction with increase of lymphatic pressure in a limb for one hour, is unaccompanied by any alteration in the specific gravity of the blood or blood-plasma, arterial and venous, of muscle or of skin, and also that the two together do not lead to any alteration in the circumference of the limb or any of the ordinary appearances of œdema.

It is a matter of some interest to know for how long a period a condition of increased venous pressure may be kept up without the occurrence of œdema. The experiments referred to in this paragraph were carried out in a much more rough manner than those detailed above, nevertheless they throw some light on the question. A friend and myself placed elastic bands around one of our arms below the bend of the elbow, and of sufficient tightness to cause distension of the veins on the backs of our hands, but not sufficient to stop the radial pulse. The pressure required was somewhat great, and I was obliged to remove my ligature at the end of three hours, as the pressure on my ulnar nerve caused considerable pain. My friend, however, continued to wear it for twenty hours from its first adjustment, though after the first four hours he loosened it slightly. In neither case was the slightest trace of œdema to be seen in the hand,* while the only place where œdema was visible was immediately below the ligature in my friend's arm for a distance of one inch downwards. In experiments on dogs no œdema was visible in the paw, in one case after the ligature had been applied for seven and a half hours, in a second for seven hours, in a third also for seven hours, and in a fourth for six and a half hours, though in all these cases there was a small amount of œdema in the neighbourhood of the ligature. I afterwards found that VULPIAN† speaks of the same appearance "first of all in the thigh, later in the lower part of the limb."

An additional point of interest which showed itself in the experiments on dogs was that a certain amount of œdema almost invariably appeared on the *proximal* side of the ligature. The amount was never as great as that on the distal side, but it was very evident, and pitted deeply on pressure. Reference to this fact will be made later. It is sufficient here to state that careful dissection showed that the parts above the ligature did not drain into a vein which opened into the main trunk on the distal side of the ligature, and hence that the œdematous parts above the ligature were not the seat of venous obstruction.

* In my friend's hand there was perhaps a doubtful trace, but it disappeared a few minutes after removal of the elastic ligature.

† VULPIAN, 'Leçons sur l'Appareil vaso-moteur,' Paris, 1875, vol. 2, p. 592.

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Section VII.—The Effect of Section of the Sciatic Nerve in a Limb.

By reason of the great importance attached by Ranvier to section of the sciatic nerve upon the occurrence of œdema, it was necessary also to investigate this point. The specific gravity of the muscles was the chief, though not the only subject of consideration; but, inasmuch as to repeat the results obtained would be to needlessly lengthen this paper, these subsidiary points will not be touched upon, it being assumed that the specific gravity of the muscles is a sufficient indication as to whether fluid has passed from the blood-vessels.

1. *On the Specific Gravity of Muscle.*

If, in a dog, the inferior vena cava be completely obstructed, and at the same time the sciatic nerve be cut on one side, the side on which the nerve was cut was found by Ranvier to become œdematous, while the limb in which the nerve was left intact did not become œdematous. The explanation given by Ranvier of his results was that œdema was dependent in some way upon vaso-motor action. Subsequently, however, he modified his view by regarding the vaso-motor action as being indirect and as acting through the medium of the arterial dilatation which follows upon section of the nerve. The question of time, so far as can be determined from the writings above mentioned, has not been taken into consideration. In my experiments the specific gravity of the muscle was taken as being more trustworthy evidence of œdema than mere eyesight.

The curves given by the muscles of the two sides are, as far as can be expected, identical in shape, their parallelism being only slightly modified at the end of the experiment. Even here all that is shown by the curves is that the muscles of the one limb are slightly in advance of the other. Thus about 6 hours after the commencement of the experiment the muscle on the side on which the nerve was cut rises in specific gravity, while the muscle of the side on which the nerve was left intact does not rise until an hour later. It is possible that this is by reason of the arterial dilatation in the former limb which, in normal cases, is accompanied by more rapid metabolism. This, however, comes under the *later* effects of section of the sciatic nerve. With these we are not now concerned, it is sufficient for the present to *conclude that section of the sciatic nerve has no immediate effect upon the specific gravity of the muscles supplied by that nerve.*

It will be well here to summarize the facts that have already been obtained, as they will form a basis for the latter portion of the paper.

The propositions that commenced Section IV., were, that on the assumption of the purely mechanical causation of passive œdema, the exudation must show itself by various modifications in specific gravity, and further, that if increased exudation occurred, but were not to be recognized in the tissues, it would be explained by an increased rapidity in the flow of lymph per unit of time.

It has been shown by experiment, that increase of venous pressure in a limb kept up to a very high point for an hour, does not cause any modification of the specific gravity of the blood, or the blood-plasma of the system as a whole, either arterial or venous; that it does not cause any modification in the specific gravity of the muscles or skin either in the body as a whole, or in the limb in which there is increased venous pressure. In the second place it has been shown that increase of venous pressure is not accompanied by a corresponding increase in the rapidity of the lymph-flow. Both propositions, therefore, have been answered in the negative.

It was next shown that section of a nerve has no influence upon the specific gravity of muscles supplied by it: this is contrary to what should occur upon RANVIER'S view of the exudation as being the result of increased tension.

The explanation of passive œdema as a purely mechanical phenomenon, due to increased rapidity of filtration through the walls of the blood-vessels, is therefore not borne out by experiment.

Reference has already shortly been made to the fact that a ligature placed on a dog's limb often causes œdema to appear not only on the distal but also on the proximal side of the ligature. In itself, this is a powerful argument against the influence of venous congestion as a direct cause, since the parts on the two sides of the ligature are obviously in very different conditions, so far as concerns venous congestion.

SECTION VIII.—THE EFFECT OF HÆMOSTASIS IN A LIMB.

So far as the specific gravity of the arterial blood and blood-plasma, the venous blood and blood-plasma, muscle, and skin of parts other than the affected limb are concerned, the effects of hæmostasis are practically *nil*. It has no effect, moreover, upon the specific gravity of the muscle or skin of the affected limb, but it occasions a rise in the specific gravity of the blood and blood-plasma, and the blood becomes intensely dark in colour. The flow of lymph is much diminished in quantity but is not completely stopped. The blood-pressure in the carotid undergoes a small rise with the application of the hæmostatic ligature, which is, however, of very brief duration. On removal of the ligature, the blood-pressure suddenly falls but rapidly recovers its normal height.

The changes induced by hæmostasis are consequently those entirely dependent upon a stagnant condition of blood, and only show themselves in that stagnant blood and the fluid (lymph) which is normally derived from the blood. It, however, produces some profound modifications in the tissues of the affected limb which are unrecognizable by any alteration in specific gravity but which show themselves after the hæmostatic ligature has been removed, in the manner given in detail in the following sections.

I therefore conclude that hæmostasis in a limb for one hour has no effect upon the specific gravity of the arterial blood or blood-plasma, the venous blood or blood-plasma (except in the affected limb), or of the muscle or skin. It causes, however, during its existence a diminution in the flow of lymph from the affected limb.

Section IX.—The Effect of Increase of Venous Pressure on a Limb after Hæmostasis.

It has just been stated that hæmostasis does not cause any alteration in the specific gravity of the muscle or skin either in the limb affected by it or in the corresponding limb. Bearing in mind the general association of an increase in venous pressure with the occurrence of passive œdema, the effect of this condition may be considered after hæmostasis, a means whereby a powerful modification of the nutrition of the limb can be brought about. The experiments which will be described below are, in the main, those which had been introduced after the effect of venous congestion alone had been determined. The advantage of this method is that the animal had been under observation for some little time and, therefore, that any modifications which showed themselves upon an increase of venous pressure after hæmostasis were known with certainty not to have shown themselves before that modification was introduced.

1. *On the Specific Gravity of the Arterial Blood.*

If a "medium" ligature be placed round the limb of a dog in which hæmostasis has existed for an hour, the curve given is a very different one to that which occurs with increased venous pressure before hæmostasis. Then there was no modification of the specific gravity, now the specific gravity rises with almost invariable certainty. In fact, during the whole series of experiments of this kind only one example was found of a fall, the explanation of which, however, I am not able to give. This rise in specific gravity of the blood is not due to the anæsthetic, for Roy and Cobbett,* in their work on "Collapse," have shown that an anæsthetic, such as chloroform or ether, though its use be prolonged for several hours, does not cause any alteration in the specific gravity of the blood. It is obviously due to the abstraction of water, though certainly not pure water as such, and, as will be seen hereafter, that water is found in the limb which is under investigation as œdematous fluid. The rises shown in the curves are great, and inasmuch as the fluid leaves the blood-vessels after hæmostasis to a greater degree than before only in the affected limb, the rise in the specific gravity of the blood is a good indication of the amount of œdema. Thus, in one experiment the rise was only one of two degrees, whereas in another it was one of seven degrees. It is obvious, therefore, that the amount of fluid which left the

* Roy and Cobbett. "On the Pathology of Collapse." Being published.

blood-vessels to become œdema-fluid in the latter case was greater in proportion to the total mass of blood in the animal than it was in the former. It does not, of course, follow that the amount of *recognizable* œdema is proportionate exactly to the rise in specific gravity of the blood, though as a rule such is the case. Where the lymphatics are patent, for example, the fluid drains away and hence the œdema-fluid is not recognizable as "œdema." Nevertheless, the rise in specific gravity of the blood is a certain indication of the amount of fluid that has passed through the vessel-walls in the affected part.

I therefore conclude that after hæmostasis increase of venous pressure leads to an increase in the amount of exudation through the blood-vessel walls of the affected limb, as shown by a rise in the specific gravity of the arterial blood of the system as a whole.

2. *On the Specific Gravity of the Arterial Blood-plasma.*

The general rule is that the arterial blood-plasma rises in specific gravity, but it is not uncommon for a fall to occur. Moreover, though it is generally true that a *rise* in the specific gravity of the blood-plasma goes hand in hand with a *rise* in the specific gravity of the blood, a fall in specific gravity of the blood-plasma does not, by any means, so generally accompany a fall in the specific gravity of the blood. It has already been said that a fall in specific gravity of the blood is very uncommon as the result of an increase of venous pressure after hæmostasis, but as regards the blood-plasma, a fall occurs in a notable percentage of cases. This can either mean that the corpuscles lose water, or that fluid leaves the blood-vessels of higher specific gravity than the plasma.

My conclusions upon this point are, therefore, as follows. As the result of an increase of venous pressure in a limb, after hæmostasis, the specific gravity of the arterial blood-plasma generally rises, but in a certain number of cases it falls, in spite of a rise in the specific gravity of the blood itself. In these cases we must assume that the blood-corpuscles give up a portion of their water to the plasma, or that fluid leaves the blood-vessels in the affected limb of higher specific gravity than the blood-plasma.

3. *On the Specific Gravity of the Venous Blood.*

Inasmuch as the length of time during which a given volume of blood remains in the limb which is subject to an increase of venous pressure, is greater than that during which an equal volume remains in an unobstructed limb, it is reasonable to expect that in the former case the changes produced, and amongst them those influencing the specific gravity of the blood, should be greater than in the latter case. This is clearly shown to be so by the curves given by experiments, and in this respect they differ only in degree from those given in Section IV., Paragraph 4. The degree, nevertheless, is greater after hæmostasis than it is before, which means that the amount of fluid leaving the blood-vessels of lower specific gravity than the blood is greater per unit of time than it is before hæmostasis. The main difference, however, between the effect of an increase of venous pressure on the specific gravity of the venous blood is shown by the venous blood of the system as a whole. Whereas before hæmostasis it remained constant, after hæmostasis it rises with almost invariable certainty. Usually it keeps its normal superiority in specific gravity over the blood in the corresponding artery, but this is not always the case. Frequently the difference at the end of an experiment is less than it was at the beginning, and in a few cases the specific gravity of the venous blood ends by being lower than that of the arterial blood. Inasmuch as the blood used in these experiments is taken directly from the artery or vein, as the case may be, the possibility of a chance admixture of lymph is obviated. The only explanations possible are that in these cases the body as a whole is abstracting from the blood not so much water as some of the solid constituents of the plasma, for there is no reason to suppose that the specific gravity in the vein is lowered by reason of any alteration in the mass of the corpuscles, or that the corpuscles themselves are taking up water, or, thirdly, that the tissues as a whole are supplying water to the blood to meet the drain which it has to expect in the affected limb, and that to an excess. It will be seen hereafter that the tissues of the rest of the body do throw water into the circulation to meet an excessive exudation in the affected limb, and though they cannot do so in sufficient quantity, as a rule, to obviate the rise in specific gravity of the blood, arterial as well as venous, it is probable that in some cases they may more than meet the demand, with the result that the specific gravity of the venous blood of the whole system actually sinks. For this reason I regard the last given as the most probable explanation of what is undoubtedly a fact, though not one commonly observed. A rise in the specific gravity of the venous blood in the affected limb is invariable.

I therefore conclude that the influence of an increase of venous pressure in a limb after hæmostasis is to raise the specific gravity of the venous blood in that limb, and to a greater degree than before hæmostasis, and also, as a rule, to raise the specific gravity of the venous blood in the system at large, though this is not always the case. The specific gravity, moreover, of the venous blood in the body as a whole sometimes tends to approximate to the specific gravity of the arterial blood in the body as a whole.

4. *On the Specific Gravity of the Venous Blood-plasma.*

As in the case of the venous blood, so here the difference between the alteration in specific gravity before and after hæmostasis, so far as concerns the affected limb, is one of degree and not of kind. But, in the system as a whole, there is a marked difference in the changes in specific gravity of the arterial and of the venous blood-plasma. It was shown that the arterial blood-plasma generally rises in specific gravity after hæmostasis, but a rise is uncommon in the case of the venous blood-plasma, and even if it occur it is small, whereas the general tendency is for it to fall. It will be observed that a regular gradation shows itself; the arterial blood *almost invariably rises* in specific gravity, the arterial blood-plasma *generally rises*, the venous blood, *as a rule, rises*, but shows a tendency to lose its normal superiority in specific gravity over the arterial blood and to approximate to it, the venous blood-plasma *generally falls*. A reason for this will be given when we come to consider the changes induced in muscle and skin, for the present it is sufficient to note the fact.

I therefore conclude that the effect of an increase of venous pressure in a limb after hæmostasis is to raise the specific gravity of the blood-plasma of the limb itself, and to a greater degree than before hæmostasis. As far as the venous blood-plasma of the rest of the body is concerned, there is a general, though not quite invariable, tendency for increase of venous pressure in a limb after hæmostasis to cause a lowering of specific gravity.

5. *On the Specific Gravity of Muscle.*

The effects of an increase in venous pressure after hæmostasis show themselves in the muscle of the limb which has been the subject of hæmostasis, but also in other parts of the body.

In the limb itself the specific gravity of the muscle invariably falls, and as a rule the fall is sufficiently great to be quite out of the range of experimental error.

In the corresponding muscle of the other limb, as a general rule there is a rise in specific gravity, though this is not always the case, for the specific gravity may here remain constant. The rise on this, the unaffected side, never appears to be replaced by a fall, that is to say, the identity of the specific gravity of corresponding muscles on the two sides after hæmostasis no longer remains, but the lines connecting various pairs of observations always diverge. So far as curves themselves go that are made up of observations on different muscles (though corresponding muscles be used for each *pair* of observations) at the beginning and at the end of the experiment, it is possible that a fall may be observed in the curve given by junction of the first and final results on the unligatured side, though this fall is not so great as in the case of the ligatured side. A divergence therefore exists, but it is impossible to state more as a conclusion than that the specific gravity of the muscle on the *ligatured side* has fallen. No information concerning the unligatured limb is given thereby. In certain experiments, therefore, one muscle was used throughout. The Sartorius was chosen on account of its length of muscular fibre and its general absence of tendon, and also of its accessibility. With care, it is possible to leave a very large portion of the muscle uninjured, and covered by its overlying tissues. From this portion further observations may be taken without great danger of any error being introduced. In a large dog, in this way, half-a-dozen or more observations may be taken from the same muscle on each side, and thus truly comparative curves may be obtained. As the result of such a method of investigation, it is seen that not only does the muscle on the affected side fall, but also that the muscle on the unaffected side rises in specific gravity. This rise is not necessarily equal to the fall on the affected side, and probably it is, as a rule, not so great; though, on this point, I have not sufficient data to speak with safety. Upon the analogy of the blood, however, it seems reasonable to expect that such will be proved to be the case.

My conclusions, therefore, are that an increase in venous pressure in a limb after hæmostasis causes not only a fall in the specific gravity of the muscle in the affected limb, but also a rise in the specific gravity of the muscles of the body as a whole.

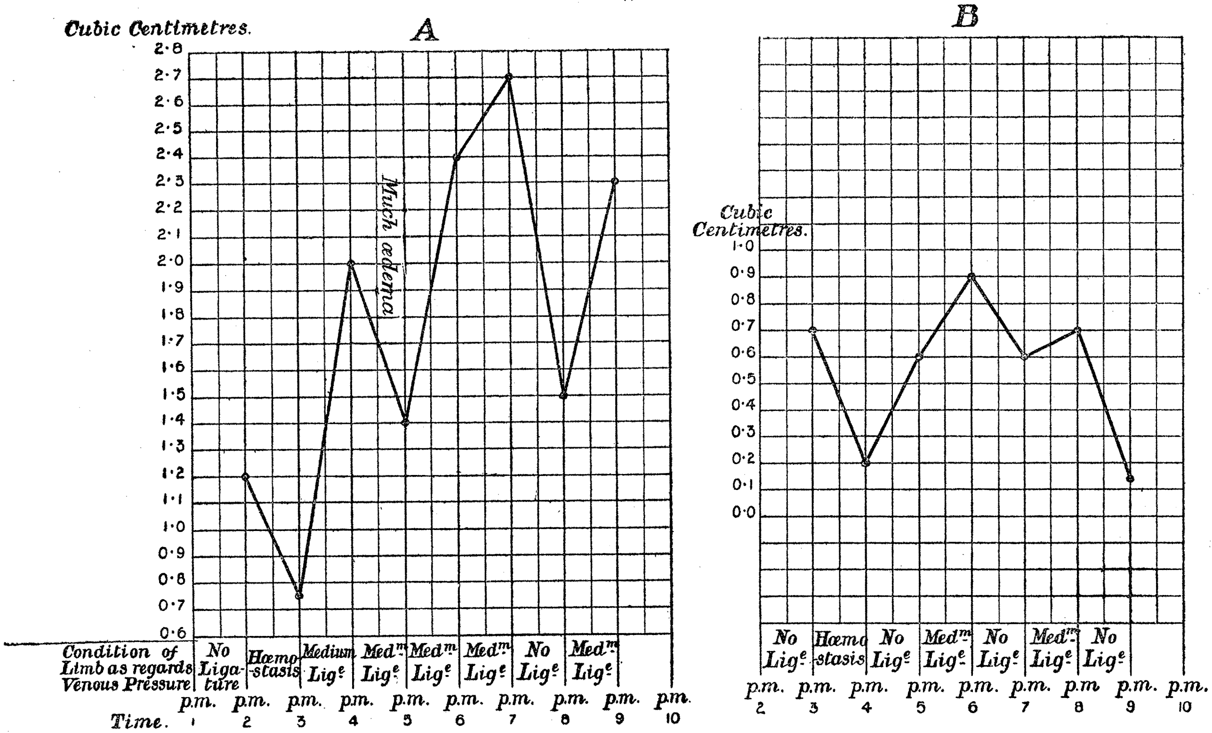
6. *On the Specific Gravity of Skin.*

The changes undergone by the skin are similar in kind to those undergone by muscle. Here it is definitely seen that the rise on the unaffected side is not so great as the fall in the corresponding skin of the affected side.

I therefore conclude that an increase of venous pressure in a limb after hæmostasis causes a fall in the specific gravity of the skin on the affected side, and that it also causes a rise in specific gravity of the skin on the unaffected side, but that this rise is not so great as the fall in the affected limb.

7. *On the Amount of Lymph-flow per Unit of Time.*

Fig. 1.



Curves showing the influence of the venous pressure in a limb after hæmostasis on the amount of lymph-flow per unit of time.

In *A* the ligature was left untouched between 3 P.M. and 7 P.M.; in *B* it was applied at 5 P.M. and 7 P.M. The curves are not meant to indicate any degrees of venous pressure beyond normal pressure, moderately great obstruction, and complete obstruction.

The amount of lymph-flow per unit of time is a very valuable indication of the amount of fluid that leaves the blood-vessels; and in that it is continuously under observation during the whole of the experiment, whereas observations upon the specific gravity of muscle and skin are more or less disjointed, it shows more readily the real effect of an increase of venous pressure.

The curves given above show conclusively that the amount of lymph-flow after hæmostasis increases with an increase of venous pressure, but they show also that, directly that increase of venous pressure is removed, the amount of lymph-flow diminishes. During hæmostasis only does the amount of lymph-flow apparently act in a contrary manner, but since in hæmostasis the whole of the blood-supply to the limb is temporarily cut off, hæmostasis can hardly be regarded as coming under the category of an increase of venous pressure, though it is granted that the blood in the limb under hæmostatic conditions becomes excessively venous in character.

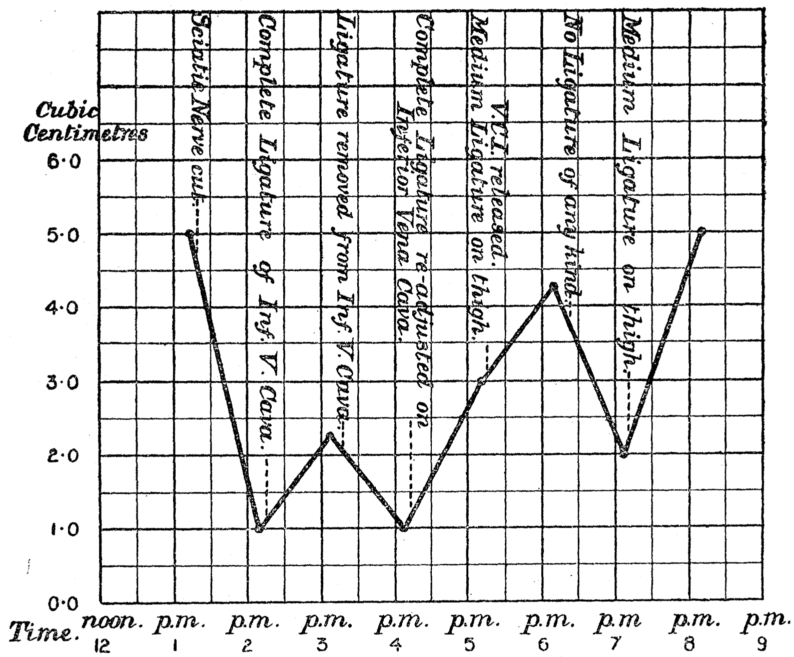
The point that needs elucidation is in curve A. It will be noticed that between 4 P.M. and 5 P.M. there is a considerable fall in the amount secreted, whereas the condition of venous pressure remains unaltered. It was noted at the time of the experiment that there was during this hour a sudden and rapid onset of œdema with pitting on pressure to "fully the depth of a quarter of an inch over the front of the leg." This point is of some importance, as it shows that a condition of lymphatic obstruction is not essential to the occurrence of œdema. In this experiment, on the other hand, the lymphatic vessel was patent with the definite object of collecting the lymph, while the normal assistance given to the lymph-flow by muscular movement was roughly imitated by the rapid squeezing of the paw from below upwards, which, as already mentioned in Section III., was an essential portion of my method of collecting the lymph. The importance of this part of the observation lies in the fact that its tendency is completely to negative COHNHEIM'S assumption that œdema is "the result of diminished absorption."

I therefore conclude that, after hæmostasis, the effect of an increase of venous pressure in a limb is to increase the amount of lymph-flow per unit of time, but that that increase of the amount of lymph-flow gives place to a diminution as soon as the venous pressure in the limb is allowed to return to normal.

A subsidiary conclusion is the following:—Œdema may show itself in a limb along with full patency of the lymphatic vessels, and consequently a free exit for the lymph.

8. *On the Amount of Lymph-flow in a Limb in which the Sciatic Nerve has been cut, during and after Complete Ligature of the Inferior Vena Cava.*

Fig. 2.



Curve showing the amount of lymph-flow per unit of time in a limb in which the sciatic nerve has been cut, during and after ligature of the inferior vena cava (RANVIER'S experiment).

In this experiment there was one hour between the section of the nerve and the ligature of the inferior vena cava. The ligature on the inferior vena cava, moreover, was of such a kind that it could be untied and retied at pleasure. It is obvious that the severed condition of the sciatic nerve was the constant condition throughout the experiment.

The curve given above shows, in the first place, that the immediate effect of section of the sciatic nerve is a sudden fall in the amount of lymph-flow.* Ligature of the inferior vena cava increases this amount somewhat, though it does not allow it to equal the normal outflow. The conditions that are represented by RANVIER'S experiment are consequently seen to be accompanied by a diminution in the amount of lymph-flow, which is contrary to what would be expected upon RANVIER'S explanation of œdema. With the removal of the ligature from the inferior vena cava, the lymph-flow is again diminished, to be again increased on readjustment of the complete ligature on the inferior vena cava. More effective in increasing the amount of lymph-flow is a medium ligature on the thigh, as is seen by the rise of the curve after 5 P.M. and 7 P.M.

This series of experiments has been placed here rather than under Section VII.

* The diminution in the amount of lymph being contrary to expectation, coagulation in the cannula was always carefully excluded as a possible cause.

because the results are more those depending upon variations of venous pressure after a modification has been introduced (complete ligature of the inferior vena cava for two periods of an hour each) which probably is nearly akin to hæmostasis. The flow of venous blood from the limb being almost entirely stopped, since the anastomoses cannot be very numerous between the inferior and superior venæ cavæ, the supply of arterial blood must rapidly diminish and come to almost a standstill. That the two conditions are not quite the same is shown by the increase in the amount of lymph-flow caused by ligature of the inferior vena cava, whereas hæmostasis is accompanied by a diminution. Both, however, agree in that, while they exist, the amount of lymph-flow is very considerably below the normal.

*The conclusions to be drawn from the curve given above are firstly, that section of the sciatic nerve is followed by a diminution in the outflow of lymph, and secondly, that after ligature of the inferior vena cava, the lymph-flow in a limb, in which the sciatic has been cut, varies in quantity with the pressure in the veins, being increased when the pressure is increased, and diminishing when the pressure in the veins returns to normal.**

9. *On the Circumference of the Limb and its Appearance as regards Œdema.*

After hæmostasis the limb becomes larger as the result of an increase in venous pressure; the increase in size, moreover, is considerable. Frequently the limb at the end of the experiment had increased in circumference by a quarter. This, however, is not the greatest increase that has been met with in the course of these experiments. In one case the limb increased in circumference by more than one-half. It is probable that the results obtained on the unaffected side are not absolutely correct. With perfect measurement it is reasonable to suppose that the limb instead of remaining of constant size, as was practically found to be the case, would show a small diminution in circumference. It is by reason of the general rise in specific gravity that takes place in the muscles and skin on this side that such is thought to be probable. This point, however, is of much less importance than the other, viz., that there is a considerable and unmistakable increase in circumference of the limb that has undergone hæmostasis. In all cases, the measurement of the affected limb was taken immediately after the venous congestion had been relieved by removal of the ligature.

The actual appearance of the limb is that met with in typical œdema. The skin pits on pressure, the natural depressions on each side of the tendo achillis become filled up, and the lower part of the limb becomes more or less cylindrical. The œdema shows itself first, and to the greatest extent, in the paw and the lower part of the limb, in contra-distinction to those cases in which, as the result of a simple ligature

* Though the amount of lymph-flow varies *directly* with the venous pressure, there is no evidence in the above curve that it varies *proportionately* with the venous pressure.

which has been applied for some considerable time, it shows itself in the neighbourhood of the ligature first, if not alone. In fact, the appearance is in every respect comparable to the œdema which occurs in the lower extremities of persons suffering from cardiac disease.

Microscopically the fibrous tissue which lies beneath the cutis vera is found to be stretched, while the normal interspaces between the meshes are widely distended, and, if the preparation have been made by previously boiling (POSNER's method) the part before cutting sections, the interspaces are found to contain a coagulated albuminous material. The fibrous tissue between the muscular bundles is similarly distended, and the actual bundles are further apart from one another than is the case with normal muscle. There is an indication that the muscular elements themselves undergo some modification, as they are found to take up picro-carmine more readily than the muscular elements of the other limb, in the case of a frog whose limb has been rendered œdematous by a ligature, and into whose circulation a solution of picro-carmine is subsequently injected. This part of the subject has, however, not yet been worked out fully.

I therefore conclude that the effect of an increase of venous pressure in a limb after hæmostasis is to increase the circumference of the limb, and that this increase in circumference takes place first and to the greatest degree in the distal portion of the limb.

Microscopically the tissues which have thus increased in size show that this increase is due to a distension of their fibrous supporting meshwork by an albuminous fluid. There are also indications that the muscular elements in an œdematous limb undergo some modification in nature.

To summarise the results observed as the effect of an increase of venous pressure in a limb after hæmostasis, we have,

In the affected limb, a rise in specific gravity of the arterial blood and blood-plasma, a great rise in the specific gravity of the venous blood and blood-plasma, a fall in the specific gravity of the muscle and skin, an increase in the lymph-flow, an increase in the circumference of the limb, and, lastly, the general appearances of œdema;

In the unaffected limb, which may be taken as more or less completely representing the rest of the body, there is a rise in the specific gravity of the arterial blood and blood-plasma, a rise, but less marked than that of the arterial blood, or sometimes a slight fall, in the specific gravity of the venous blood, a fall in the specific gravity of the venous blood-plasma, and a rise in the specific gravity of the muscle and skin.

SECTION X.—THE EFFECT OF ACTIVE CONGESTION IN A LIMB AFTER HÆMOSTASIS.

It is unnecessary to give the results of active congestion after hæmostasis, in detail, as they differ, with the exceptions noted below, in degree only from those obtaining under conditions of increased venous pressure after hæmostasis, and these have already been fully described. The notable differences are those which concern the arterial blood-plasma and certain changes in the limb itself. The latter may be shortly disposed of in the present paragraph, but the changes in specific gravity of the arterial blood-plasma are sufficiently marked and unexpected to warrant their consideration in a separate sub-section. The differences to be observed in the limb, which is the subject of active congestion are, firstly, that it becomes markedly warmer than its fellow, whereas, when it is the subject of increased venous pressure, it is as a rule colder, and secondly, the enormous rise that takes place in the specific gravity of the venous blood and blood-plasma of the limb in which there is increased venous pressure, is no longer found. The specific gravity of the venous blood-plasma, it is true, is slightly higher than it is in the unaffected limb, but there is no apparent difference to be made out between the specific gravity of the blood taken from veins on the two sides.

The modifications in the case of active congestion after hæmostasis are smaller than in that of increased venous pressure after hæmostasis. This is no doubt because the disturbing cause is not completely removed when a ligature is applied in order to raise the venous pressure.

I therefore conclude that the effects of active congestion in a limb after hæmostasis are, in the main, similar in kind to those occurring with an increase of venous pressure in a limb after hæmostasis, though they are smaller in degree. Important differences, however, are to be found in the affected limb where there is an absence of that extreme rise in specific gravity of the venous blood and blood-plasma which occurs in a limb in which the venous pressure is increased, and also the substitution of a raised temperature in the case of active congestion for the lowered temperature which occurs along with an increase of venous pressure.

1. *On the Specific Gravity of the Arterial Blood-plasma.*

The result is not what might be expected, seeing that the specific gravity of the whole blood rises, for the arterial blood-plasma constantly falls in specific gravity. It is difficult to see in what way these two facts may be reconciled, unless it be that the corpuscles give up water to the plasma, although the blood loses water as a whole. It is, of course, obvious that the removal of water which occurs in the affected limb has to be met, and this supply of excessively watery plasma to the limb is such a way of meeting it. It is possible, however, that the fall in specific gravity may be due to an excessive amount of lymph poured into the vascular system from the affected limb. The specimen of blood taken from the femoral artery, though it would have suffered a removal of water in the lungs, would not as yet have been subjected to the far greater removal of water in the kidneys. For this purpose it would have to pass four times through the heart instead of the twice which it has accomplished when removed for observation.

Whatever the explanation, the fact remains clear that *active congestion in a limb after hæmostasis causes a fall in the specific gravity of the arterial blood-plasma.*

SECTION XI.—THE EFFECTS OF PROLONGED COMPLETE ANÆMIA OF A LIMB.

The effects of prolonged complete anæmia of a limb are considerable, and very different from what would be expected from a consideration of the effects of hæmostasis. It is necessary to know them in order to judge of the after-effects of active congestion and increase of venous pressure, but the actual information given is of extreme importance, not so much from the point of view of œdema, as from that of other conditions with which we are not now immediately concerned.

1. *On the General Blood-pressure.*

Other than an initial rise on the application of the bandage that produces the complete anæmia, and a fall on the removal of the bandage, both of which are small and of short duration (the blood-pressure returning to normal in two or three minutes), the effects of prolonged complete anæmia are not evident in any modification of the general blood-pressure.

I therefore conclude that the effects of prolonged complete anæmia of a limb upon the general blood-pressure are confined to a rise on the application and a fall on the removal of the bandage producing the anæmia, both of which are small and of short duration.

2. *On the Specific Gravity of the Arterial Blood.*

If in a dog a limb be rendered completely anæmic, the effect upon the specific gravity of the arterial blood is very marked. During the first hour there is a rapid and considerable rise in specific gravity, but after that time the rise becomes less rapid and the blood becomes constant in specific gravity, but at a higher level than at the commencement of the anæmic period. This course of events is not quite invariable, for the specific gravity of the arterial blood in some cases may remain throughout the anæmic period the same as it was before the bandage was applied. This, however, obtains only in a small minority of cases.

I therefore conclude that the effect of prolonged complete anæmia of a limb on the specific gravity of the arterial blood is to produce at first a rapid and considerable rise, and that the blood remains constant at this new level so long as the conditions of anæmia remain unaltered.

3. *On the Specific Gravity of the Arterial Blood-plasma.*

The arterial blood-plasma rises in specific gravity during complete anæmia of a limb. The rise is not necessarily great, but no exceptions have been found to the rule that a rise occurs.

I therefore conclude that complete anæmia in a limb leads to a rise in the specific gravity of the arterial blood-plasma.

4. *On the Specific Gravity of the Venous Blood.*

The changes that occur in the specific gravity of the venous blood are in the same direction as those for the arterial blood. As a rule, however, at the latter part of complete anæmia, lasting three hours, the specific gravity of the venous blood approximates to that of the arterial blood, and, therefore, tends to lose the superiority that it normally has. In a minority of cases the specific gravity of the venous blood at the end of the experiment has increased its primary superiority over the arterial blood. From the greater difficulty, however, of obtaining the venous blood without clotting, owing to its slower flow, I have not a sufficient number of trustworthy observations between the initial and final observations taken during complete anæmia, and hence my conclusions only refer to the final effects. From the point of view of an investigation on œdema these are sufficient, but it is evident that they must properly be supplemented by intermediate observations if the effect of anæmia alone be the main subject of investigation.

My conclusions, therefore, are that prolonged complete anæmia of a limb has for its final effect an increase in the specific gravity of the venous blood, and that though the specific gravity of the venous blood tends to lose its normal superiority over that of the arterial blood, in a minority of cases it actually increases that superiority.

5. *On the Specific Gravity of the Venous Blood-plasma.*

Here also a rise in specific gravity takes place, but it is not so great as in the case of the arterial blood-plasma.

6. *On the Specific Gravity of Muscle.*

Complete anæmia of a limb induces a fall in the specific gravity of the muscle in the other limb. This fall begins immediately upon the application of the bandage causing anæmia, and is most marked during the first portion of the anæmic period. In some cases the specific gravity continues to fall slightly for a short time after removal of the ESMARCH's bandage, in the majority it reaches its limit of fall before the removal of the bandage, and maintains that lower level.*

I therefore conclude that complete anæmia of a limb causes a fall in the specific gravity of the muscle of the opposite limb, that that fall principally takes place in the first portion of the anæmic period, and that when it has reached its lower limit it remains constant during the rest of the anæmic period.

* The specific gravity of the muscle in the anæmic limb was not taken, as it was necessary in view of subsequent investigations to injure it as little as possible. Inasmuch as all blood and lymph were removed from the limb by the very nature of the bandage and its tightness it is presumable that its muscle was raised in specific gravity.

To sum up the changes that occur in prolonged complete anæmia, they are principally a rise in the specific gravity of the arterial blood, which occurs chiefly in the first portion of the anæmic period, and a fall in the specific gravity of the muscles, which also chiefly occurs in the first portion of the anæmic period. When these have reached their respective limits they tend to remain constant, and so create a new position of equilibrium for the body. The changes that are found in the blood-plasma of artery and vein and in the venous blood are subservient to these two great changes.

For the purpose of our investigation, therefore, the new levels obtained at the end of the anæmic period must be regarded as the starting points for comparison with later results produced by other modifying circumstances introduced. It must be remembered, however, that the results obtained are not simply those obtained from supplying nutriment to a starved tissue; but, inasmuch as it has been seen that an increase of volume of blood circulating in the body (that removed from the limb during the process of applying the ESMARCH'S bandage) produces certain changes in specific gravity, it must be assumed that allowing the circulation again to flow through the anæmic limb (which practically amounts to decreasing the amount of blood which was circulating in the body) must also not be without its effect.*

SECTION XII.—THE EFFECT OF ACTIVE CONGESTION IN A LIMB AFTER PROLONGED COMPLETE ANÆMIA.

In accordance with the well-recognized physiological law that active congestion follows upon anæmia of a part, it was found, in the experiments which are to be detailed below, that the temperature of the limb rose when the ligatures and bandages were removed. At the same time it became manifestly swollen and the circulation was evidently more rapid through it than through its fellow.

1. *On the Specific Gravity of the Arterial Blood.*

The active congestion which follows on complete anæmia of a limb of a dog, kept up for three hours, has apparently no effect upon the specific gravity of the arterial

* It is obvious from the results obtained above that the volume of blood circulating in the body is not a matter of so little importance as was formerly supposed. It was usually taught that the veins, and particularly the veins of the splanchnic area, could accommodate a large increase of blood or other fluid. This occurred without any permanent rise in the general blood-pressure. So far as the general blood-pressure is concerned this teaching is no doubt true, but the other part of the doctrine, so far as concerns the veins, must evidently be modified by the additional statement that the muscles take up a very large proportion of any extra amount of fluid that may be in circulation. The part played by the tissues has evidently been under-estimated, if not entirely ignored. [A communication on this subject was made by the author to the Physiological Society, May 12, 1894, and is to be found in the 'Proceedings' of that Society.—September 29, 1894.]

blood. Occasionally, however, a small rise is seen, but it is in no way comparable with the rise that occurs in the corresponding condition after hæmostasis.

I therefore conclude that active congestion in a limb after lengthened complete anæmia has little or no effect upon the specific gravity of the arterial blood.

2. *On the Specific Gravity of the Arterial Blood-plasma.*

The effect of active congestion after anæmia upon the specific gravity of the arterial blood-plasma is very marked. A rapid fall takes place, the chief part of which occurs immediately upon the establishing of the active congestion. This is similar to what obtains in the case of active congestion after hæmostasis. It is by far the most marked event that occurs during active congestion in parts other than the affected limb.

With reference to its effect upon the arterial blood-plasma I therefore conclude that active congestion in a limb after prolonged complete anæmia leads to a rapid and marked fall in the specific gravity.

3. *On the Specific Gravity of the Venous Blood.*

The venous blood behaves much in the same way as under the corresponding conditions after hæmostasis, and hence it is unnecessary to repeat the remarks made there. It may be shortly stated that the tendency is for the specific gravity of the venous blood to approximate towards that of the arterial blood.

4. *On the Specific Gravity of the Venous Blood-plasma.*

The specific gravity of the venous blood-plasma during active congestion after lengthened complete anæmia, falls, as is the case with the arterial blood-plasma.

In the case of both the venous blood and blood-plasma, though it is probable that differences exist between the specific gravity on the two sides, such differences have been found insufficient for detection.

5. *On the Specific Gravity of Muscle.*

The only change of importance occurs in the affected limb. Here the muscle which, by expression of blood and lymph, is during the anæmic period of higher specific gravity than its fellow on the opposite limb, for the first portion of the time of active congestion, remains of higher specific gravity, and may continue to do so for over an hour. It soon, however, falls to the specific gravity of the muscle in the unaffected limb, but does not, as a rule, fall much below. The specific gravity of the muscles in the other limb apparently remains constant.

I therefore conclude that, as the result of active congestion after prolonged complete anæmia the specific gravity of the muscle on the affected side falls until it is the same, *or slightly lower than, that of the muscle on the unaffected side. The muscle of the unaffected side undergoes no apparent alteration in specific gravity.*

6. *On the Circumference of the Limb.*

During the period of anæmia of smaller circumference than the unaffected limb the now actively congested limb becomes of greater circumference. But this excess is principally due to the increased amount of blood in the limb, and not—as in the similar condition after hæmostasis—to the occurrence of œdema. Within a very short time, an hour or less, it measures no more than it did at the commencement of the experiment. Similarly, there are to be observed none of the ordinary coarse signs of œdema.

To sum up, the changes that are brought about by active congestion in a limb that has been kept devoid of blood for a lengthened period are not marked, with the single exception of the blood-plasma. In the case of this fluid there is a very definite fall in specific gravity. The amount of œdema is small and transitory.

SECTION XIII.—THE EFFECT OF AN INCREASE OF VENOUS PRESSURE IN A LIMB THAT HAS BEEN SUBJECT TO LENGTHENED COMPLETE ANÆMIA.

The effects of an increase of venous pressure in a limb that has been subject to lengthened complete anæmia are, so far as concerns the specific gravity of the blood, muscle, &c., in all respects, save in degree, similar to those which occur after hæmostasis. In all the experiments done upon this branch of the subject the differences in specific gravity induced were less than those after hæmostasis.

If, therefore, we compare the effects of hæmostasis and of complete anæmia upon the production of those changes which make up "œdema," it is seen that hæmostasis is by far the more potent agent, and further that it produces a greater amount of œdema than anæmia, even if it be allowed to act for only one-third of the time. The evidence that anæmia leads to œdema is not large, and consists principally in a summation of small changes, with the sole exception of the change that occurs in the considerable fall in the specific gravity of the arterial and venous blood-plasma. This difference between the action of hæmostasis and anæmia is quite analogous to what occurs in the case of patients. It is a matter of common observation that passive œdema accompanies conditions in which the interference is with the return of venous blood. Nevertheless, it is well known that in some cases of ligature of the main artery of a limb—*e.g.*, the femoral artery, for popliteal aneurism—the leg and foot sometimes become œdematous. This is by no means always the case, and it is regarded by surgeons with uneasiness. The fact, however, remains that passive œdema is met with under both conditions, namely, that of venous congestion and that of anæmia from interference with the arterial supply. The observations made in the experiments which have formed the foregoing sections are therefore in complete accord with clinical experience.

SECTION XIV.—THE ABSORPTION OF WATER BY MUSCLE, AS THE RESULT OF STIMULATION OF THE NERVE.

If the gastrocnemius of a frog be isolated with a portion of its nerve, and that nerve be stimulated by the interrupted current as long as contractions are produced by a maximum current, it will be found, if the muscle be not removed from the body, that the stimulated muscle is several degrees lower in specific gravity than the corresponding muscle on the other side. A more accurate method has already been given in Section III.

On removing the stimulated muscle and its control, and placing them for the same length of time in normal saline solution, it is found that the stimulated muscle, without exception, is of lower specific gravity than the control. However much water, therefore, the unstimulated muscle may have absorbed, the stimulated muscle has absorbed more.

In the following table are given the results of three such experiments.

TABLE Showing the Fall in Specific Gravity of Muscle as the result of Stimulation.

	Sp. gr. of gastrocnemius. Unstimulated side.	Sp. gr. of gastrocnemius. Stimulated side.	Length of time of immersion in normal saline solution.
			minutes.
Frog 1	1062	1058	3
Frog 2	1063	1060	15
Frog 3	1065	1057	30

The absorption of salt solution begins immediately after the immersion, and is evidently not completed for some considerable time. It must be remembered that the stimulated muscle was still capable of contraction in the experiments typified above, and inasmuch as the same result is to be observed in a muscle which has not been removed from the body, it is reasonable to conclude that the process described is a normal one. The absorption of water and consequent diminution of specific gravity of the muscle in the frog's body, without doubt, goes on at the same time as the exercise of function. In the experiment under oil it cannot do so until the muscle is placed in the saline solution.

I therefore conclude that under normal conditions prolonged contraction of a muscle is followed by an absorption of water which leads to a fall in specific gravity of the muscle as compared with the specific gravity of the corresponding muscle, kept under similar conditions, but at rest.

Section XV.—The Effect of Active Congestion in a Limb after the Persistence *in situ* of the Waste-products of Functional Activity of its Muscle.

1. *On the Specific Gravity of the Arterial Blood.*

If, in a dog, a limb be rendered anæmic in the usual way, and the sciatic nerve be stimulated immediately after complete anæmia has been produced, the functional activity of the muscles, which, however, cannot show itself well on account of the tightness of the bandage, leads to the formation of waste-products in the muscles supplied by that nerve. By still keeping the limb anæmic for a certain length of time these waste-products are kept at the site of their formation.

Upon removal of the bandage active congestion ensues, which leads to a rise in the specific gravity of the arterial blood. This rise begins to occur very soon after removal of the bandage, and may readily be detected in half-an-hour. Though constant, it is not, however, great; no doubt, because there is every facility afforded to the active congestion to do its work. Nevertheless a rise of two or three degrees in specific gravity, which is very uncommon in the case of active congestion without stimulation of the nerve, is here the rule.*

I therefore conclude that active congestion in a limb, after the persistence in situ *of the waste-products of functional activity of its muscle, produces a greater rise in the specific gravity of the arterial blood than occurs in the similar condition after prolonged complete anæmia without functional activity of muscle.*

2. *On the Specific Gravity of the Arterial Blood-plasma.*

The change induced is similar but greater than that in the case of active congestion after prolonged complete anæmia, viz., a rapid and marked fall in specific gravity takes place.

3. *On the Specific Gravity of Venous Blood.*

The effects of active congestion after the persistence *in situ* of the waste-products of functional activity of its muscle upon the specific gravity of the venous blood, differ according to which limb is under investigation. In the unaffected limb the specific gravity of the venous blood becomes identical with, or lower than, that of the arterial blood. In the affected limb it is higher than that of the arterial blood, in so much that a difference of two degrees may obtain between the specific gravity of the blood on the two sides.

I therefore conclude that active congestion in a limb after the persistence in situ *of the waste-products of functional activity of its muscle, leads, in the venous blood, to an*

* It must be remembered that "prolonged complete anæmia" was allowed to cover a period of three hours; complete anæmia, with functional activity, only one hour.

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approximation towards, or a fall below, the specific gravity of the arterial blood, if the unaffected limb be under consideration, but to a rise if the affected limb be under consideration. A difference of two degrees may obtain between the specific gravity of the venous blood on the two sides.

4. *On the Specific Gravity of Muscle.*

The specific gravity of the muscle on the unaffected side rises considerably, as much as 5° having been noticed. As to what fall takes place in the muscle of the affected side it is somewhat difficult to speak, because of the lack of information as to the specific gravity of the muscle when in complete anæmia. It can only be stated that it has always been found one or two degrees lower than that of the *initial* specific gravity of the muscle on the other side.

I therefore conclude that active congestion in a limb after complete anæmia with persistence in situ *of the waste-products of the functional activity of its muscle leads to a marked and rapid rise in the specific gravity of the muscle on the unaffected side and to a fall in specific gravity of the muscle on the affected side, and that these modifications are greater than in the case of prolonged complete anæmia without functional activity.*

5. *On the Circumference of the Limb.*

The effect of persistence *in situ* of the products of functional activity is also to be seen in an increase in circumference of the limb. Whereas active congestion after prolonged complete anæmia leads to no apparent increase in circumference of the affected limb, similar conditions, in which functional activity is brought about and in which the waste-products have been allowed to remain *in situ* for a short time, invariably lead to an increase in circumference of the limb. The increase is not always great, but it is always greater than could be accounted for by experimental error. Speaking generally, the limb increases by about 6 per cent. of its original size in half an hour. The condition, however, does not go on to the production of an amount of œdema that can be recognized beyond question by pitting. This is no doubt because of the absence of any condition that could lead to a cumulative effect.

SECTION XVI.—CONCLUSIONS AS TO THE PATHOLOGY OF PASSIVE ŒDEMA.

In the first portion of this paper it has been shown by experiments in which the pressure in the veins and in the lymphatics was raised to a very great degree, that increase of venous pressure or of lymphatic pressure, *per se*, is unable to cause œdema or increase of lymph in the tissues, while it followed as the result of the method by which the experiments were performed that venous obstruction combined with lymphatic obstruction was equally powerless. It was further shown that œdema may occur even when the lymphatic vessels are patent. It is therefore necessary to abandon the old view that the œdema of passive congestion is of purely mechanical origin.

All the experiments on œdema which have been given in detail in the foregoing pages have been accompanied by anæmia. But by anæmia is not here to be understood lack of blood merely, for it is evident that in venous congestion the actual amount of blood in the limb at a given time is greater than normal. The essential point is that the supply of blood, however great it may be, is unequal to the needs of the tissues.

Inasmuch, therefore, as it has been shown that œdema follows prolonged complete anæmia and hæmostasis, it follows that starvation of the tissues plays an important part in the production of œdema.

Further, since the active congestion which, by a well-recognized law in physiology, follows upon anæmia, is also present after prolonged complete anæmia and hæmostatic anæmia, as is seen by the increased temperature of the limb under observation, the mechanism by which œdema is produced is presumably identical with that which normally leads to active congestion after anæmia.

So far, therefore, as concerns the effect of starvation of the tissues, I would suggest that the occurrence of œdema is similar in kind, though excessive in degree, to what occurs in the normal physiological condition of the limb. Though it is not actually known that the amount of lymph that flows from a part which is the subject of normal active congestion is increased, and therefore the amount of fluid which leaves the blood-vessels is increased, such is very probably the case. In the experimental œdema described above, the excessive supply of fluid by the blood-vessels does occur, but apparently is only to meet the excessive demand which results from the very great degree of starvation in which the tissues have been placed by the prolonged withholding of blood containing their normal supply of nutrition.

But though starvation of the tissues plays a very important part, there are certain facts that show that it is not a complete explanation.

It has repeatedly shown itself during the foregoing pages that the amount of œdema-fluid poured out is greater when the limb has been exposed to the action of venous blood than when it has simply been deprived of all blood of whichever kind. It follows, therefore, that however important the part may be that is played by starvation of the tissues, that played by the presence of venous blood is more important still.

The probability that this action of the venous blood is in some way bound up with the large proportionate amount of the products of tissue metabolism is supported by the following considerations :—

a. In normal physiological conditions, functional activity is accompanied by active congestion.

b. It has been shown in Section XIV., that in the case of muscle, at all events, the exercise of function is accompanied by certain modifications which lead to an absorption of water. Inasmuch as the chief modification with which we are acquainted that is induced by functional activity, is an increase of the amount of tissue waste-products held in the part, it is reasonable to suppose that this access of fluid is in some way or other connected with the removal of those waste-products. Even on purely mechanical principles the larger the amount of salts held within a dialyser the larger the amount of water that enters it from the outside.

c. We can, however, go further than this, for the experiments in Section XV. show that the effect of persistence of the metabolic waste-products in the part is to increase the amount of œdema.

These considerations give a satisfactory explanation of the facts stated above, that hæmostatic anæmia is so much more effective as a cause of œdema than complete prolonged anæmia, and that an increase of venous pressure after either hæmostasis or anæmia is more effective than active congestion alone.

The demand of the tissues under these conditions is too great for the blood to supply it immediately, even with active dilatation, and hence œdema occurs, but the possibility of its meeting that demand is still less if the active congestion, which is the utmost that can be done by the vascular system, be hampered by the presence of an increase of venous pressure. Here, not only is the rapidity of the blood-flow, which is so essential a part of active congestion, impeded, but also the amount of waste-products that can be removed in the blood is diminished, and hence the demand of the tissues, instead of lessening, as it should do, becomes more and more imperative, with the result that the amount that leaves the blood-vessels is increased for an indefinite period, and consequently the amount of œdema increases.

That a functionally active part does not normally become œdematous in the ordinary sense of the term, though its *tendency* is in that direction, is no doubt due to the fact that the products of tissue change are carried away as soon as formed, and that the accompanying active congestion is fully able to meet the demand. It is only when they become stored up in greater quantities than normal that they become a source of danger to the part, and that the call of the tissues for their removal is so urgent that the fluid poured out by the blood-vessels accumulates to such an extent as to constitute œdema.

It is therefore evident that the tissues play a part that has hitherto been unrecognized in the production of œdema.

Complete anæmia and hæmostasis, however, not only produce an effect upon the tissues of a limb; they must also have some effect upon the blood-vessels, and particularly the capillaries and small veins. It is certain that these are starved as well as the tissues, and though, on the assumption that the endothelial cells lining them are secretory, they cannot, in the absence of blood, be hampered by any products of their own functional activity, yet it is evident that they must form waste-products as a part of their very life. Microscopically no differences have been discovered, though during the course of this investigation they have repeatedly been looked for, between the endothelial cells of the smallest vessels in cases in which there was œdema, and in cases in which they were normal; nevertheless it is certain that some modification must occur. It is reasonable to suppose, therefore, that the exudation from the blood-vessels is modified in some as yet imperfectly known manner in quality or in quantity. At all events, the chemical properties of the lymph from a normal limb are somewhat different from those of lymph from an œdematous limb. One point, however, has come out clearly during the course of the previous experiments: it is that elastic distension of blood-vessels is not the same as the active dilatation which occurs after hæmostasis or anæmia.

After either hæmostasis or anæmia the lymph-flow varies directly with the venous pressure, whereas before they are introduced there is no such dependence upon the venous pressure. So far, therefore, the occurrence of œdema may be termed "mechanical," for the blood-vessels now act more or less like a dead filter or dead membrane. Whether this is to be taken as indicating that the vessel walls have become damaged in some as yet unrecognized way, and have largely lost their normal power of restraining the outflow of fluid as the result of mere pressure, or whether this is a condition compatible with a perfectly living active cellular wall, and occurs normally as a part of the phenomena known as "active congestion," must for the present be left uncertain.*

The œdema which accompanies venous congestion may, therefore, be regarded as being an excess of the normal physiological process whereby the nutrition of the tissues and the removal of their waste-products is secured. Normally the degree of starvation and the amount of waste-products stored up in the parts are sufficiently small to be adequately dealt with by active dilatation of the arteries supplying the part; but if the starvation be so great, or the amount of waste-products stored up be so considerable as to be beyond the powers of the circulation (as soon as the affected tissues call for an increased blood supply), the demand on the part of the tissues still continues, and the excessive amount of fluid poured out by the blood-vessels constitutes œdema. So soon as the demand has been met, the removal of fluid by the lymphatics exceeds the output by the vessels, and therefore the œdema begins to disappear, but if from some cause, such as occurs in the later stages of cardiac disease, the primary cause of the insufficient supply of blood depends upon a central irremediable lesion, the demand continues to be greater than the supply, and therefore the œdema increases.

Section XVII.—Summary of other Conclusions.

It may, perhaps, prove convenient if the chief conclusions, other than that contained in Section XVI., arrived at in the foregoing pages be restated here.

* Since modifications of the venous pressure bring in their train modifications in the amounts of waste-products contained in the tissues, by more or less impeding their removal, it is possible that this resemblance to "a dead filter or dead membrane" may be more apparent than real.—September 29, 1894.

1. Increase of the venous pressure alone, lymphatic pressure alone, or both combined, in a limb for one hour, has no effect upon the specific gravity of either the blood, blood-plasma (arterial and venous) of the body as a whole, the muscle or the skin of the affected limb or other parts, nor is it accompanied by any increase in the amount of lymph-flow. The venous blood and blood-plasma, however, in the affected limb rise in specific gravity.

2. Section of the sciatic nerve has no immediate effect upon the specific gravity of muscle.

3. Hæmostasis in a limb for one hour has no effect upon the specific gravity of the arterial blood or blood-plasma, the venous blood or blood-plasma (except in the affected limb), or of the muscle or skin. It causes, however, during its existence a diminution in the flow of lymph from the affected limb.

4. As the result of an increase in venous pressure in a limb after hæmostasis the specific gravity of—

a. The arterial blood of the system as a whole rises.

b. The arterial blood-plasma generally rises, but in a certain number of cases it falls, in spite of a rise in the specific gravity of the blood itself.

c. The venous blood and blood-plasma in that limb rise, and to a greater degree than before hæmostasis. The venous blood of the rest of the body generally rises, but tends to lose its normal superiority over the arterial blood. The venous blood-plasma of the rest of the body generally falls.

d. The muscle and, to a less extent, the skin on the affected side fall; on the unaffected side they rise.

5. The effect of an increase in venous pressure in a limb after hæmostasis is to increase the amount of lymph-flow, but that increase of the amount of lymph-flow gives place to a diminution as soon as the venous pressure in the limb is allowed to return to normal.

6. The effect of an increase of venous pressure in a limb after hæmostasis is to increase the circumference of the limb, and this increase in circumference takes place first and to the greatest degree in the distal portion of the limb.

7. Œdema may show itself in a limb along with full patency of the lymphatic vessels, and consequently a free exit for the lymph.

8. Section of the sciatic nerve is followed by a diminution in the outflow of lymph.

9. After ligature of the inferior vena cava, the lymph-flow in a limb in which the sciatic nerve has been cut, varies in quantity with the pressure in the veins, being increased when the pressure is increased, and diminishing when the pressure in the veins returns to normal.

10. The effects of active congestion in a limb after hæmostasis are, in the main, similar in kind to those occurring with an increase of venous pressure in a limb after hæmostasis, though they are smaller in degree. Important differences, however, are to be found in the affected limb, where there is an absence of that extreme rise in the

specific gravity of the venous blood and blood-plasma which occurs in a limb in which the venous pressure is increased, and also the substitution of a raised temperature in the case of active congestion for the lowered temperature which occurs along with an increase of venous pressure.

11. Active congestion in a limb after hæmostasis causes a fall in the specific gravity of the arterial blood-plasma.

12. Prolonged complete anæmia of a limb has no effect upon the general blood-pressure beyond a rise on the application, and a fall on the removal, of the bandage producing the anæmia, both of which are small and of short duration.

13. As a result of prolonged complete anæmia of a limb the specific gravity of—

a. The arterial blood rises rapidly and to a considerable degree, and remains constant at this new level so long as the conditions of anæmia remain unaltered.

b. The arterial blood-plasma and, to a less extent, the venous blood-plasma rise.

c. The venous blood ends by rising and, though it tends to lose its normal superiority over that of the arterial blood, in a minority of cases it actually increases that superiority.

d. The muscle of the opposite limb falls rapidly and remains at this lower limit during the rest of the anæmic period.

14. Active congestion after anæmia leads to a rapid and marked fall in the specific gravity of the arterial blood-plasma, a fall in the specific gravity of muscle on the affected side, but no apparent change either in the specific gravity of the arterial blood or the muscle on the unaffected side.

15. The effects of an increase of venous pressure in a limb that has been subject to prolonged complete anæmia are, so far as concerns the specific gravity of the blood, muscle, &c., in all respects, save in degree, similar to those which occur after hæmostasis. The differences in specific gravity induced are less than those after hæmostasis.

16. Under normal conditions prolonged contraction of a muscle is followed by an absorption of water which leads to a fall in specific gravity of that muscle as compared with the specific gravity of the corresponding muscle kept under similar conditions, but at rest.

17. Active congestion in a limb after the persistence *in situ* of the waste-products of functional activity of its muscle, produces a greater rise in the specific gravity of the arterial blood than occurs in the similar condition after prolonged complete anæmia without functional activity of muscle.

18. Active congestion in a limb after complete anæmia, with persistence *in situ* of the waste-products of the functional activity of its muscle, leads to a marked and rapid rise in the specific gravity of the muscle on the unaffected side and to a fall in specific gravity of the muscle on the affected side, and these modifications are greater than in the case of prolonged complete anæmia without functional activity.