THE SUPPLY OF OXYGEN TO THE TISSUES AND THE REGULATION OF THE CAPILLARY CIRCULATION.

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In a previous paper I have deduced from the distribution and number of capillaries (1), the diffusion rate for oxygen (2) and the oxygen consumption of the various tissues that the oxygen pressure everywhere in the organism and especially in the muscles must be practically equal to that of the capillary blood, the pressure head necessary to maintain the oxygen supply being extremely low. This deduction does not agree with the results of certain earlier investigations of the oxygen pressure in the tissues of warm blooded animals, and it will be necessary therefore to try and clear up the discrepancies.

We can leave out of account as untrustworthy the determinations based upon the method of Ehrlich (3), as the power of tissues to reduce certain stains has very little to do with the presence or absence of free molecular oxygen. As pointed out in my monograph on the respiratory exchange (4) (p. 77) the tension determinations on secretions (Strassburg (5), Fredericq (6)), which have usually shown that free oxygen is practically absent, are likewise untrustworthy, because oxygen is used up at a comparatively rapid rate (Pflüger (7), Krogh (4)) in the fluids in question, and there is definite evidence that in certain secretions (urine, Krogh (4)) the O_2 pressure is normally not much, if at all, lower than in the venous blood. The experiments of Tobiesen (8) show that any gas mixture (or pure gas) introduced into the pleural cavity of man will finally get an oxygen tension of 3–4 p.c., and similar results have been found for the abdominal cavity of animals. Though it must be admitted that the introduction of air into the body may possibly influence the circulation in the adjoining tissues and increase their oxygen supply, the results of the tension determinations support on the whole the contention that mammalian tissues generally possess a rather high oxygen tension.

This conclusion is borne out also for the salivary glands by the ingenious experiments of Verzár(9), but in the case of muscles Verzár found that their oxygen tension must be comparatively low and perhaps 0, since a diminution of the arterial supply (and pressure) of oxygen caused a distinct decrease in the oxygen absorption of the muscular tissue.

Working in this laboratory on the relation between the oxygen pressure in water and the oxygen consumption of a fish Gaarder(10) found that the consumption increased with the pressure even up to a whole atmosphere. The increase in consumption corresponded to the increase in physically absorbed oxygen, and Gaarder concluded that the diffusion from the capillaries into the tissues is incapable of maintaining a positive oxygen pressure. This conclusion like Verzár's is seemingly at variance with my countings of capillaries and calculations of the oxygen pressure head.

I was led to undertake the investigations detailed in this and the two preceding papers by a comparison of Verzár's result for muscles with the circulation rate determinations made on man by Lindhard and myself(11, 12). These show that during rest the venous blood is about 65 p.c. saturated with oxygen, while during work the utilisation of the oxygen is much increased and the O_2 saturation of the mixed venous blood may fall to 16 p.c. or thereabout. The corresponding O_2 tensions will approximate 35 mm. and 12 mm. respectively[1]. At the same time the oxygen consumption of the body is increased from 3 c.c. even to 30 c.c. per kg. per minute. During heavy work the percentage saturation of the whole blood can be taken to represent pretty nearly the conditions in the working muscles, and during rest the muscular gas exchange is usually below the average for the whole body. It cannot therefore be doubted that during work a much increased volume of oxygen diffuses from the capillaries into the muscles, while the available pressure appears to be considerably diminished, when with Verzár and Barcroft we take the O_2 pressure in the muscular tissue to be very low. The increase in the rate of blood flow through the capillaries and even a passive distension of them caused by the increased blood-pressure would obviously be of no avail to explain the discrepancy, and I was led to the conclusion that

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[1] That the utilisation of the oxygen in the blood is much increased during work has also been shown by Verzár (13) for the cat's gastrocnemius.

if Verzár's results were substantially correct the only possibility must be an increase in the number of available capillaries.

The conception to which I arrived was, that in the normal resting muscle a comparatively small number of capillaries arranged at fairly regular distances should be open, so as to allow the passage of blood while muscular work should cause the opening up of a larger number, thereby diminishing the distances which the oxygen molecules and other substances used by the muscle had to diffuse. This conception which is illustrated by the diagram, Fig. 1, has been put to the test of observation and experiment and found to be substantially correct.

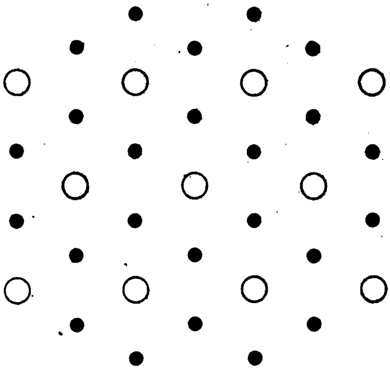

Fig. 1. Diagram of transverse section of muscle capillaries. ○ = open, ● = closed.

Direct observations of the capillary circulation.

1. The tongue of a frog (deeply narcotised with urethane) is pinned out and examined from the papillary side by transmitted light with a low power (binocular microscope, 65 diameters). Just after the pinning out the tongue is usually of a bright red colour and circulation is observed in a large number of papillæ. Later the tongue becomes pale, and circulation can be observed in the capillaries of a few papillæ only. Many are quite bloodless, but in some the capillaries are filled with blood which does not circulate. By local irritation with a needle circulation can be induced in any papilla from which the blood has disappeared, but not always in those in which the blood flow has stopped. In the course of about ten minutes generally the circulation thus set up becomes slower and slower, and finally the blood disappears anew from the capillaries under observation.

2. The geniohyoid muscles and the caudal portion of the hyoglossus are made accessible to observation by transmitted light by operative removal of the skin and the mylohyoids. The mouth of the frog is opened, the tongue drawn out and a small mirror is arranged in the mouth to illuminate the muscles through the mucous membrane. When the operation has been very cautiously made and bleeding is avoided the muscles are pale and circulation is observed in a few capillaries only, while some may contain blood which does not circulate. Tetanisation of

the muscles for a few seconds produces a greatly increased circulation (maximum usually after 15–20 seconds) and a large number of capillaries become visible. Afterwards the circulation is again diminished and may revert to the original state after 10–20 minutes.

On one occasion a single capillary was watched continuously after the stimulation. At first the red corpuscles passed in a continuous current, but a few minutes later they came one by one at intervals, which rose gradually to 5–15 seconds. At the same time the corpuscles became visibly transformed during their passage, being sausage shaped and distinctly longer than in the venule into which the capillary opened. Finally the circulation stopped completely, the capillary being empty and strongly contracted, and at that time no circulation could be observed in any of the visible capillaries supplying the same venule. In the venule itself there was, however, a slow current of blood with red corpuscles flowing one by one at distinct intervals, and this current was rhythmical and synchronous with the pulsations of the heart. I take this to show that one of the capillaries connected with that vein must have been open, the pulsation being accounted for by the absence of interference.

In another experiment of the same kind a record of the observations was dictated and the exact moments noted as follows:

Stimulation of nerve during 5 seconds.
After 24 sec. distinctly increased circulation.
„ 4′ 25″ corpuscles come through in a single file without intervals.
„ 4′ 55″ intervals of about the length of 5 corpuscles.
„ 5′ 25″ intervals increasing to length of 10 corpuscles.
„ 6′ 15″ corpuscles one by one or in small groups at long intervals.
„ 11′ 30″ no distinct alteration.
„ 13′ 10″ circulation in observed capillary stopped, but visible in others.

In a third experiment the average distance between the open capillaries of a resting *M. geniohyoideus* was estimated at 0·8 mm. After tetanisation it became reduced to 0·1 mm. The time of latency between tetanisation and the opening of capillaries has in several experiments been found to vary between 13 and 30 seconds.

3. As the observation by transmitted light is inconvenient and can only be applied to a few muscles I have tried observation by reflected light and found it to give excellent results on the muscles of the frog. As illuminant I have used direct sunlight or bright daylight, but the best results have been obtained by a small incandescent lamp (4 volt pocket lamp) mounted on a handle so that it could be brought very

close to the field of observation. By means of this arrangement I have examined a large number of muscles on many different frogs. The general results of these observations are as follows:

The capillary circulation in resting muscles is very variable, but as a rule feeble. It depends to a certain extent on the narcosis. A very deep narcosis will produce closing of a large number of capillaries and therefore bring out very strongly the changes following upon stimulation. The most normal results are usually obtained by injection of 0·2 to 0·25 gr. urethane on a frog of 35–40 gr. weight. The results obtained with this dose correspond closely to those obtained after injection of curari (1 mg. of an active preparation). Certain muscles (especially the *M. rectus abdominis*) are habitually well filled with blood, which appears to circulate in all or almost all the capillaries. (Average distance between capillaries about 60μ.) In most of the muscles of the trunk the circulation is feeble with distances between open capillaries varying between 200 and 500μ. In the limbs the circulation is often more feeble still, and sometimes it may be difficult to detect here and there an open capillary.

When the circulation in a muscle is not extremely feeble the open capillaries are generally seen to be arranged at fairly regular intervals.

By electrical stimulation or by gentle massage an increased circulation can be brought about in any muscle where it was feeble beforehand with the invariable result that the number of visible capillaries is greatly increased. Their average distances, observed in several cases, can be diminished to 60–70μ. By cautious administration of the urethane the respiratory movements of the floor of the mouth can be maintained while voluntary movements are suppressed, and in this case a fairly large number of open capillaries are observed in the contracting mylohyoids.

4. Similar observations have been made by reflected light on the muscles of urethanised guinea-pigs[1], but in this case special illuminating arrangements have been found necessary. I have used a small arc lamp and filtered the light through a dilute solution of methylene blue. The lamp was arranged to give a parallel beam of rays and by means of a concave mirror placed on an adjustable stand these were concentrated on the muscle under observation. The colour of the light caused the blood to appear very dark on a background of blue green. The platysma and prætracheal muscles proved to be especially well suited for these observations, though in some cases the vibration caused by the pulse in the carotids was very troublesome. The capillaries are too narrow to be readily seen by the greatest magnification which I found practicable

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[1] The most suitable dose is about 0·8 gr. urethane to an animal of 400 gr. weight.

(binocular microscope, 65 diameters), but the observation is facilitated by the movement of the blood. Resting corpuscles are practically invisible. Just after the exposure of a muscle the circulation is feeble, the distance between those capillaries through which blood is flowing being about 200 μ. While the muscle is exposed to air and the strong light the circulation is increased, and it is often possible to see the blood flow begin in one capillary after another. The distance between the capillaries may fall to 60 μ or lower, but reliable measurements cannot be made. When the muscle is moistened with saline and a cover glass applied, or when it is protected by the skin being drawn over it the circulation decreases again, but the distance between capillaries is usually not increased beyond 100–150 μ.

Electric stimulation of a muscle for a few seconds always causes a considerable increase in the number of open capillaries, and in several cases spontaneous contractions have been observed in the platysma accompanied by a similar reaction on the part of the capillaries.

Capillaries in injected specimens.

As I found it very difficult to obtain reliable measurements of the average distance between the open capillaries in living muscles I endeavoured to work out a method by which the condition at any given moment could be studied after fixation. I hoped to attain this end by injecting into the circulation of a living animal a suspension of particles which would be evenly distributed in the blood and by their presence indicate the capillaries through which the blood had been flowing. I tested a large number of different suspensions, mostly of small microorganisms, but none of these was satisfactory[1] and finally I had to have recourse to india ink. The particles in this fluid (Pelikan Perl Tusch. Günther-Wagner) are of ultra-microscopic size, and I greatly feared that they might penetrate into capillaries which were closed to the red corpuscles, but as far as I have been able to ascertain this does not take place. I have never seen a capillary containing india ink without red

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[1] Among the suspensions tested were fat globules from milk, some of which proved to be too large, while none of them could be stained deeply enough; small starch grains from rice, which were a little too large even for the frog and could not be stained satisfactorily; various bacteria, which became agglutinated; spores of Penicillium and finally the smallest known species of yeast (Saccharomyces exiguus) the cells of which could be stained deeply brown or black by silvering. The latter were not quite bad for experiments on frogs, but sometimes formed concretions which could not pass the capillaries. For much kind help and advice during these experiments I am indebted to Dr Vilh. Yensen of the University Pathological Institute, Professor of Anatomy, Dr F. C. C. Hansen, Dr Klöcker of the Carlsberg Laboratory and Mr Schmit Yensen of the Veterinary Serum Institute.

corpuscles. To the commercial preparation of india ink certain antiseptic substances have been added, and it was necessary therefore to dialyse for several days against a Ringer solution.

1. In the frog (*R. esculenta*) the injection is made through the vena cutanea magna[1] which is easily accessible from the ventral side through the abdominal portion of the *M. pectoralis*. About 0·5 c.c. of the suspension was usually allowed to run in from a micro-burette in the course of a few minutes. In most cases the frog was bled to a similar extent through the peripheral end of the vein, but I do not think this essential.

In the injected frogs the circulation could be studied directly under the binocular microscope, and the facts described in the previous section have been repeatedly verified on such, but in addition observations were made on excised portions of muscles and other tissues obtained after stopping the circulation by clamping the bulbus aortæ. These specimens were pinned on to small cork plates and stretched as accurately as possible to their natural dimensions. After being observed directly by reflected light they were fixed in 5 p.c. formalin and after the usual treatment finally mounted as microscope slides.

The observations of fresh material showed the differences between different muscles which have been described above. Muscles which had been tetanised before stopping the circulation were almost black and showed a large number of capillaries, while most of the others were pale and showed very few. The skin was always well injected. The tongue when not stimulated was generally white and nearly bloodless, and the empty stomach and intestines usually showed very slight signs of circulation only. The liver always became jet black.

In some of the mounted muscle preparations the number of injected capillaries per mm.^{2} of the transverse section was estimated by counting. I thought at first that it would be impossible to make such countings on actual transverse sections of the muscles, because the injected capillaries are never uniformly black, but show numerous interruptions, caused chiefly by red corpuscles, and most of the countings have been made therefore on thick longitudinal sections or thin muscles mounted *in toto* according to the method described elsewhere (1). Countings of the capillaries in areas of 0·04–0·15 mm.^{2} cannot of course give very accurate results, but the differences between resting and stimulated muscles come out very clearly nevertheless, and for approximate calculations of the necessary oxygen pressure head they are quite sufficient. Two countings

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[1] I have also tried the *V. abdominalis*, but with the result that most of the injected substance was retained by the liver.

of a stimulated sartorius have given 305 and 340 capillaries per mm.^{2} respectively, while unstimulated but unusually well injected sartorii have given 85, 96 and 100. A stimulated extensor tarsi gave 195 capillaries, but in the corresponding unstimulated muscle the injected vessels were too few to be counted. There were certainly not more than five in a mm.^{2}. Three different preparations of the *M. rectus abdominis*, which is habitually vascularised, gave respectively 115, 155 and 180.

In the mucous membrane of the empty stomach and intestine the injection is very far from being complete, many capillaries being closed. The distance from any point in the tissue to an open capillary does not seem to exceed about $200\,\mu$ and seldom $100\,\mu$.

In the brain of the frog all the capillaries which are visible with total injection seem to become injected vitally also, and the supply of oxygen to any point in the tissue must be abundant—provided the diffusion rate for oxygen is not very much lower than in muscles.

2. On guinea-pigs of about 400 gr. weight I have usually injected 4 c.c. india ink through the jugular vein. Direct observation of several muscles after the injection confirmed the results obtained without injection. Considerable differences were observed between the degrees of vascularisation of different resting muscles, and on one of the animals the greater part of the muscular system appeared to have a larger number of open capillaries than usual. In this particular case the narcosis appeared to be less deep with occasional movements, but whether there is a causal connection between these phenomena I cannot tell. After killing the animals by blowing air into the jugular vein several muscles and other organs were examined more closely and from some microscope slides were prepared.

On the fresh muscles a number of countings were made of the capillaries visible in a single field with a low power and without using the vertical adjustment, and the positions of the capillaries on the micrometer scale were noted. By this simple method a general idea of the number of capillaries and the regularity of their distribution can be obtained. I give some instances of such countings.

Objective I. Magnification 90 diameters. 1 scale division $= 22\mu$.
„ III. „ 230 „ „ „ $= 8{\cdot}6\mu$.

Muscle from abdominal wall	Capillaries at scale divisions
Upper layer, Obj. I	10 13 16 21 21 24 28 31 33 35 38 44 50 55 61 65 67 72 75 78 Average distance 3·8 divisions $= 83\mu$.
Deeper layer, Obj. III	29 32 35 40 42 47 52 54 56 60 Average $3{\cdot}4 = 29{\cdot}6\mu$.

Diaphragm, Obj. III ... 20 22 23 25 27 30 32 35 37 39 41 42 44 46
48 50 51 53 55 57 59 62 64 66 68 70 71 73
75 77 79 81 Average 1·96 = 17μ.

Prætracheal muscle,
Obj. III ... 22 25 32 37 42 47 52 60 65 69 72
Average 5·0 = 43μ.

These countings show a fairly regular distribution of open capillaries, which are however very different in number in the different muscles, being closest together in the diaphragm, which had been working vigorously up to the death of the animal, and widest apart in the upper layer of the abdominal wall. Some of these preparations have since been re-examined by the far more accurate method of taking optical transverse sections and have given the following results:

	Section examined			Number of capillaries	Capillaries per mm.^{2}	2R μ
	Depth mm.	Length mm.	Area mm.^{2}			
Abdominal wall Upper layer	0·101	0·8	0·081	7	86	125
	0·095	0·8	0·076	6	70	
	0·081	0·8	0·065	6	92	
Deep layer	0·068	0·64	0·043	25	580	49
	0·095	0·48	0·045	22	490	
Diaphragm	0·054	0·29	0·016	43	2700	18
	0·054	0·145	0·0078	20	2550	
	0·058	0·262	0·0151	37	2450	

Optical sections showing the distribution and approximate diameters of the open capillaries in equal portions of three muscles with 200, 700 and 2500 capillaries per mm.^{2} are given in Fig. 2. The results obtained by measuring the diameters of capillaries will be discussed below.

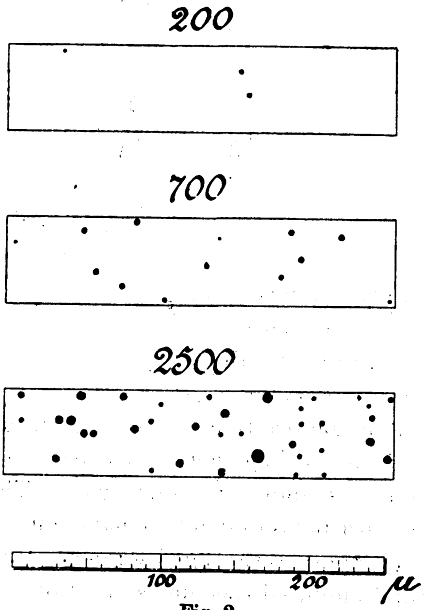

Fig. 2.

I have also tried a method of studying the state of the capillary circulation which should not involve any interference with the circulation. I have simply cut out small pieces of the muscles to be studied from the living animal (narcotised with urethane) fixed them in 5 p.c. formalin and stained 40μ sections with a weak solution of eosin. So far this method has not repaid the trouble spent upon it. A reliable differentiation of the red corpuscles from the other histological elements could not be secured, though in a few cases they became quite distinct. Even if this difficulty can be overcome, as I think it can, the method has the drawback of not showing whether the blood in the capillaries has been circulating or stagnating.

The diameters of capillaries.

In the preceding paragraphs the capillaries have been alluded to as being either open or closed, but this, though indicating the most important difference, is a very incomplete presentation of the case. The muscle capillaries which allow the passage of blood vary in diameter from about 2 to $10\,\mu$, but in the resting muscle their average diameter is always very small viz. about $4{\cdot}5\,\mu$ in the frog and $3{\cdot}5\,\mu$ in the guinea-pig. The red corpuscles of the frog are on an average $22\,\mu$ long, $15\,\mu$ broad and $4\,\mu$ thick in the middle, and those of the guinea-pig are $7{\cdot}2\,\mu$ in diameter and about $2\,\mu$ thick. *A priori*, therefore, it seems almost incredible that they can pass through vessels of the dimensions given, but in the frog their actual passage can be easily observed in the living muscles under the microscope. The corresponding observation on the guinea-pig is difficult to make, but after injection of india ink the passage of corpuscles through extremely narrow capillaries can be seen distinctly, and mounted specimens of vitally injected muscles or of muscles stained with eosin, which can be observed and measured under the highest

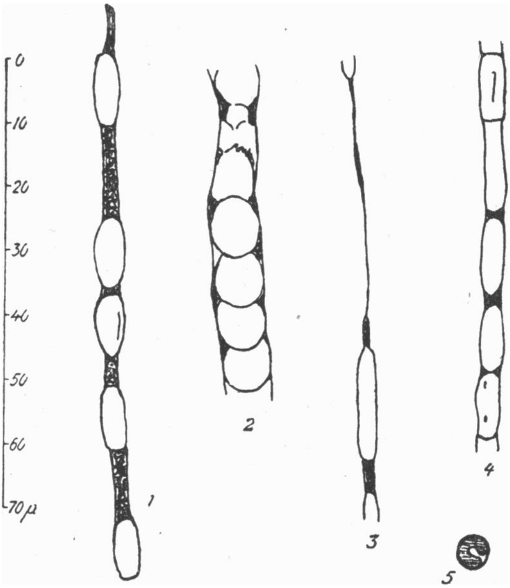

Fig. 3.

powers, leave no room for doubt. In the case of the injected vessels the presence of india ink between and along the corpuscles shows that they have been moving along during the life of the animals. Fig. 3 shows four different capillaries from the abdominal wall of a guinea-pig drawn by means of a prism. During their passage the red corpuscles become deformed according to the size of the capillaries. If the diameter of the vessel is about 4–5μ (in the guinea-pig) the edges of the corpuscles are rolled in, as shown diagrammatically in Fig. 3, No. 5, and the diameter along the vessel is not materially increased, but in still narrower vessels the corpuscles become sausage shaped and their length can be increased to 14μ or more (guinea-pig). The pressure necessary to bring about this change seems to be slight, but as soon as the corpuscles are released their shape becomes normal again. Their plasticity and elasticity are equally wonderful. When the corpuscles are much deformed, however, it is readily observed on the frog that their passage is comparatively slow on account of the resistance offered by them.

In working muscles a number of the capillaries show much greater diameters up to 10·4μ, and through these the corpuscles pass in a continuous current and without any change of form. Nevertheless the average diameter of the capillaries in the diaphragm of the guinea-pig was found to be only 5·0μ. In Fig. 2 the diameters of the open capillaries are recorded approximately but accurate measurements have not been made in this case.

In smooth muscles and in mucous membrane the capillaries appear to be on the whole wider, the corpuscles passing through with little or no deformation.

To show the variations in capillary diameters I give the following measurements in micromillimetres.

	Frog, *M. sartorius*				Guinea-pig			
	Resting		Stimulated		Abdominal wall		Diaphragm	
	7·3	5·2	7·2	7·4	2·2	4·0	4·4	4·2
	3·5	2·4	7·6	7·3	4·1	1·8	4·8	4·0
	2·5	4·1	6·0	8·0	3·0	3·8	7·4	2·8
	10·6	3·6	7·0	4·9	4·2	3·0	8·2	5·8
	2·9	4·3	7·6	4·2	4·5	3·5	3·3	5·4
	4·6	2·1	4·1	6·7	2·7	6·5	6·7	10·4
	5·6	2·7	9·6	6·7	3·7	3·1	2·2	3·5
	5·5	3·3	5·5	10·7	2·5	2·9	4·2	4·6
	4·0	2·9	7·4	5·6	2·9	5·0	4·7	5·5
	4·4	4·0	4·9	7·0	2·8	3·3	3·1	5·4
Average	4·3μ		6·8μ		3·5μ		5·0μ	

The pressure heads necessary for the supply of oxygen to muscles.

From the data given above and assuming the 0_2 consumptions given below, column *a*, the pressure heads have been calculated for a small number of typical instances according to the formula given in another paper (1)

$$T_0 - T_R = \frac{p}{d}\left(1{\cdot}15R^2 \log\frac{R}{r} - \frac{R^2 - r^2}{4}\right).$$

They are recorded in column *e*.

In the frog the oxygen dissociation curve of the blood is very steep and the oxygen pressure in the veins and capillaries therefore very low[1] (about 2–4 mm.). With ten open capillaries per mm.^{2} there must be lack of oxygen in considerable portions of the muscle, but with 90 the supply of oxygen is sufficient and a positive, though necessarily low, pressure must obtain everywhere. There can be no doubt from the observations that in resting muscles of the frog oxygen lack is a very frequent and probably normal occurrence.

	a	*b*	*c*	*d*	*e*	*f*	*g*†	*h*
	O_2 consumed per minute Vols. % of the tissue	Number of capillaries per mm.^{2} cross section	R μ	$2r$ μ	$T_0 - T_R$ mm. Hg.	Total surface of capillaries in 1 cm.^{3} muscle cm.^{2}	Total capacity of capillaries Vols. % of the tissue	Surface of 1 cm.^{3} blood in capillaries cm.^{2}
Frog muscle								
Rest	0·03	10*	180	4·4	10	1·4	0·015	9500
	0·03	90	60	4·4	0·7	12	0·14	8500
Work	0·3	325	31	6·8	1·2	70	1·2	6000
Guinea-pig muscle								
Rest	0·5	31*	100	3·0	45	3	0·02	15000
	0·5	85	61	3·0	12	8	0·06	13000
	0·5	270	34	3·8	3	32	0·3	10500
Massage	0·5	1400	15	4·6	0·4	200	2·8	7000
Work	5	2500	11	5·0	1·4	390	5·5	7000
Maximum circulation	10	3000	10	8	1·2	750	15	5000

* These figures are taken from estimations of distances between capillaries ($2R$) on living animals. The corresponding values for $2r$ are from measurements on preparations with 90 (85) capillaries per mm.^{2}.

† For the calculation of the figures in column *g* the average sectional area of the capillaries measured has been utilised.

In artificial injections of fishes a very small number of the capillaries existing become injected. This must mean that the others were closed, and it is safe to conclude that here also the oxygen pressure is normally

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[1] Unpublished determinations by Miss Leitch and the writer.

0 in very considerable portions of the muscles. This conclusion is confirmed by the experiments of Gaarder (10), mentioned above.

In the guinea-pig the oxygen tension of the venous blood is probably about 30 mm. With 30 open capillaries per mm.^{2} there must be oxygen lack, but with 85 there will be a positive pressure everywhere, though it will be considerably below that of the blood. 85 is the lowest number of capillaries actually counted, but, as pointed out above, I believe from the observations made on living muscles that it is not really typical for the resting muscle, and I expect that further investigations will show the capillary circulation to be regulated so as to maintain the pressure at 0 in certain parts of the muscle in accordance with the conclusions of Verzár.

After massage and during work the oxygen pressure in the muscular tissue becomes practically equal to that of the blood, and it is evident that in these cases the circulation takes place through a much larger number of vessels than would be necessary to insure the supply of oxygen. It is therefore not improbable that the increase in number of open vessels may be brought about to meet other requirements of the muscle.

In column *f* I have calculated the total surface of the open capillaries in 1 cm.^{3} muscular tissue. This is the area primarily available for diffusion and exchange of substances of any kind whatever between the blood and the tissue. When many capillaries are open this area is enormously increased.

In column *g* I have given the total volume of capillaries in per cent. of the tissue or, what amounts to the same, the percentage of capillary blood present in the muscles. When it is remembered that the total quantity of blood in a guinea-pig of 400 gr. is about 4 p.c. of the weight (14) and in a frog of 30–40 gr. about 4·5 p.c. (15) it is seen that the muscles contain during rest very little blood as compared with the whole organism. During work the amount of blood present in the capillaries of the working muscles is enormously increased. In the diaphragm of the guinea-pig it exceeds slightly the average for the whole body, and when the circulation in a muscle is at its maximum it may even rise to four times the average for the whole body.

The mechanism regulating the capillary circulation.

As far as I have been able to ascertain the prevailing conception of capillary circulation among physiologists seems to be that the capillaries are passive, that blood is flowing continuously through all of them at rates which are determined by the state of contraction or dilatation of the corresponding arterioles, and that the dilatation of an arteriole will cause a rise of pressure in the corresponding capillaries, which will become passively expanded to contract again by their own elasticity when the pressure is reduced. It is obvious that such a view cannot be reconciled to the observations and experiments given above.

Some authors, who have observed that capillaries are sometimes bloodless, while the blood is flowing freely through a number of others around them, or that blood may be flowing through single capillaries, while the majority are closed, assume, that certain capillaries will not normally admit red corpuscles but only plasma (*Vasa serosa*) and that they are opened up when the pressure becomes high (Cohnstein and Zuntz, 1888(16)) or that "the capillary course from artery to vein offers various degrees of resistance" (Langley(17)). Langley adds: "It is probable that in the mammal there is a similar arrangement and that it is of considerable importance in shock, allowing some blood to pass to an organ when the blood-pressure is very low."

Such a view might explain a number of my observations on the assumption that the capillaries emanating from a single arteriole possess very different coefficients of elasticity and require very different pressures to be opened up. It should be pointed out, however, that if such an arrangement existed the blood would always flow through the same definite channels when the capillary pressure is low (as during rest in muscles) and the distribution of oxygen and nutritive substances would be very unequal, the cells lying nearest to the open capillaries being well supplied, while those at the greatest distance were starved. There is, moreover, abundant evidence to show that the capillaries are not merely passively distended by pressure but actively dilating and contracting.

This view has been maintained by a number of observers of whom Stricker(18), studying in 1865 the nictitating membrane of the frog, is, so far as I am aware, the first. Stricker's observations were followed up by Golubew(19), Tarchanoff(20) and, especially, Rouget(21) (1873–79) who confirmed the existence of contractile capillaries in the nictitating membrane and in certain fœtal and larval capillaries. Rouqet further described certain branched cells which were arranged on the outside of the contractile capillaries and which he considered as the contractile elements. These cells were again observed by P. Meyer(22) who claims their presence also on the capillaries of the bladder and gut of newts and frogs. By Mayer's results, Steinach and Kahn(23) (1903) were led to examine the contraction process more closely. These authors worked chiefly on the capillaries of the excised nictitating membrane of the frog and found that they showed spontaneous contractions and dilatations, though the internal pressure obviously remained at 0. They could induce contractions by stimulation of the dorsal sympathetic, and they were able to observe also spontaneous contractions in the capillaries of various organs taken from mammals.

A very important research, to which my attention has been drawn by Prof. Langley, was published as early as 1880 by Roy and Graham Brown(24). These authors studied the circulation in the web and other organs of the frog (tongue, mesentery, etc.), and they devised methods for measuring under the microscope the pressure in capillaries, small arteries and veins. They found that the capillaries studied show very frequent changes in diameter, and that capillaries belonging to the same arteriole may show simultaneous changes in opposite directions. They observed that when the pressure difference between the inside and outside of a capillary is reduced almost to 0 "the effect on the diameter is usually so slight as to be barely appreciable," while the vessel is at once emptied and collapsed when the outside pressure is raised, if ever so slightly, above the internal. Similarly a measurable increase in diameter cannot be induced by raising the inside pressure, but may come about spontaneously with a low as well as with a high pressure. The capillaries cannot therefore be more than slightly elastic but must possess active contractility.

Roy and Graham Brown have studied further some of the factors which produce active dilatation of capillaries and found that chloroform, mustard, etc., have a powerful action in this direction. They were unable to confirm the results of Severini(25) viz. that CO_2 causes dilatation and O_2 contraction of capillaries.

I can confirm from numerous observations the fundamental fact that capillaries do not contract measurably by elasticity when the pressure is reduced by closing or cutting the arteries, and I may add that the pressure necessary to force muscle capillaries open when they are actively contracted is very much higher than the normal arterial pressure as evidenced by the results of artificial injections. By such injections of fresh resting muscles nearly the same results may be obtained as from vital injections, viz., single capillaries are injected at long and more or less regular intervals. Only when all veins are tied and the pressure is raised to something approaching a whole atmosphere a complete injection can be obtained.

Especial importance attaches to the observation of Roy and Graham Brown that the calibres of capillaries are constantly changing. By the enormous number of available capillaries we can imagine the open channels as constantly shifting over the field and thereby producing a uniform irrigation throughout.

It should be mentioned finally that in recent years pharmacological evidence has been brought forward in support of the view that capillaries may react independently of the arteries and the arterial pressure. Heubner (26) has shown for instance that injection of certain salts of heavy metals ($AuCl_4Na$) causes an enormous number of capillaries to be opened up, of which no trace could be seen before the injection, while an action upon arteries could not be ascertained[1].

Dale and Richards (29) have brought forward evidence to show that histamin and adrenalin under certain conditions produce active dilatation of capillaries and "it is suggested that the current conception of the peripheral resistance to blood flow, as determined almost exclusively by the tone of the arterioles, allows too little importance to capillary tone as a factor."

That the mechanism regulating the calibre of capillaries is mainly situated in the capillaries themselves and must consist of contractile elements is, I think, established by the experiments and observations given above. The nature of the contractile elements, their innervation (sympathetic?, antidromic?) and their liability to influences from substances acting directly upon them must be a matter for further study, and though certain conclusions can be drawn from the observations recorded I shall reserve these for a future publication in which they can be put on a broader basis. Two essential points must however be touched upon.

1. By the direct macroscopic and microscopic observation of muscles and other tissues (mucous membranes of frogs) an intimate connection can be established between the colour of the tissue and the state of contraction or relaxation of the capillaries. When the open capillaries are few and narrow the tissue is pale; when they are numerous and wider the colour is more or less red. A muscle injected vitally with india ink can show all shades from a barely visible gray to black. The blood colour of a tissue is obviously not influenced at all by the velocity of the blood flow, but solely by the amount of blood *present*, and while the amount of blood present in the small arteries and veins is undoubtedly variable and must contribute to the colour, the variations are small compared with the variations in capacity of the capillary system. From the figures in column *g* p. 468 it follows that the maximum amount of blood which

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[1] Several other substances have been claimed by Heubner, Jacoby (27) and Holzbach (28) to act specifically on the calibre of capillaries, but the evidence seems scarcely conclusive.

can be present in the capillaries of guinea-pig muscles is not less than 750 times the minimum. The blood colour of a tissue depends therefore practically on the state of contraction of the capillaries and not primarily on that of the arterioles.

This fact being grasped it becomes at once apparent that the capillariomotor regulation must play an enormous role not only in muscles, but in the skin and in all mucous membranes, in which changes in colour are the most obvious signs of vasomotor influences. The hyperæmic condition (in the clinical sense) of any organ is brought about by a large number of capillaries being open and more or less dilated, and in the anæmic condition most of the capillaries are closed, and most of those which remain open are more or less contracted.

2. The objection might be raised that the existence of a complete vasomotor mechanism for the capillaries would make the well-known arteriomotor mechanism rather superfluous. I have little doubt that the *current* of blood through a tissue could be regulated, at least temporarily, by the capillariomotor system alone when the arterioles were dilated, but this would involve a very high capillary pressure and probably give rise to exudation. The arteriomotor system regulates the *pressure* in the capillaries, and evidence can be adduced pointing to the simultaneous occurrence in the same tissue of contracted arterioles and dilated capillaries. I shall only mention as an example the well-known case of local hyperæmia with a more or less blue coloration. In such a case the blood must be flowing very slowly since the greater part of its oxygen has disappeared from the capillaries. A slow current through dilated capillaries must mean that the arterioles are strongly contracted.

SUMMARY.

Microscopic observations, chiefly made by reflected light, are recorded to show that in the resting muscles of frogs and guinea-pigs most of the capillaries are in a state of contraction and closed to the passage of blood.

By tetanic stimulation of the muscles or by gentle massage a large number of capillaries are opened up. They can be observed to contract again afterwards. In spontaneously contracting muscles a large number of capillaries are likewise opened.

When the circulation is not extremely feeble (in the frog) the open capillaries are arranged at fairly regular intervals.

A method of *intra vitam* injection of india ink is described by which the capillaries which were open at the time become easily distinguishable in microscope slides prepared from the muscles.

The number of open capillaries per mm.^{2} of the muscular cross section has been counted in such preparations of resting and working muscles.

The average diameter of the open capillaries in resting muscles is much less than the dimensions of the red corpuscles which become greatly deformed during their passage. In working muscles the capillaries are somewhat wider.

The oxygen pressure head necessary for the supply of the tissue has been calculated from the countings and measurements for some typical cases. The oxygen pressure in resting muscles is, sometimes at least, very low, but in working muscles it approaches very near to that of the blood.

The evidence, showing that the capillaries are not merely passively dilated by blood-pressure but constantly perform active changes in calibre, is discussed.

It is shown that clinical hyperæmia and anæmia are due mainly to changes in the calibre of capillaries and in the number of open capillaries.

Evidence is brought forward pointing to the arteriomotor and capillariomotor systems being able to act in opposite directions.

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