ON THE EXCHANGE OF BLOOD-GASES IN BRAIN AND MUSCLE DURING STATES OF REST AND ACTIVITY.

By LEONARD HILL, M.B., *Assistant Professor of Physiology, University College, London, and Grocers' Research Scholar;* AND D. N. NABARRO, B.Sc.

(*From the Physiological Laboratory of University College, London.*)

SOME short time since in his Croonian lecture[1] Mosso brought forward experiments to prove that the brain is a seat of active combustion. By a long series of thermometric observations published in his recent monograph[2] he has reached the conclusion that the temperature of the brain is frequently higher than that of the rectum, or even than that of the aortic blood. He has further found that the temperature of the brain rises still higher, when that organ is stimulated to activity either by direct excitation or by drugs.

It becomes apparent, when one considers the quantity of blood which passes through the brain in any given time, that if Mosso's results be correct, the formation of heat must be very great. This must be so, in order that the temperature of the brain should be raised perceptibly above that of the blood.

Hitherto, it has been found impossible, even by the most delicate thermometric instruments (such as the wire-resistance thermometer used by Rolleston[3]) to demonstrate the formation of heat in nerve. The heat which is produced by the brain, therefore, must owe its origin, as Mosso himself suggests, to the activity of the nerve cells, and the small amount of cortex must be capable of evolving heat sufficient to raise the whole brain above the temperature of the aortic blood which is continually circulating through every part of it. Even if we allow that in the conducting of impulses the nerve fibres can produce some amount of heat, yet the question of any active combustion in these fibres is certainly negatived by the delicate researches of Rolleston.

The position of Mosso, therefore, is that the thin cortical shell of the dog's brain is endowed with such active metabolism, that it is capable of generating heat sufficient in amount to raise the brain above the temperature of the aortic blood which is ever streaming through its capillaries, and which is at the same time carrying away this heat from every part of that organ.

It is difficult to ascertain the true temperature of the blood, as one of us (Hill) recently found in a similar research with W. M. Bayliss[4]. In order to obtain concordant readings from any two thermometers which are placed in water it is necessary that the water should cover a certain empirical amount of the thermometer-stems, but it is very difficult to be sure, in the case of experimenting upon an animal, that exactly the same amount of stem is covered by tissues which are of the same temperature along the whole length of the stems. Thus the thermometric method is far inferior to the thermojunction method. When a thermometer is placed in the carotid artery so that the bulb lies in the aortic blood-stream, the stem of the thermometer will lie in tissues which are rapidly cooling below the blood temperature, and the reading of the thermometer may be below that of the aortic blood.

The positive results of Ludwig and Speiss on the formation of heat in the salivary glands were negatived by Bayliss and Hill.

The cerebral circulation changes passively with every alteration of the general arterial or venous blood-pressure. This has been demonstrated by Roy and Sherrington[5] and confirmed in a research, as yet unpublished, by one of us (Hill) and W. M. Bayliss. In particular, it must be remembered that, through the influence of gravity on the circulation of the blood[6], the cerebral circulation will be affected by every change of position in an animal, and also it will be affected by any alteration in respiration or by movements on the part of the animal.

We have found that an epileptic fit produced by cortical excitation or by administration of absinthe has an enormous effect on the cerebral circulation and on the general distribution of blood in the body. The injection of strychnine is followed by an equally striking effect. These are methods employed by Mosso to obtain elevations of temperature in the brain during the activity of that organ.

Even granting that Mosso always obtained the true aortic temperature, many of the recorded changes of cerebral temperature might, nevertheless, have been caused by the determination of venous blood to the brain through those changes in venous pressure which were produced by his experimental methods.

It will be remembered that Claude Bernard[7] and later Heidenhain[8] found the blood in the right side of the heart to be considerably warmer than the aortic blood. It may be that Mosso did not obtain the true aortic temperature. His results in that case might be entirely due to the conditions of his experiments altering the relative distribution of the blood in the brain and the body. It seems to us that the precautions taken by Mosso to eliminate the source of error which we have indicated were not sufficient.

On the other hand, the blood which flows from the venous sinuses when the torcula Herophili is opened is less venous in colour than that of the femoral vein. Mosso's conclusions seemed entirely opposed to this fact and led us to investigate the relative exchange of blood-gases in the brain and in the muscles.

Method. The research was carried out by means of the simple form of gas-pump which has been planned by one of us (Hill) for such researches and described in this *Journal*, vol. XVI. 1894. In the first place we reinvestigated the accuracy of this pump in every possible way. In the description of the pump it will be remembered that no drying chamber is mentioned. The gases, saturated with water vapours, are driven over into the eudiometer and any water which becomes condensed in the pump is returned to the blood bulbs by a simple manipulation of the tap. By the use of this method we have found that only a negligeable quantity of carbonic acid is lost in absorption by the water. We have passed measured quantities of dry carbonic acid into the froth bulbs which contained some gas-free water, and we have been able to pump out the same quantity of gas within an error of two or three hundredths of a cubic centimetre. We have determined, after the complete extraction of blood-gases with this pump, that no more carbonic acid can be obtained from blood by the addition of acid. Lastly, and this is the final test of the working value of any blood pump, we have made a fresh series of determinations of samples taken from the same defibrinated blood, and append an example.

Four samples of defibrinated blood.

Vol. p.c. grms. blood	1	2	3	4	Average	Greatest difference
Total	38·08	38·61	39·25	38·74		
CO_2	17·14	17·15	17·87	17·69	17·51	0·73
O	17·88	18·34	18·38	18·57	18·29	0·69
N	3·06	3·12	3·00	2·48		

When tested in every way, the working error of the pump is therefore under 1 p.c., and this error is of no moment in comparative work, and seems to us to be entirely compensated for by the simplicity of the pump and its rapidity of action.

A complete experiment, the collection and weighing of six samples of blood from an animal, and the extraction and analysis of the blood-gases, has been carried out by us in three hours. Eight to ten grams of blood is sufficient for each sample, and this quantity can be rapidly and simultaneously drawn from an artery and vein, the condition of the animal remaining uniform.

It seems to us that very considerable errors may, in the older methods of Ludwig and Pflüger, be due to the collection in each sample of so large a quantity of blood as 50—60 c.c., as alterations might arise in the condition of the animal during so long a time of collection. It is probable that these errors more than counterbalance the errors in the reading of the eudiometer, which are increased by our use of smaller amounts of blood.

In the earlier set of our experiments, successive samples of blood were collected from the carotid artery, the torcula Herophili and the deep femoral vein. In some cases samples of carotid blood were collected before and after the collection of the samples of venous blood, in order to eliminate variations in the general state of the animal. We found that in the condition of rest the gases of the carotid blood generally remained remarkably constant throughout the course of an experiment.

In order to provoke a state of cerebral and muscular activity essential oil of absinthe was intravenously injected, and samples of blood were obtained from the veins and artery in the conditions of tonus and clonus. During the alterations in respiration consequent upon the development of the fit, we found that the gases of the carotid blood varied very largely. In the later part of our work, therefore, when we investigated the active conditions we changed our method, and both in states of rest and activity collected the samples of carotid blood simultaneously with the venous samples. This became our final method of procedure.

Schoefer and Ludwig, and Hirschmann and Sczelkow[9] have shown that the gaseous contents of the carotid and femoral blood are practically the same; Pflüger[10] confirmed this fact. The average of Pflüger's results was as follows:—

Carotid	13·9 O	28·7 CO_2
Femoral	13·99 O	29·5 CO_2.

In this way, error was, we believe, almost eliminated, for we simultaneously obtained, in each state, samples of blood going to or coming from the brain or muscles. These samples of blood weighed 8—10 grms, and were collected in small bulbs which had been rinsed out with oil, and the rate at which the bulbs filled was noted in each case. The blood was immediately transferred from these small bulbs to the vacuum froth-bulbs of the pump and defibrinated by shaking with mercury. The froth-bulbs, after the necessary weighing, were kept in the cold until the gases were extracted. This course was followed because it was impossible to draw the blood straight from the torcula into the vacuum froth-bulbs. By comparative experiments it was found that the percentages of the blood-gases were unaltered by this method. Blood taken from the carotid artery either into the small bulbs or directly into the vacuum bulbs yielded similar results, *i.e.* within the limits of error of the pump. This is to be expected from the fact that the blood when it flows into the small bulbs is covered with a skin of oil, and the rate of exchange of gases from within or from without is exceedingly slow through any skin of fluid. The animals employed in the research were dogs; and the experiments were carried out under morphia narcosis. In a few experiments chloroform was employed in the place of morphia. When the animal was anæsthetised a cannula was placed in the central end of the carotid artery, another cannula was placed in the femoral vein just below the opening of the deep femoral vein and pointing towards its mouth. Both femoral vessels were ligatured below the deep femoral branches. The small blood-bulbs were connected by short rubber tubes with the ends of these cannulas, and the samples were at any time obtained by opening the clips placed on the rubber tubes. A second short piece of rubber tubing was placed on the other end of the blood-bulbs. As soon as the bulbs were filled with blood, strong clips were placed on this rubber tubing, the bulbs were disconnected from the cannulas, connected up with the froth-bulbs of the pump and the blood passed over into the latter.

In order to obtain the cerebral venous blood the torcula Herophili was trephined and the tubular end of one of the small bulbs was pushed directly into the trephine hole. The bore of this hole exactly fitted the trephine hole and the blood from the superior longitudinal sinus flowed directly into the blood-bulb. It has been objected that the blood in the torcula might be contaminated by arterial blood coming from the cavernous spaces in the bone. This does not occur to any appreciable

extent, because we have always found that if a clot formed at the opening of the superior longitudinal sinus the bulb refused to fill.

After filling the bulb with blood the hole was closed by a piece of brass rod which was screwed into it. Throughout the experiments, therefore, the flow through the transverse sinuses was uninterrupted, and similarly the flow of the deep femoral vein was uninterrupted. In both cases the blood was drawn off into a temporary side channel.

In many of the earlier experiments, samples were collected from each animal, both from the deep femoral vein and also from the torcula Herophili.

In our later work in order to avoid experiments of too complicated a nature it was found better to collect samples during rest and activity from one only of these veins. Torcula samples were collected from one series of consecutive animals and femoral vein samples from another series.

The results of such a series are given in the following tables:—

Summary of Six Consecutive Experiments. Carotid Artery and Torcula.

Corrected to 0° C. and 760 mm.

Carbonic acid	Normal			Tonic Fit			Clonic Fit		
	Art.	Torc.	Diff.	Art.	Torc.	Diff.	Art.	Torc.	Diff.
1	36·50	40·39	+3·89	43·34	47·24	+3·90	25·01	28·23	+3·22
2	37·70	40·04	+2·34	Analysis lost			35·85	37·48	+1·63
3	36·29	41·80	+5·51	40·63	45·61	+4·98	25·83	30·29	+4·46
4	42·55	45·03	+2·48	48·44	50·69	+2·25	30·42	35·97	+5·55
5(1)	46·32	51·75	+5·43	48·80	53·65	+4·85	Sample not obtained		
5(2)	45·84	50·37	+4·53						
6	40·85	43·78	+2·93	43·73	48·05	+4·32	35·82	35·93	+0·11
Average	40·86	44·74	+3·87	44·98	49·04	+4·06	30·59	33·58	+2·99
Oxygen									
1	17·04	13·67	−3·37	11·35	6·31	−5·04	18·65	11·85	−6·80
2	11·65	10·39	−1·26	Analysis lost			5·90	3·70	−2·20
3	16·61	11·30	−5·31	13·39	8·61	−4·78	16·75	9·61	−7·14
4	17·54	15·52	−2·02	Analysis lost			15·99	13·17	−2·82
5(1)	17·14	10·80	−6·34	15·14	11·62	−3·52	Sample not obtained		
5(2)	16·64	14·22	−2·42						
6	21·07	17·89	−3·18	20·81	14·36	−6·45	21·53	18·99	−2·54
Average	16·81	13·39	−3·42	15·17	10·22	−4·95	15·77	11·46	−4·31

Summary of Eight Consecutive Experiments. Carotid Artery and Femoral Vein.

Corrected to 0° C. and 760 mm.

	Normal			Tonic Fit			Clonic Fit		
Carbonic acid	Art.	Vein	Diff.	Art.	Vein	Diff.	Art.	Vein	Diff.
1	40·12	49·89	+ 9·77	45·22	53·03	+ 7·81	Analysis lost		
2	35·56	46·15	+10·59	29·55	59·23	+26·68	20·38	51·42	+31·04
3	37·94	45·89	+ 7·95	41·78	50·25	+ 8·47	25·58	39·19	+13·61
4	32·05	38·81	+ 6·76	33·48	50·11	+16·63	36·97	51·93	+14·96
5	27·38	42·75	+15·37	Analysis lost			14·52	33·71	+19·19
6	43·44	48·40	+ 4·96	41·92	59·15	+17·23	Analysis lost		
7	34·96	41·44	+ 6·48	29·81	43·06	+13·25	29·21	47·09	+17·88
8	49·59	57·83	+ 8·24	54·93	61·99	+ 7·06	Analysis lost		
Average	37·63	46·39	+ 8·76	39·53	53·43	+13·90	25·33	44·66	+19·33
Oxygen									
1	16·84	3·51	−13·33	15·32	4·84	−10·48	Analysis lost		
2	18·34	4·47	−13·87	18·55	4·36	−14·49	18·87	5·46	−13·41
3	16·38	3·01	−13·37	14·07	3·11	−10·96	19·21	7·14	−12·07
4	20·60	4·49	−16·11	19·51	2·29	−17·22	17·89	6·34	−11·55
5	17·94	2·08	−15·86	Analysis lost			14·62	2·05	−12·57
6	17·19	5·11	−12·08	16·95	2·47	−14·68	Analysis lost		
7	20·07	13·29	− 6·78	21·39	2·54	−18·85	22·70	9·14	−13·56
8	17·42	5·03	−12·39	13·20	3·48	− 9·72	Analysis lost		
Average	18·10	5·12	−12·98	17·05	3·30	−13·75	18·66	6·03	−12·63

In the following table is a comparison of the average difference between the blood-gases in the deep femoral vein and the carotid artery and between those in the torcula and carotid artery.

Femoral Vein and Torcula. Average Differences Compared.

		Normal	Tonic	Clonic
Carbonic acid	Torcula	+ 3·87	+ 4·06	+ 2·99
	F. Vein	+ 8·76	+ 13·90	+ 19·33
Oxygen	Torcula	− 3·42	− 4·95	− 4·31
	F. Vein	−12·92	− 13·75	− 12·63

It will be seen at a glance that the metabolism of the brain is very low, and that it is scarcely increased during the stages of an epileptic fit.

The metabolism of the muscles is during rest twice or thrice as great as that of the brain and is enormously increased in both the tonic and clonic stages of the fit.

We drew the same conclusion from our earlier set of experiments in

which successive instead of simultaneous samples of blood were taken. These experiments have been omitted as far as they relate to the active state, owing to errors which we now know to arise from changes in the arterial blood during the fit. The results in the state of rest are published in a table at the end of this paper.

The result is manifest, without taking into account the rate of blood flow. Chauveau and Kaufmann[11] estimated that the rate of flow was three times as fast from active muscle as from resting muscle.

The method they employed was to collect the blood which flowed from the cut end of the vein in given times. From the published experiments of Stewart[12] we gather that the rate of flow of the blood through the brain is approximately the same as through the muscles of the leg, *i.e.* the circulation time of the blood from the carotid artery to the jugular vein is about the same as from the femoral artery to the femoral vein. Stewart's electrical resistance method gives us the values in the intact animal, and undoubtedly this is far the most accurate mode of experimenting on this difficult subject. There is no evidence therefore that the rate of flow is much greater through the brain than through the muscles, and to negative the results obtained in our experiments it would have to be as much as twice to six times as great. From our own observations on the time that the blood-bulbs take in filling we are led to believe that the rate of flow through the muscles is from twice to six times as fast during an epileptic fit.

We did not find the rate of flow always so uniformly increased through the brain. This, we believe, to be due in part to the greater difficulty in the course of an experiment of accurately estimating the rate of flow from the torcula, for a blood clot may cause partial blocking of the outlet of the superior longitudinal sinus and thus impede the filling of the blood-bulb.

We know that the blood-pressure rises enormously during the absinthe fit, and the cerebral venous pressure passively follows this rise, and the cerebral arterioles do not share in the general constriction. In active muscle, on the other hand, the capillaries dilate, so that the conditions for increased rate of flow are probably about the same in both organs.

If we multiply our results by two to six the metabolism of active muscle will become enormously greater than that of the muscle in rest.

Turning to earlier observations we find that Sczelkow[13] obtained a difference of

$$\left.\begin{matrix} O - 9 \\ CO_2 + 6{\cdot}71 \end{matrix}\right\} \text{ in resting muscle,}$$

and of

$$\left.\begin{matrix} O - 12{\cdot}26 \\ CO_2 + 10{\cdot}79 \end{matrix}\right\} \text{ in active muscle.}$$

Sczelkow collected three samples consecutively:—

(i) From the vein in state of rest.
(ii) From the vein in state of activity.
(iii) From the artery.

He took from each animal 50—60 c.c. of blood for each sample.

His method cannot be considered altogether satisfactory, both on account of the large amount of blood withdrawn from the animal and because the samples of arterial blood were not taken simultaneously with those from the veins.

The gaseous exchange in the masticatory muscles of the horse was estimated by Chauveau and Kaufmann[11], both when the animal was at rest and when it was engaged in chewing. The difference between the venous and arterial blood obtained by these authors was—

	Rest	Activity	
CO_2	+ 8·7	+ 10·20	+ 30·60
O	− 11·4	− 13·65	− 40·95

Chauveau and Kaufmann multiplied their results in activity by three, owing to the increased rate of flow. If we multiply our own results and Sczelkow's results by three also, the following comparison between the three determinations of gaseous exchange in the muscles can be drawn—

		Rest	Activity	
Sczelkow	CO_2	+ 6·71	+ 32·37	
	O	− 9	− 36·78	
Chauveau and Kaufmann	CO_2	+ 8·7	+ 30·60	
	O	− 11·4	− 40·95	
			Tonic	Clonic
Hill and Nabarro	CO_2	+ 8·76	+ 41·70	+ 57·99
	O	− 12·92	− 41·25	− 37·89

A. Schmidt[14] employed a method of artificial circulation in order to avoid the errors which might arise from changes in the condition of the animal. His method was severely criticised by Pflüger[15], and his results cannot be accepted as exact, as the conditions of the normal animal were by no means fulfilled.

It seems to us that far the most exact method is to take samples of blood from the artery and the vein simultaneously. By this means any change in the animal's condition is eliminated, as the difference determined is always that between the blood going to and coming from the organ.

The greater difference in the blood taken from the muscles in the clonic stage is very noticeable. Pflüger[15] suggested that the vessels of the muscles are partly occluded during the tetanus and hence more carbonic acid is given off after tetanus than during it. We have found that during clonus the animals breathe rapidly and the carotid blood becomes far more arterialised. The output of carbonic acid from the lungs is therefore greatly increased.

On the other hand, the animal in the tonic stage is partly in a condition of asphyxia.

In the brain the difference is less in the clonic than in the tonic stage.

From the above experiments it is clear that our results do not bear out the conclusions of Mosso, for it would appear that when compared with the muscles the brain is not a seat of active combustion, and considering the very small increase in CO_2 in the torcular blood it seems to us very improbable that the temperature of the brain should be perceptibly greater than that of the blood.

Summary of all the experiments in the state of rest and morphia narcosis.

Average of 52 Arterial Samples	= CO_2	37·64 %
	O	18·25 %
Average of 42 Torcular Samples	= CO_2	41·65 %
	O	13·49 %
Average of 28 Femoral Vein Samples	= CO_2	45·75 %
	O	6·34 %

Average Differences.

	Art. Torc.	Art. Vein
CO_2	+ 4·01	+ 8·11
	− 4·76	+ 11·91

Table of earlier experiments in the resting state. Samples collected successively.

Corrected to 0° and 760 mm. Vols. per 100 grms. Blood.

No. of Exp.	Artery		Torcula		Fem. Vein		Diff. A. & T.		Diff. A. & V.	
	CO_2	O	CO_2	O	CO_2	O	CO_2	O	CO_2	O
1	34·01	20·84	41·07	12·45			+7·06	−8·39		
2	35·46	17·59	37·31	13·53			+1·85	−4·06		
3	45·15	16·31			51·20	7·32			+ 6·05	− 8·99
4	38·60	17·92	41·73	14·17	44·64	10·99	+3·13	−3·75	+ 6·04	− 6·93
5	39·68	18·88	43·04	13·61	47·48	5·35	+3·36	−5·27	+ 7·80	−13·53
6	41·14	15·71	41·86	14·31	48·29	5·37	+0·72	−1·40	+ 7·15	−10·34
7	33·51	21·61	35·39	23·48	42·40	10·23	+1·88	+1·87	+ 8·89	−11·38
8	44·49	16·77	48·52	13·74	54·32	6·94	+4·03	−3·03	+ 9·83	− 9·83
9	21·87	20·75	38·57	16·48	39·08	5·09	+6·70	−4·27	+ 7·21	−15·66
10	36·51	17·83	38·46	16·20	42·25	11·83	+1·95	−1·63	+ 5·74	− 6·00
11	34·63	17·04	35·85	15·31			+1·22	−1·73		
12	31·30	17·08	39·47	11·45			+8·17	−5·63		
13	29·30	18·25	34·85	11·18			+5·55	−7·07		
14	38·25	26·30	40·39	18·96			+2·14	−7·34		
15	38·31	19·16	40·40	13·82			+2·09	−5·34		
16	39·18	18·73	42·57	14·66			+3·39	−4·07		
17	38·39	22·91	43·54	18·57			+5·15	−4·34		
18	37·62	23·48	45·35	19·67			+7·73	−3·81		
17	40·60	16·77			49·38	3·97			+ 8·78	−12·80
18	39·30	15·53	42·96	11·95			+3·66	−3·58		
			44·66	10·49			+5·36	−5·04		
19	32·85	20·30	33·13	18·25	45·10		+0·28	−2·05	+12·25	
	34·90	20·95	38·22	15·57			+3·32	−5·38		
20	38·20	15·04	44·47	11·87	44·37	2·20	+6·27	−3·17	+ 6·17	−12·84
	37·76	18·01	44·80	9·40			+7·04	−8·61		
21	35·24	17·69	40·20	11·12	39·98	5·01	+4·96	−6·57	+ 4·74	−12·68
22	39·54	17·66	41·00	11·04			+1·46	−6·62		
	38·50	19·12	44·96	10·46			+6·46	−8·66		
			42·47	16·48			+3·97	−2·64		
23	32·70	17·41			44·27	0·98			+11·57	−16·43
24	36·34	16·87			44·01	7·59			+ 7·67	− 9·28
25	40·01	10·88	46·21	5·85	47·14	0·80	+6·20	−5·03	+ 7·13	−10·08
26	28·92	12·61			35·95	5·75			+ 7·03	− 6·86
	32·90	16·76	35·75	12·34			+2·85	−4·42		
27	40·51	21·69			48·28	8·15			+ 7·77	−13·54
	41·80	21·38	45·32	15·93			+3·52	−5·45		
28	38·93	21·68	46·26	17·39	53·69	9·05	+7·33	−4·29	+14·76	−12·63

REFERENCES.

1. Mosso. Proc. Roy. Soc. 1892.
2. Mosso. Die Temperatur des Gehirns. Leipzig. 1894.
3. Rolleston. This Journal, xi. 208. 1890.
4. Bayliss and Hill. This Journal, xvi. 351. 1894.
5. Roy and Sherrington. This Journal, xi. 85. 1890.

6. Hill. Proc. Roy. Soc. 1894. This Journal, XVII. 353. 1895.
7. Claude Bernard. Leçons sur la chaleur animale, p. 32. 1876.
8. Heidenhain. Pflüger's Archiv, IV. 1871.
9. Hirschmann and Sczelkow. Ctbltt. f. med. Wiss. 1866.
10. Pflüger. Pflüger's Archiv, V. 1872.
11. Chauveau and Kaufmann. Comptes Rendus. 1886.
12. Stewart. This Journal, XV. 1894.
13. Sczelkow. Sitz. d. Akad. d. Wiss. Wien, XLV. 1862.
14. Schmidt. Arb. aus d. phys. Anst. zu Leipzig. 1869.
15. Pflüger. Pflüger's Archiv, VI. 1872.