THE GASEOUS METABOLISM OF THE LIVER. PART I. IN FASTING AND LATE DIGESTION.

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To determine the gaseous exchange of the liver the total blood supply of the liver must be estimated. We have determined the rate of flow to the liver by the portal vein and the rate of flow from the liver by the hepatic vein. We have taken the arterial supply to be the difference between the two.

The oxygen used by the liver has been estimated in two ways.

(1) In the majority of experiments the following was the procedure. Let the observed difference in oxygen content of 1 c.c. of blood from the portal vein and hepatic artery be A and that between the hepatic vein and hepatic artery B, and the ratio of flow in c.c. per minute along the portal vein r and the hepatic vein R.

The oxygen used by the liver L is

$$L = (B \times R) - (A \times r).$$

(2) In the minority of experiments—let the observed difference between the oxygen content of the blood in the portal and hepatic veins be C, the other quantities involved being as above,

$$L = B \times (R - r) + (C \times r).$$

In some of the experiments the blood of the portal vein was cut off from the liver and diverted into the jugular or brachial vein and the oxygen taken up by the liver determined by the differential analysis of hepatic vein blood against arterial.

Cats were used in the experiments. They were anæsthetised with chloroform followed by A.C.E. mixture and urethane. The blood-pressure was recorded from one carotid artery, and arterial blood was drawn from one femoral artery which was tied. Hirudin solution was put in the cannulas inserted into the various veins and hirudin injected into the circulation just before the diversion of the inferior vena cava blood,

as mentioned below. With regard to hirudin injection an interesting point was observed. It is well known that the injection of hirudin into a systemic vein caused a fall of blood-pressure and, if the injection is at all rapid, a temporary stopping of respiration. These effects are almost entirely absent if the hirudin is injected into the portal vein, there is little or no fall of blood-pressure and no cessation of respiration. After the discovery of this fact, we invariably injected the hirudin into the portal vein. In one or two of the later experiments it was found possible to collect the necessary samples of blood without the injection of hirudin at all.

In determining the rate of blood flow the method frequently used by one of us was employed, the blood being allowed to flow along a horizontal glass tube of 5 c.c. capacity and the time it takes to fill each c.c. of the tube being signalled by hand on to a tracing with a time record of fifths of a second.

The collection of portal vein blood. In order to collect a sample of portal blood without disturbing the supply of portal blood to the liver until the moment when the collection is made, a cannula is tied into one of the last veins opening into the main portal vein. The last contributing vein, the gastro-duodenalis, is generally too small or too much divided to be convenient, so we have used the next distal vein, which is mainly splenic but receives blood also from the pancreas and stomach. This vein is ligatured and a cannula tied into it, directed towards and close to the portal vein. The vein can be reached with very little disturbance by raising the lobes of the liver and gently drawing the duodenum to the left. Ligature of the vein does not cause the spleen to distend as there is abundant collateral circulation. These collateral veins can be easily seen, and that they afford a ready path for the splenic blood was shown by injection after death.

It is very important that the sample of portal vein blood should be collected at the pressure existing at the time in the portal vein and this is secured in the following way. A rubber tube connects the cannula to a graduated glass tube held horizontally in a screw clamp by which it can be raised and lowered. When the blood is to be collected it is allowed to flow into the rubber tube and the horizontal glass tube is lowered until the blood just rises to its proximal end, where it fluctuates slightly with the variations of the portal pressure. On occluding now the portal vein close to the liver, the blood flows along the horizontal tube at portal pressure, and the rate of flow of 4 or 5 c.c. is determined. For occluding the portal vein a thread is placed under

it close to the liver, care being taken that the thread does not include nerves or lymphatics. With this thread in the hand the vein is nipped with rubber covered forceps without pinching other structures and without any pressure on the liver or portal viscera. About 2 c.c. of the blood is retained for the oxygen determination the rest being returned at once into the portal vein. The time required for collecting a sample of blood and determining its rate of flow is five to ten seconds, so that the portal blood is cut off from the liver for that time.

The collection of hepatic vein blood. The whole of the blood of the inferior vena cava below the liver is diverted into the jugular or brachial vein in the following manner. For tying the inferior vena cava a thread was placed under the vena cava above the right suprarenal vein which is the last vein discharging into it below the liver. When the right suprarenal vein was unusually high, it was ligatured off, and the thread placed under the inferior vena cava just below it. In the earliest experiments a T cannula for diverting the blood was then put into the inferior vena cava below the renal veins but the method was abandoned as the necessary clamping of the vein while the T cannula was being inserted caused a large fall in general blood-pressure. In the next series of experiments the right renal vein was used for diverting the blood to the brachial or jugular, and the flow in the inferior vena cava was not interfered with until the diversion was made. In some of the experiments however the flow to the jugular was unsatisfactory and the general blood-pressure gradually fell. We therefore decided to put a large-mouthed cannula into the inferior vena cava by way of the femoral vein. The right femoral vein was cleared for about 2 cms. above Poupart's ligament, a cannula pushed up the vein 5 or 6 cm. and tied in. The mouth of the cannula then lies in the inferior vena cava 3 to 4 cm. below the right renal vein. There was no arrest of the inferior vena cava blood during the manipulation and after the vein is tied below the liver there is a much better flow of blood to the jugular than when the renal vein was used. A further advantage of this last method was that a smaller abdominal incision, only large enough to get at the large vessels near the liver, suffices and the larger part of the intestines was not uncovered at all.

After the inferior vena cava blood is diverted a cannula directed upwards is tied into the upper end of the vena cava just below the liver. When the inferior vena cava is clamped just above the liver this cannula will deliver hepatic vein blood only. In Exps. 1 to 7 a thread was placed under the vena cava between the liver and the diaphragm

and low enough to exclude the small phrenic vein, but this entails a good deal of handling of the liver, and we considered it better to avoid this and to neglect, for the present, the small amount of blood of the phrenic vein by leaving the liver quite undisturbed and clamping the inferior vena cava in the thorax immediately above the diaphragm. So that when the hepatic vein blood was collected in the later experiments the thorax was opened on the right side and artificial respiration put on, and continued until the end of the experiment.

Table I gives the rate of flow of blood in the blood vessels of the liver in six experiments with fasting animals. Table II gives the rate of flow of blood in the blood vessels of the liver in five experiments with fed animals.

TABLE I. *Animals fasting.* 36 *hours without food.*

Exp.	Rate of flow in hepatic vein, c.c. per min.	Rate of flow in portal vein, c.c. per min.	Difference giving the flow in hepatic artery, c.c. per min.	Carotid b.-p. when hepatic vein blood was collected	Carotid b.-p. when portal vein blood was collected
2	24·0	20·7	3·3	58	56
3	15·0	9·6	5·4	70	80
4	19·3	16·2	3·1	66	82
5	36·0	28·6	7·4	110	126
6	45·0	20·0	25·0	66	80
7	36·0	20·0	16·0	90	80

TABLE II. *Animals fed.* 18 *hours after food.*

8	33·3	22·0	11·3	36	82
9	36·3	16·0	20·3	64	40
10	40·0	24·0	16·0	60	42
11	48·0	20·0	28·0	96	80
12	40·0	24·0	16·0	88	116

The fasting cats had received no food the day before the experiment. The fed cats were given milk and meat the day before the experiment the last meal being about 6 o'clock in the evening and the experiment was performed about midday, that is about 18 hours after. This considerable interval after food perhaps accounts for the fact that only a slight increase in the portal vein flow was observed, while the decided increase in the arterial supply points to the post-prandial increase in the metabolism of the liver.

It will be seen from the tables that the flow of blood through the liver is greater in the fed than in the fasting animals and that the increase is chiefly arterial. We do not consider the figures in the two series are quite comparable, since in the experiments with the fed

animals the larger flow in the hepatic vein may be due to nipping the inferior vena cava in the thorax, instead of below the diaphragm. In Exp. 8 of the fed series the two methods were tried and nipping in the thorax gave a flow of 33·3 c.c. per min. against 30 when nipped below the diaphragm. It will be seen from the tables that the rate of flow does not vary with the arterial blood-pressure.

Our results give a lower rate of flow than was obtained with a recording stromuhr by Burton-Opitz in dogs in the hepatic artery and portal vein and by Schmid in cats in the portal vein. In these experiments it may be remarked that the portal vein was clamped for about ten minutes while the connections were made to the stromuhr, and although the flow was not actually recorded until a few seconds after the clamps were removed, it is doubtful whether the portal organs can have recovered so soon from the stasis and the distension of the blood vessels. In our experiments the flow through the portal organs is not interfered with for a moment and the rate of flow is determined at the normal pressure in the vein.

Some statement may be made at this point as to the accuracy of the analytical methods of gas analysis in the experiments we are about to describe.

The following experiments give duplicate readings of (1) the difference between the portal and arterial bloods:

·085 c.c.	·117	·093	·087	·136	·098
·079 c.c.	·114	·103	·099	·123	·092

and (2) the difference between the hepatic and arterial bloods:

·143 c.c.	·148	·147	·130	·079	·107	·137	·097
·144 c.c.	·163	·149	·132	·077	·095	·123	·099

The greatest divergence between the members of any pair of analysis is about 12 %, from which it may be supposed that any single analysis is within about 5 or 6 % of the mean value. Any greater error than this would arise from the inaccuracy in the collection of the blood. That such errors exist is clear from a consideration of the results of successive determinations of the metabolism of the same liver for instance. In Exp. 11 two determinations with precisely the same procedure give ·034 and ·029 c.c. per gram per min., figures which differ from one another by about 15 % whilst two determinations from the liver which were made by an essentially different procedure, the hepatic vein being clamped in one case in the abdomen and in the other in the thorax, differed by 25 %. This may be regarded as an extreme case.

Experiments upon animals which had received no food for 36 hours.

The gaseous exchange of the liver obtained from the animals which had not been fed for 36 hours is given in Table III.

TABLE III. *Animals fasting.*

	Portal Organs		Liver	
Exp.	Weight	O_2 taken up per gram per min.	Weight	O_2 taken up per gram per min.
1	140	·012	—	—
2	160	·013	76	·005
3	80	·012	77	·005
4	111	·011	109	·007
5	178	·013	89	·017
6	152	·013	74	·012
7	220	·008	99	·018
Average	148	·012	87	·011

These data we may consider in detail.

The gaseous exchange of the portal viscera. In Exp. 7 the apparently small gaseous exchange per gram per min. is due not to an absolutely small exchange, but to a great development of the muscular and connective tissue elements of the intestine which was abundantly evident to the naked eye and which caused the organs to attain to a weight of 220 grams. These elements are known, from the work of Cohnheim, Brodie and Vogt etc. to use relatively little oxygen, hence their hypertrophy leads to an apparently small gaseous exchange per gram per min. Setting this experiment aside for the present it will be seen that the oxygen taken up per gram per min. varied from ·011 to ·013 c.c. This degree of constancy is remarkable especially when the variability of the conditions under which it was attained is considered.

The following table gives the oxygen exchange and the blood flow through the tissues in question per gram per min.

	Exp. 1	2	3	4	5	6
Oxygen used	·012	·013	·012	·011	·013	·013 c.c.
Blood flow	·09	·15	·06	·20	·25	·12

It appears then that in the different experiments the difference in the blood flow was very great, this difference was no doubt largely due to surgical shock causing local dilatation. It does not seem, therefore, that within the limits of blood flow in the above table, there is any reason to suppose that in the fasting animals the gaseous exchange depends upon the blood flow. This result is in harmony with that obtained by Barcroft and Franz Müller in the submaxillary gland.

The above statement raises the question of the adequacy of the blood supply. In some of the experiments we have data as to the amount of oxygen in the venous blood.

Exp.	1	2	3	4	6
Percentage saturation of venous blood	15	29	32	46	23 %
Oxygen used... ...	·012	·013	·012	·011	·013

The experiments, however, yield no satisfactory data for the calculation of the oxygen pressure in the capillaries of the viscera contributing to the portal vein.

The liver. The divergence in the results is as remarkable as the uniformity in the case of the other viscera.

With regard to a possible connection between the oxygen used and the vascular condition of the liver it is clear that little information is to be obtained by comparing the oxygen used up by the liver with the total blood flow, since it might on the one hand be mostly blood already much reduced by the viscera or on the other hand blood rich in oxygen coming along the hepatic artery. But we have one very instructive experiment, which, though it was performed on a fed animal, may be cited here. In it the blood flow along the portal vein was almost constant in two sets of determinations whilst the blood flow along the hepatic artery varied greatly.

A. Blood flow along hepatic artery	B. Blood flow along portal vein	C. Ratio of A/B	Oxygen used by liver
12 c.c. per min.	18 c.c. per min.	·67	·034 c.c.
28 ,,	20 ,,	1·4	·030 ,,

In these two cases the vascular conditions were as different as they could be; in the first the blood in the hepatic vein was only 3 % saturated whilst that of the portal vein was 23 % saturated with oxygen, in the second case the portal blood was much the same (30 % saturated) whilst the blood of the hepatic vein was, owing to the very copious arterial supply, much richer in oxygen attaining a saturation of 43 %; nevertheless the amount of oxygen used by the liver was the same in each case. The liver like the submaxillary seems to use the oxygen it needs so long as the supply is sufficient irrespective of the amount which is brought to it in the blood.

Relative importance of portal and hepatic supplies. In several of our experiments as well as measuring the differences between the oxygen in the arterial and hepatic and the arterial and portal bloods respectively, we measured rather roughly the oxygen in the arterial blood. With the knowledge of this we get the actual amounts of oxygen in the

arterial, portal and hepatic bloods respectively. From the data which we have already given we can deduce the amounts of oxygen brought to the liver (1) by the hepatic artery and (2) by the portal vein and compare these quantities with the oxygen used by the liver. The following five experiments upon fasting animals are of this character.

Exp.	Oxygen in arterial blood	Oxygen in portal blood	Oxygen in hepatic blood	Oxygen brought to liver by		Oxygen used by liver
				Portal vein	Hepatic art.	
2	·142 c.c.	·041 c.c.	·042 c.c.	·85 c.c.	·47 c.c.	·35 c.c.
3	·152	·049	·059	·47	·82	·41
4	·190	·114	·088	1·85	·59	·77
5	·120	·038	·017	1·09	1·00	1·61
6	·135	·033	·074	·66	3·00	·91
7	·128	·033	·029	·66	2·06	1·76
			Totals	5·58	7·94	4·81

The fact which emerges from these figures is the essential part played by the hepatic artery in contributing to the oxygen supply of the liver. In Exps. 5 and 6 the whole quantity of oxygen brought to the liver by the portal vein was only about two-thirds and in Exp. 7, one-third, of that used by the liver. In Exp. 2 the portal blood was not at all reduced, in Exp. 4 on the other hand the hepatic blood was considerably poorer in oxygen than the portal. The same was the case in Exp. 5 but as an offset against Exps. 4 and 5 stand Exps. 2 and 6 in which the blood in the hepatic vein was considerably richer in oxygen than that in the portal vein. We conclude that the liver, at all events when at rest, takes its oxygen essentially from its arterial supply.

This result cannot be attributed to experimental shock. In the above experiments the liver did not depend upon the arterial blood for its oxygen because of want of oxygen in the portal blood as the following figures testify.

	Exp. 2	3	4	5	6	7
Percentage saturation of portal blood	30	32	60	32	24	26 %

In none of the above experiments was the portal blood at all nearly reduced—moreover it must be borne in mind that the most serious cause of experimental deficiency which we have to avoid is that of dilatation in the abdominal viscera, and although it is true that this lowers the general arterial pressure it does so rather at the expense of the blood flow in other parts of the body than in the organs which are drained by the portal vein.

When the full importance of the hepatic arterial supply became evident we performed one or two experiments with the object of ascertaining whether the oxygen supply of the liver was affected if the portal blood was withdrawn from it entirely. This was not difficult to manage. A T cannula was inserted into the rubber tubing along which the blood was flowing from the lower portion of the body. At the required moment the T was connected with the cannula in the splenic vein and the portal vein was tied close to the liver.

The following are the data which such an experiment yielded.

		Blood flow of liver in c.c. per min.			Oxygen used by liver in c.c. per gm. per min.
		Hepatic vein	Portal vein	Hepatic art.	
Exp. 5.	Before diversion ...	36·0	28·6	7·4	·018 c.c.
	Immediately after diversion	17·1	0	17·1	·018
	25 minutes after diversion	27·3	0	27·3	·030
Exp. 6.	Before diversion ...	45	20	25	·012
	25 minutes after diversion	28	0	28	·014

From the above table it will be clear that the oxygen taken in by the liver was not changed immediately by the cutting off of the portal blood. Indeed after 25 minutes supply of pure arterial blood the liver in Exp. 5 was taking in much more oxygen than previously. This, being as it is the result of a single experiment we do not wish to lay any stress upon it at the present time further than to make it clear that we have no reason from the experimental side to regard it with suspicion.

Experiments upon animals fed about 18 *hours previously.* In Table IV we give a general summary of the results which we have obtained on animals which have been fed the evening before our experiment. When this table is compared with Table III it will be clear that whereas the highest result given in that table for the metabolism of

TABLE IV. *Animals fed.*

	Portal organs		Liver	
Exp.	Weight	O_2 taken up per gram per min.	Weight	O_2 taken up per gram per min.
8	162	·011	73	·034 ·045
9	132	·018	80	·050
10	148	·018	111	·030
11	120	·013 ·015	64	·034 ·029
12	141	·016	71	·024
Average	140	·015	80	·035

the liver in the unfed animal is ·018 c.c. per gram per min., the lowest figure for the fed animal is ·024. From this value the figures range to ·050. Thus the lowest figure for the cat which has been fed the evening before is 50 % higher than the highest figure for the cat that had not been fed for 36 hours and the highest figure is almost 300 % higher. These results leave no room for doubt that the oxidations in the liver are demonstrably increased greatly as the result of a meal and that this increase lasts for at least 18 hours.

On the whole we have found greater difficulty in maintaining the fed animals in a satisfactory condition than we did in the case of the unfed ones. From the table given below it will be obvious that the amount of oxygen used by the liver in Exp. 9 must be regarded as a minimum rather than an actual value, though its value, ·05 c.c. per gram per min., is the highest we have obtained. In it the hepatic blood was entirely reduced. Practically the same might be said about the first period of Exp. 11 in which the oxygen used was ·034 c.c. per gram per min. were it not for the fact that in a subsequent period the oxygen used by the liver was not increased though the hepatic blood was particularly rich in oxygen.

The following table gives data for fed animals similar to those which we have already given for fasting ones, regarding the relative importance of the portal and hepatic supplies of oxygen.

	Oxygen in 1 c.c. of blood			Oxygen brought to liver, c.c. per min.		Oxygen used by liver, c.c. per min.
Exp.	Arterial	Portal vein	Hepatic vein	Portal vein	Hepatic art.	
9	·174	·0174	0	·28	3·53	4·0
11 (1)	·140	·032	·004	·58	1·56	2·17
(2)	·131	·039	·056	·78	3·67	1·92
12	·189	·094	·088	2·25	3·02	1·72

In the case of the fed animals the arterial supply plays an even more important rôle as regards oxygen than in the case of the fasting animals, this is so evident that it is unnecessary to make any analysis of the figures such as we did in the former case.

Comparison of the liver with other organs of the body. The lowest values obtained for the oxygen used per gram of liver per minute are considerably lower in the case of the resting organ than the corresponding data yielded by the salivary glands and the pancreas which have a "coefficient of oxidation" (Chauveau and Kaufmann) of about ·02 c.c. The highest figures yielded by the resting liver approach this value, and are about equal to what we regard as minimal values for the kidney.

The active livers in our experiments also had a lower coefficient than active submaxillary glands, pancreas or kidneys, but in making these comparisons it must be borne in mind that the degree of activity which can be induced in these organs by such methods as stimulation of the chorda tympani, injection of secretin or of certain diuretics respectively is probably much more nearly maximal than that induced in the liver of a cat by a meal of meat and milk 18 hours before the experiment, indeed in a future paper we hope to give an account of experiments which will support this statement.

SUMMARY.

1. The coefficient of oxidation for livers of cats which have been unfed for 36 hours is from ·005 to ·018 c.c. per gram per minute; for animals fed 18 hours before the experiment, ·024–·050 c.c.

2. The corresponding coefficients for the viscera drained by the portal vein taken together are ·008–·013 c.c. for the unfed and ·011–·018 c.c. for animals fed 18 hours previously.

3. The hepatic artery is the dominating source of oxygen supply to the liver especially in the case of the fed animals.

4. The amount of oxygen used does not appear to be governed by the blood supply if above a certain limit, either in the liver or in the intestines.

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