CIX. METABOLISM OF NORMAL AND TUMOUR TISSUE.

VIII. RESPIRATION IN FRUCTOSE AND IN SUGAR-FREE MEDIA.

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THE aim of the work presented in this series of publications is to determine the nature of the foodstuffs utilised by various types of surviving animal tissue and the proportions in which they are consumed. To this end, in Parts II and IV [Dickens and Šimer, 1930, 2; 1931, 2] the tissues were classified according to the magnitude of their respiratory quotients in glucose-containing media; but the complete interpretation of these quotients requires far more data than are at present available. For example, when the R.Q. approaches unity, preponderating carbohydrate oxidation may not be assumed, unless protein oxidation is known to be slight; for pure protein oxidation ending in ammonia production causes the R.Q. to approach unity. Again, lowered R.Q. is commonly regarded as an indication of fat oxidation, though direct proof of this with surviving tissue is lacking: here also protein oxidation would lead to uncertainty, for when the end-product is urea the R.Q. is about 0.8. Complete analysis of the R.Q. thus demands proof of the utilisation of the different foodstuffs and a study of the nature of the end-products. Work is proceeding with these ends in view, and we hope shortly to publish an account of ammonia and urea formation under our experimental conditions.

Evidence for the consumption of carbohydrate by a given tissue may be obtained in the absence of the extensive data required for the complete understanding of the R.Q. The interpretation of chemical estimations of sugar disappearance may be difficult, but disappearance of glycolysis under aerobic conditions, or prevention of ammonia formation by the presence of sugar suggests carbohydrate oxidation. Again, if the R.Q. and the oxygen uptake fall in the absence of sugar, carbohydrate oxidation may reasonably be inferred. In the present paper, by a systematic study of the oxidative metabolism of the various tissues in the absence of added substrate, we attempt to decide which tissues are able to oxidise glucose. In addition, we have studied the oxidation of fructose by these tissues. Fructose is of interest because as previously shown [Dickens and Greville, 1932, 1, 2] unsuspected differences in anaerobic lactic acid formation are revealed by the use of fructose as substrate; and further because the peculiar oxidation of fructose by brain led Loebel [1925] to the view that lactic acid is probably not an intermediate product in the complete oxidation of hexoses. It is therefore of peculiar interest to compare wherever possible the anaerobic fructolysis of the various tissues with their carbohydrate oxidation in the presence of fructose and to calculate the Meyerhof quotient where fructose is the substrate.

EXPERIMENTAL.

Methods.

Measurements were made by the methods of Dickens and Šimer in phosphate media [1930, 1] and in bicarbonate media [1931, 1]. These are referred to in the tables as P and B respectively. In addition, some measurements in bicarbonate were made by Warburg's two-vessel method [Warburg, 1924] (B* in the tables). The media were as previously described, but contained, in addition to Ca and K, magnesium chloride in 0.00087 molar concentration. Unless it is stated otherwise, in the phosphate experiments the tissue was washed for 5 to 10 minutes before the experiment by suspending it at room temperature in sugar-free phosphate Ringer solution through which a stream of oxygen was passed, and in the bicarbonate experiments the tissue was rinsed under the same conditions in sugar-free bicarbonate Ringer solution in a stream of oxygen containing 5 % CO_2 . For embryo and retina warmed Ringer solution was used; the latter tissue was merely rinsed in several changes of oxygenated Ringer solution, and the preparation and determinations were carried out in a dim red light. Anaerobic measurements of glycolysis were all made by Warburg's method in bicarbonate-containing Ringer solutions. The tissues used were from fed animals.

Results.

The results are given in Tables II, III and IV for adult normal, embryonic and tumour tissues respectively. For the sake of simplicity the data are summarised in Table I, where for several tissues the mean values from the other tables are given, but in other cases, when the number of observations is less, rounded figures are inserted. In deriving the figures in this table for respiration in glucose and for the anaerobic glycolysis, consideration has been given to results already published in this series.

Respiration with and without glucose. The nervous tissues, brain cortex and retina, possessing a R.Q. of unity, are markedly dependent on the presence of glucose both for their respiration and for their anaerobic glycolysis. It is interesting to note that in our experiments both with rat and with rabbit brains a R.Q. of about 1 is maintained with the greatly diminished oxygen uptake in the absence of added substrate. It seems unlikely that when deprived of hexose the brain can change its type of metabolism to that of fat oxidation. Possibly some of the oxygen uptake under these conditions is due to protein oxidation [Loebel, 1925] although alanine is neither oxidised [Loebel, 1925] nor deaminated [Krebs, 1932] by this tissue. It will be seen that for the maintenance of its respiration retina is even more dependent than brain on its supply of sugar (Fig. 1); here, however, the low respiration and the small amount of retina available make the determination of R.Q. in the absence of substrate almost impracticable.

In contrast to the nervous tissues, kidney, liver and spleen suffer relatively little fall in respiration when deprived of glucose [compare Meyerhof and Lohmann, 1926, 1]. In kidney, the respiration is fairly constant in the presence of glucose, but falls off appreciably with time in its absence (Fig. 3). Q_{O_2} is remarkably constant in either medium from one experiment to the next (Table II), and the mean values agree remarkably well with those given by Meyerhof and Lohmann. The R.Q. is definitely raised by the presence of glucose. In spleen, although Q_{O_2} is little increased by sugar, evidence of glucose consumption is provided by the raised R.Q. In liver, the R.Q. and Q_{O_2} appear to be independent

Table I. *Summarised results.*

Tissue	Sugar	R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$
<i>Adult normal tissues:</i>					
Brain cortex (rat)	Glucose	1.01	12.8	1.5	11.5
	Fructose	0.99	9.7	0.3	1
	None	1.00	3.9	-0.4	0.5
Brain cortex (rabbit)	Glucose	—	7.5	1.5	12
	Fructose	1.01	8.5	0.5	3
	None	1.02	5	-1	—
Retina (rat)	Glucose	1.00	22	22.5	64
	Fructose	1.01	16	0.3	3.5
	None	—	4	—	3.5
Testis (rat)	Glucose	0.88	11.2	7.2	12
	Fructose	0.82	9.3	2.7	4
	None	0.6-0.8	5.2	1.9	2
Kidney (rat)	Glucose	0.85	20.6	0	6
	Fructose	0.90	25.5	0.2	2
	None	0.80	17.6	-1	1
Spleen (rat)	Glucose	0.91	11	5	8
	Fructose	0.83	11	4	3
	None	0.83	9	0.5	3
Liver (rat)	Glucose	0.68	7	3	1.5
	Fructose	0.78	7.5	3	4
	None	0.66	7.8	2	1.5
<i>Embryonic tissues:</i>					
Chick embryo (5 day)	Glucose	1.00	10	2	15
	Fructose	0.92	9.3	0	1.5
	None	0.89	8.3	0	1.5
Rat embryo (13-14 day)	Glucose	1.00	11	—	12
	Fructose	0.98	11.5	0	3
	None	0.7-1	9	0.5	2
Rabbit embryo	Glucose	1.00	8.5	—	13
	Fructose	1.00	7	—	2
	None	1.00	6.5	—	—
Rat yolk-sac	Glucose	1.00	11	2	20
	Fructose	0.98	10	1	15
	None	0.93	11.5	0	2
<i>Tumour tissue:</i>					
Jensen rat sarcoma	*Glucose	0.84	9.6	11	31
	*Fructose	0.84	11.1	7	13
	*None	0.80	10.0	0	2
	†Glucose	—	11	20	30
	†Fructose	—	10	7	10

* Methods of Dickens and Šimer [1930, 1; 1931, 1].

† Method of Warburg [1924].

of glucose, at least in the fed animals used in our experiments. The portion of the oxidation covered by carbohydrate in liver is presumably to be referred to the oxidation of the glycogen reserves [Takane, 1926]: by a preliminary aerobicosis these may be induced to yield a large anaerobic glycolysis, the magnitude of which is quite unaffected by the presence of glucose [Rosenthal, 1929; 1931]. There is, therefore, no evidence at present that glucose can be utilised either aerobically or anaerobically by isolated post-adsorptive liver tissue.

Intermediate between these tissues and the nervous tissues, testis shows a large decrease in respiration when deprived of glucose (Fig. 2), the R.Q. at the same time falling by a variable amount. It is assumed from the R.Q. that these four tissues, liver, kidney, spleen and testis, possess a mixed fat-carbohydrate metabolism. It may further be assumed that liver, spleen and kidney have

Table II. *Adult normal tissues.*

Exp. No.	†Medium	Time hrs.	Glucose				Fructose				No addition			
			R.Q.	Q _{O₂}	Q _M ^{O₂}	Q _M ^{N₂}	R.Q.	Q _{O₂}	Q _M ^{O₂}	Q _M ^{N₂}	R.Q.	Q _{O₂}	Q _M ^{O₂}	Q _M ^{N₂}
Brain cortex (rat):														
1	P	2	1.01	12.8	—	—	1.03	10.9	—	—	1.04	4.0	—	—
2	B	3	1.00	12.8	1.9	—	1.01	9.0	0.5	—	—	—	—	—
3	B	3	—	—	—	—	0.97	9.3	0.0	—	—	—	—	—
4	B	2½	1.01	12.5	1.0	—	—	—	—	—	0.96	3.7	-0.4	—
											0.96	3.7	-0.4	—
Brain cortex (rabbit):														
5	B*	3	—	7.6	1.5	12.0	—	9.2	0.6	3.2	—	—	—	—
6	B	3	—	—	—	—	1.01	7.9	0.7	3.3	—	—	—	—
7	B	2½	—	—	—	—	—	—	—	—	1.02	4.8	-1.2	—
Retina (rat):														
8	P	5	1.00	24.4	—	—	1.02	14.6	—	—	—	4.5	—	—
							0.99	16.2	—	—	—	3.0	—	—
9	B	5	—	20.3	22.5	—	—	17.2	0.3	—	—	—	—	—
10	B	1	—	—	—	64.0	—	—	—	3.5	—	—	—	3.5
Rat testis:														
11	P	3	—	—	—	—	0.83	8.8	—	—	0.57	5.5	—	—
	B	3	0.87	10.2	6.0	—	—	—	—	—	0.57	4.6	2.2	—
12	P	3	0.89	12.6	—	—	0.87	9.0	—	—	0.82	6.2	—	—
	B	3	0.88	10.2	6.8	—	0.82	8.5	2.1	—	0.82	4.8	1.8	—
13	B	2½	0.87	13.0	9.0	11.8	0.76	11.6	3.8	4.0	—	—	—	1.6
14	B	3	0.88	10.2	6.8	—	0.82	8.5	2.1	—	0.82	4.8	1.8	—
Mean			0.88	11.2	7.2	11.8	0.82	9.3	2.7	4.0	—	5.2	1.9	—
Rat kidney:														
15	P	2	0.82	21.5	—	3.5	0.92	24.0	—	2.4	0.80	16.5	—	1.3
16	P	2½	0.85	21.9	—	4.6	0.92	26.1	—	2.5	0.80	15.8	—	2.0
17	B	2½	0.85	18.0	0.0	8.0	0.88	25.1	0.4	0.7	0.81	17.8	-1.3	0.2
18	B	3	0.84	19.3	0.0	—	0.91	27.6	0.1	—	0.80	19.0	-1.1	—
18 A	B	3	0.87	22.2	2.0	7.6	0.89	24.9	0.2	2.8	0.79	18.9	-0.6	1.3
Mean			0.85	20.6	—	—	0.90	25.5	—	—	0.80	17.6	—	—
Rat spleen:														
19	B	3	0.92	10.8	4.8	—	0.81	10.5	3.6	—	0.83	8.9	0.3	—
20	B	3	0.89	11.0	5.3	—	0.85	12.3	4.0	5.6	0.83	9.0	0.6	4.4
Rat liver:														
21	P	3	0.69	6.7	—	—	0.77	7.0	—	—	0.71	7.1	—	—
22	B	4	—	—	—	—	0.77	7.4	3.5	4.0	0.70	7.8	2.0	1.4
							0.79	8.5	2.9	—	—	—	—	—
23	B	3	0.67	7.3	2.8	1.7	0.78	7.0	3.0	3.6	0.58	8.6	2.1	1.5

† For aerobic experiments. P=Phosphate. R.Q. determination by method of Dickens and Šimer (1930, 1].
B=Bicarbonate: method of Dickens and Šimer [1931, 1]. B*=Bicarbonate: method of Warburg [1924].

a foodstuff supply not available to testis: with liver this is definitely glycogen, but of its nature in spleen and kidney we cannot at present be sure.

The embryonic tissues studied (chick, rat and rabbit embryos; rat and rabbit yolk-sac; ferret chorion) have, like the nervous tissues, a high anaerobic glycolysis coupled with a relatively small autoglycolysis and resemble them further in possessing a R.Q. of unity in glucose. The strong falling off in respiration in the absence of glucose which might be expected by analogy does not, however, occur. Although deprivation of glucose usually produces a marked fall in R.Q., the decrease in oxygen consumption is either small, or, as with the rat yolk-sac, does not occur at all. How much of the respiration in absence of sugar is due to oxidation of preformed lactate in the tissue is uncertain. However, with the exception of the experiments marked (a) in Table III, the washing of the tissue before the experiment was at least as good as that of brain and testis, where the respiration falls heavily in the absence of substrate. In the two experiments marked (b), the tissue was shaken in the bath in phosphate Ringer saturated with oxygen for 10 minutes before the experiment, and this efficient washing

Table III. *Embryonic tissues.*

Exp. No.	Medium	Time hrs.	Glucose				Fructose				No addition			
			R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$	R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$	R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$
Chick embryo (5 days' incubation):														
34 ^a	P	4	1.02	10.3	—	—	0.96	9.7	—	—	0.94	8.2	—	—
35 ^b	P	3	—	—	—	—	0.96	9.3	—	—	0.87	9.2	—	—
36 ^b	P	4½	—	—	—	—	0.87	9.6	—	—	0.89	8.3	—	—
37 ^a	B	3½	1.02	9.1	2.4	—	0.89	8.5	0.0	—	0.87	7.5	0.0	—
38 ^a	B	4	—	—	—	—	0.94	8.1	-0.6	—	0.91	8.0	-0.7	—
39 ^a	B	4	—	—	—	—	0.85	10.4	0.4	—	0.84	8.7	0.3	—
Mean			[1.00]	—	—	—	0.92	9.3	—	—	0.89	8.3	—	—
Rat embryo (13-14 days):														
40 ^c	P	3	—	—	—	—	1.01	10.9	—	3.1	0.70	7.6	—	1.9
41 ^d	P	3	1.00	10.9	—	—	0.99	12.3	—	3.1	0.97	10.1	—	2.1
42 ^e	B	3	0.97	11.1	5.2	—	0.95	11.4	0.0	—	0.78	9.2	0.7	0.7
Rabbit embryo:														
43 ^f	P	3	1.00	8.6	—	13.3	1.00	7.1	—	1.8	1.00	6.4	—	—
Rat yolk-sac:														
44 ^g	P	1st hour	—	14.8	—	18.0	—	12.9	—	11.5	—	14.0	—	4.0
		2nd hour	—	12.9	—	17.0	—	11.9	—	9.0	—	12.9	—	1.0
		3rd hour	—	13.2	—	17.5	—	11.9	—	8.5	—	13.2	—	1.0
45 ^h	B	4	—	—	—	0.98	11.0	1.1	—	0.91	11.4	0.3	—	
46 ⁱ	B	4	1.04	12.0	2.3	—	—	—	—	0.94	11.8	-0.4	—	
										0.94	11.9	0.0	—	
47 ^g	B*	1	[1]	8.7	0.3	20.0	[1]	8.0	0.5	21.0	—	—	—	2.5
48	B	3	—	—	—	—	—	—	—	—	0.92	8.9	1.1	—
Rabbit yolk-sac (28 days):														
49	P	3	0.97	7.5	—	—	—	—	—	—	0.81	8.4	—	—
Ferret chorion (6 g. embryo):														
50	P	3	0.99	6.7	—	17.5	—	—	—	—	0.88	5.1	—	2.0

^a Rinsed in salt solution in dish.^b Well washed by shaking 10 mins. in Ringer solution.^c 5.3 mg. dry weight.^d 3.9 mg. dry weight.^e 6.8 mg. dry weight.^f 12.2 mg. dry weight.^g 20 day embryo.^h 19 day embryo.ⁱ 18 day embryo.

Fig. 1. Respiration of rat retina.

Fig. 2. Respiration of rat testis.

does not reduce the respiration in absence of sugar below the values obtained with the less efficient washing of the experiments (a). Further, the lactate consumption necessary to maintain this Q_{O_2} should be indicated by a large negative $Q_M^{O_2}$ which is certainly not observed. Taking the rat yolk-sac as example, we see from Exp. 44 that in the second and third hours the autoglycolysis would account for less than one-third of the respiration; the remainder, if due to lactate oxidation, would demand a negative $Q_M^{O_2}$ of about 3.

Table IV. *Tumour tissue: Jensen rat sarcoma.*

Exp. No.	Medium	Time hrs.	Glucose				Fructose				No addition			
			R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$	R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$	R.Q.	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$
24	P	2½	0.85	10.6	—	—	0.87	13.1	—	—	0.81	12.8	—	—
25	P	3	0.91	7.3	—	22	0.91	8.0	—	14.0	0.87	7.0	—	3.5
26	P	3	0.85	6.7	—	—	0.85	9.6	—	5.9	0.78	8.0	—	—
27	B	3	0.86	11.3	9.0	33	0.80	12.0	7.2	17.0	0.82	10.7	-0.7	1.5
28	B	3	0.80	11.2	11.2	40	0.88	10.6	6.4	15.1	—	—	—	—
29	B	2½	0.83	9.3	9.3	—	—	—	—	—	0.73	9.1	0.7	—
30	B	3	—	—	—	—	0.81	14.1	5.6	—	0.78	12.6	0.1	—
31	B	2½	0.77	11.1	11.8	27.5	0.77	10.8	10.2	10.8	—	—	—	1.7
							0.76	10.1	8.9	—	—	—	—	—
							0.74	11.0	11.2	—	—	—	—	—
Mean			0.84	9.6	—	—	0.84	11.1	—	—	0.80	10.0	—	—
32	B*	2	[0.78]	10.3	25.4	32.0	[0.78]	11.8	8.3	11.5	—	—	—	—
33	B*	2	[0.8]	11.7	15.4	28.0	[0.8]	8.7	6.0	9.3	—	—	—	3.0

Fig. 3. Respiration of rat kidney.

As acid consumption of such magnitude was nowhere observed in these experiments, we may assume that the maintenance of respiration in the absence of sugar is not due to consumption of preformed lactate. It is also unlikely that it is largely due to protein oxidation leading to urea or ammonia. From experiments to be reported later, it appears that the urea formation by the 5 day chick embryo and the late rat yolk-sac in the absence of sugar is negligible. In the former case ammonia was formed, which, if due to pure protein oxidation, might account in some embryos for rather less than half the respiration: in the latter, protein oxidation leading to ammonia is apparently inconsiderable. We therefore consider that the rat yolk-sac and the chick and rat embryos possess reserve foodstuffs of whose nature we are ignorant.

The Jensen rat sarcoma shows a surprisingly small fall in R.Q. when it is deprived of glucose. Crabtree [1929] found that the respiration of the Jensen rat sarcoma under experimental conditions different from ours was lower in the presence of glucose than in its absence, but our experiments give little support to this finding.

Oxidative metabolism of fructose. As fructose undergoes autoxidation in strong neutral phosphate solutions [Warburg and Yabusoe, 1924], a control experiment was performed on the oxygen uptake of the fructose-containing Ringer solutions used in the method for the determination of R.Q. in phosphate media. The pressure change in 3 hours lay within the error of experiment.

It was shown by Loebel [1925] that the rat brain cortex, although unable to convert fructose into lactic acid, could nevertheless oxidise it almost as readily as glucose, and with a R.Q. of unity. This finding is fully confirmed by the results shown in Table II, not only in phosphate media, but also in bicarbonate media where in our experiments the aerobic and anaerobic measurements were made under almost identical conditions of p_H and bicarbonate content. It is interesting to note the effect on the value of the Meyerhof quotient. In Exp. 5 with rabbit brain, the respiration experiment was performed by Warburg's two-vessel method, and the initial p_H in both aerobic and anaerobic experiments was 7.5. The calculation of the Meyerhof quotient for glucose and fructose is given below:

Sugar	Hour	Q_{O_2}	$Q_M^{O_2}$	$Q_M^{N_2}$	$Q_M^{N_2} - Q_M^{O_2}$	Meyerhof quotient
Fructose	1	9.2	1.4	6.3	4.9	0.53
	2	9.6	0.5	1.7	1.2	0.13
	3	8.7	0.1	1.5	1.4	0.16
Glucose	1	8.2	2.8	16.0	13.2	1.6
	2	7.3	0.9	10.6	9.7	1.3
	3	7.2	0.7	9.3	8.6	1.2

It appears that the view that fructose is directly oxidised by brain without conversion into lactic acid is correct. If we add to the respiration in absence of sugar the amount of respiration which could be supported by the difference between the fructolysis and the autoglycolysis, then both in Loebel's experiments and in ours the resulting value of Q_{O_2} falls far short of the Q_{O_2} attained in fructose. Again, if the anaerobic fructolysis of brain could be raised, like the autoglycolysis of liver, by a preliminary aerobiosis [Rosenthal and Lasnitzki, 1928], it might be that aerobic conditions would render brain tissue capable of converting fructose into lactic acid preparatory to its oxidation. We have, however, found that a 30 minutes' preliminary aerobiosis produced no increase in the anaerobic fructolysis of brain. We may therefore conclude that fructose is indeed directly oxidised by brain cortex.

Another clear case of direct oxidation of fructose is provided by retina (Fig. 1). This tissue, which resembles brain cortex particularly in its dependence on sugar for the maintenance of its respiration and also in its inability to convert fructose into lactic acid, is now seen to resemble brain cortex further in its ability to oxidise this sugar directly (see Table II). Meyerhof and Lohmann [1926, 1] showed that the aerobic acid production by brain cortex in glucose disappeared when fructose was the substrate: this is seen more dramatically in retina (Table II), where the large aerobic glycolysis characteristic of this tissue is replaced by a negligible fructolysis.

Testis shows a slight tendency to convert fructose into lactic acid [Dickens and Greville, 1932, 2]. The strong falling off in respiration of this tissue in the

absence of sugar is prevented by fructose (Fig. 2), although R.Q. and Q_{O_2} do not reach the values they attain in glucose. Liver, as shown by Rosenthal, possesses a variable but often strong fructolysis. It is therefore not surprising that the R.Q. is considerably raised by this sugar. It is remarkable, however, that the respiration is not influenced; for it may be noted that a large increase in Q_{O_2} is produced by replacing glucose by lactate in pre-absorptive liver [Meyerhof and Lohmann, 1926, 2] and this effect is still definite in post-absorptive liver [Dickens and Šimer, 1930, 2].

The respiratory data in the case of spleen do not show whether fructose is utilised. Since, however, the presence of fructose reduces the aerobic ammonia production by this tissue, as will be shown in a later publication, it is probable that fructose is oxidised to some extent.

Kidney provides an interesting case. Meyerhof and Lohmann [1926, 1] showed that fructose increased the respiration above the value in glucose. The increase shown in Table I agrees well with that found by these authors. We show that the R.Q. also is raised above the value in glucose. Since the anaerobic fructolysis of kidney is only one-third of the glucolysis, this would appear to be a case of direct oxidation. However, caution is necessary in this case. Rosenthal and Lasnitzki [1928] found that the anaerobic glycolysis could be accelerated about 50 % by preliminary aerobiosis. We have observed an "extra-fermentation" of the same order both in glucose and fructose. It is therefore not impossible that under optimum aerobic conditions kidney may be capable of forming far greater quantities of lactic acid than are shown by the anaerobic figures given in the tables. Nevertheless, it is difficult to explain why the kidney oxidises fructose more readily than glucose.

The aerobic utilisation of fructose by the various embryonic tissues is of interest in view of the remarkably varied power of converting this sugar into lactic acid which these tissues possess [Dickens and Greville, 1932, 1]. The rat yolk-sac has an anaerobic fructolysis approaching its glucolysis. The R.Q. is raised to unity by fructose, whilst Q_{O_2} is practically equal to that in glucose and in sugar-free solutions, and the aerobic fructolysis is small. Thus with fructose as well as glucose, the respiration is capable of removing almost all the glycolysis. The embryo does not convert fructose into lactic acid, and it is of interest to see whether it can oxidise it. The manometric data for the chick embryo do not give any definite information on this point, but the results of ammonia estimations suggest that some oxidation may occur. For the rat embryo the R.Q. measurements provide definite evidence of aerobic utilisation of fructose. Whilst the results with embryo are not striking, they at least show that fructose can diffuse into the tissue, and that the failure of the embryo to fructolyse is not due to an impermeability towards this sugar.

The R.Q. of the Jensen rat sarcoma is raised by fructose to the value attained in glucose. *d*-Lactate produces an increase in R.Q. above the value in sugar-free Ringer solution of the same order, as is shown by the following experiment:

	R.Q.	Q_{O_2}	$Q_M^{O_2}$
No addition	0.76	- 10.9	0.0
0.2 % <i>d</i> -lactate	0.79	- 12.7	- 0.7

For the better study of the aerobic acid production in this tissue, Exps. 32 and 33 were performed by Warburg's method, as the Dickens-Šimer method for the determination of respiratory quotient in bicarbonate media gives much lower values of $Q_M^{O_2}$ with Jensen rat sarcoma than does the two-vessel method.

It will be seen that there is a considerable aerobic fructolysis: the reduction by oxygen of the acid production in fructose is remarkably small. Both fructose and glucose therefore seem to be capable of saturating the tissue with lactic acid, supplying it under aerobic conditions faster than it can be utilised. The lactate oxidation of Jensen rat sarcoma is insufficient; and there is no evidence that fructose can be directly oxidised by this tissue. The power to oxidise carbohydrates is clearly small, but we cannot as yet state what fraction of the total oxygen uptake is to be referred to carbohydrate oxidation. The failure of the respiration to fall off in the absence of sugar increases the difficulty in determining this fraction; but it is hoped that a study of the nitrogenous end-products will assist us to assess its magnitude.

SUMMARY.

1. The oxidative metabolism of surviving adult normal tissues (brain cortex, retina, testis, liver, kidney, spleen), embryonic tissues (rat yolk-sac, chick and mammalian embryos) and tumour tissue (Jensen rat sarcoma) has been studied in the absence of sugar and compared with that in the presence of glucose. Tissues of fed animals were used.

2. The nervous tissues (brain, retina) suffer a large fall in respiration when deprived of glucose. Kidney and spleen are less affected, but testis shows a marked dependence on the supply of sugar. As a result of the experiments, it seems probable that brain, retina, testis, kidney and spleen all oxidise glucose though to differing extents; but there is no evidence that the oxidative metabolism of post-adsorptive liver is affected by glucose.

3. The respiration of the embryonic tissues studied falls very little when they are deprived of glucose. They appear to contain reserve foodstuffs of whose nature we are ignorant.

4. The respiration of Jensen rat sarcoma is not decreased in the absence of glucose: the R.Q. falls slightly.

5. The oxidative metabolism of the same adult normal, embryonic and tumour tissues has been studied with fructose as substrate. It appears probable that all these tissues oxidise this sugar to a greater or less extent. Brain and retina oxidise it strongly, with a R.Q. of unity, probably without intermediate conversion into lactic acid. The R.Q. of testis, kidney and liver is raised by fructose above the value in the absence of sugar. Rat embryo and yolk-sac have a R.Q. of approximately 1 in its presence.

6. Jensen rat sarcoma has the same R.Q. in glucose and in fructose, and with this tissue in fructose as in glucose strong acid production persists in the presence of oxygen.

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