CLXXXIV. THE METABOLISM OF NORMAL
AND TUMOUR TISSUE.
VII. THE ANAEROBIC CONVERSION OF FRUCTOSE
INTO LACTIC ACID BY TUMOUR AND
ADULT NORMAL TISSUES.

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It was shown in Part VI of this series [Dickens and Greville, 1932, 1] that whilst the various embryonic tissues all readily convert glucose into lactic acid, they differ in their behaviour towards fructose, their rate of attack on this sugar varying from zero to a value equal to that on glucose. The ability to convert fructose into lactic acid is thus not by any means an invariable property of rapidly growing normal tissues; and the varying behaviour of the different tissues towards fructose renders this sugar a valuable agent for the study of their carbohydrate metabolism. In the present communication we describe the anaerobic attack on fructose of the adult normal tissues on the one hand, and of the rapidly growing malignant tissues on the other.

Experiments were made on slices of surviving tissue by the method of Warburg; full details of technique have been given in Part VI. The terms *glycolysis*, *glucolysis*, *fructolysis*, *autoglycolysis* and *relative fructolysis*, which were defined and discussed in that paper, are used in the present description.

NORMAL TISSUES.

All measurements were made on the tissues of fed albino rats. The tissues are arranged according to the extent of their attack on glucose.

Liver.

Isolated adult liver tissue is remarkable in that it does not form lactic acid from glucose, the presence of which, even in high concentrations, has no appreciable effect on the anaerobic glycolysis; moreover, glucose does not affect the extra-fermentation caused by preliminary aerobiosis [Rosenthal, 1929; 1931]. On the other hand, it is well known that the liver may readily attack fructose [Oppenheimer, 1912; Rosenthal, 1930, 1, 2; 1931]. Rosenthal has made a thorough study of the anaerobic conversion of fructose into lactic acid by rat-liver; this only occurs in fed animals, in which it varies greatly

from animal to animal under identical external conditions, but is greatest on the whole in the summer months. On increasing the fructose concentration the fructolysis rises rapidly, reaching a maximum at about 1.6 %; and the rapid fall with time of fructolysis, which occurs during the first hour with liver in 0.2 % fructose, is prevented when the concentration is raised above 0.4 %. These latter observations we have confirmed. Thus for the demonstration of fructolysis in liver, fed animals in the summer months must be used, the fructose concentration may have to be raised, and the livers of several animals should be tested. These conditions have been borne in mind when studying the tissues described below, but in these we have found no evidence of the seasonal variation seen in liver.

Intermediate tissues.

The tissues of this group convert glucose into lactic acid, but not as readily as the nervous tissues.

Kidney usually attacks fructose slightly, as will be seen from Table I, in which the relative fructolysis for the second hour is given in the last column. Increase of fructose concentration has little, if any, effect. With submaxillary gland and spleen the anaerobic attack on fructose is negligible, but testis attacks the sugar slightly (Table I).

Table I. *Adult normal tissues* $Q_M^{N_2}$.

Date	Glucolysis		Fructolysis		Autoglycolysis		Relative fructolysis (2nd hr.) %
	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	
Kidney:							
27. i. 32	8.1	—	2.7	—	1.7	—	(16)
7. vii. 32	5.5	3.4	4.9	1.3	4.0	1.2	5
11. vii. 32	3.8	3.3	(0.2 %) 3.25	1.55	1.75	0.9	27
			(0.7 %) 3.4	1.6	—	—	29
			(1.5 %) 3.85	1.8	—	—	38
12. vii. 32	5.7	3.4	3.75	1.75	2.3	1.2	25
13. vii. 32	4.8	4.6	3.4	2.0	2.6	1.4	19
Submaxillary:							
7. vii. 32	8.3	6.9	2.6	0.6	3.7	0.5	0
12. vii. 32	11.7	9.9	2.3	1.1	2.7	1.0	0
Spleen:							
23. i. 32	—	—	1.6	—	0.9	—	—
7. vii. 32	7.4	6.7	3.3	1.8	2.7	1.5	7
12. vii. 32	12.0	11.4	2.2	1.8	2.3	1.5	3
Testis:							
23. i. 32	—	—	2.8	—	0.6	—	—
29. ii. 32	13.0	11.0	4.5	4.0	2.0	1.0	30
7. vii. 32	7.5	7.5	3.0	2.8	2.2	1.8	18
12. vii. 32	9.3	8.7	2.9	3.1	2.1	2.3	13
Brain:							
14. i. 32	13.8	9.2	1.1	0.7	1.0	0.1	7
			1.1	0.7	0.8	0.1	7
13. vii. 32	12.5	9.6	2.4	0.6	—	—	—
Retina:							
29. iii. 32	64.0	—	3.0	—	3.5	—	0
30. iii. 32	—	—	4.0	—	—	—	—

Nervous tissues.

These tissues show a high glucolysis, but they lack the power to convert fructose into lactic acid. This has already been shown for nerve [Gerard and Meyerhof, 1927] and brain [Loebel, 1925], with whose observations the figures for both winter and summer brain in Table I agree well. Retina does not show the slightest anaerobic attack on fructose, in spite of its great attack on glucose (Table I).

TUMOUR TISSUES.

Tumours of the rat, mouse, rabbit and fowl have been used in our experiments.

Rat tumours. Warburg *et al.* [1924] report on an anaerobic fructolysis of $Q_M^{N_2}$ 3.3 with the Flexner-Jobling carcinoma, the glucolysis being 23.9. Rosenthal [1930, 2] has made a number of observations with the Jensen rat sarcoma. He finds an anaerobic fructolysis equal to about one-sixth of the glucolysis, but some 45 minutes after the vessels are put in the thermostat the fructolysis rises, reaching a steady value about 30 minutes later. The rise amounts on an average to 60 %, varying between 0 and 135 %. We have confirmed the existence of this phenomenon in the Jensen sarcoma (see Fig. 1 (a)): as an

Fig. 1 (a). Jensen rat sarcoma.

Fig. 1 (b). Mill Hill fibro-sarcoma I.

G, Glucolysis; F, fructolysis; A, autoglycolysis.

average of 12 experiments on different tumours $Q_M^{N_2}$ in the period before the rise was 8.2, and after the rise the average steady value was 12.2. Whilst the latter value is about 30 % higher than Rosenthal's average, the average increase of 49 % found by us is in fair agreement with his figure. Since a sudden increase in the rate of acid production in manometric experiments

may sometimes be due to a growth of contaminating bacteria, and since, when asepsis was not observed in the preparation of the tissue, the fructose solutions after removal from the vessels were almost invariably found to be contaminated with *B. welchii*, experiments on two tumours were carried out with aseptic precautions, in which sterility after the experiment was proved by the complete absence of growth overnight in anaerobic tubes. In both experiments an increase in the fructolysis occurred 50 minutes after the vessels were put in the bath, the increases being 30 and 36 %. As these are quite normal values, it appears that the usual contamination has no effect in these 3-hour experiments. Some simultaneous values of the glucolysis, fructolysis and autoglycolysis of Jensen rat sarcomas are given in Table II, the relative fructolysis for the second hour being given in the last column.

Table II. *Tumour tissues* $Q_M^{N_2}$.

Date	Glucolysis		Fructolysis		Autoglycolysis		Relative fructolysis (2nd hr.) %
	1st hr.	2nd hr.	1st hr.	2nd hr.	1st hr.	2nd hr.	
Jensen rat sarcoma:							
15. ii. 32	26.0	23.0	8.0	12.0	3.0	2.0	48
3. iii. 32	33.0	23.0	8.9	10.0	3.8	1.7	39
4. iv. 32	36.0	31.0	9.8	10.2	6.7	2.2	28
5. iv. 32	30.0	24.5	9.1	9.5	2.5	1.7	35
			10.4	10.8	—	—	
			8.0	8.7	—	—	
30. vi. 32	31.0	27.0	8.9	12.7	2.6	2.3	42
26. vii. 32	36.5	34.0	11.0	15.5	3.1	2.0	42
Mean values	32.1	27.1	9.3	11.2	3.6	2.0	39
Mouse carcinoma 63:							
25. vii. 32	12.8	11.2	1.9	0.6	4.9	1.1	0
26. vii. 32	14.4	12.8	2.8	1.2	3.2	1.4	0
			(0.6 %) 4.8	2.4	—	—	9
Mouse glycogen carcinoma 113:							
25. vii. 32	24.7	24.3	2.5	1.3	2.0	0.7	3
	17.8	17.4	2.3	1.3	3.1	1.2	0
26. vii. 32	7.6	7.6	1.4	0.7	1.1	0.4	4
			(0.6 %) 3.8	1.0	—	—	8
Mouse sarcoma 3187:							
25. vii. 32	29.5	25.5	4.0	1.2	3.0	1.2	0
26. vii. 32	38.0	33.0	7.5	2.5	4.7	0.8	5
			3.7	1.3	—	—	2
Brown-Pearce tumour:							
7. iv. 32	16.5	—	2.0	—	1.8	—	(0)
18. iii. 32	10.5	9.0	2.8	1.1	2.2	1.4	0
			3.9	1.7	—	—	—
Rous chicken sarcoma:							
24. ii. 32	21.0	19.0	14.5	9.5	8.0	1.5	46
22. iii. 32	—	—	7.5	5.5	3.7	1.1	—
			5.4	3.6	—	—	—
31. iii. 32	53.0	41.0	10.0	4.0	4.0	0.5	9
Mill Hill fowl fibro-sarcoma No. 1:							
19. iii. 32	20.0	18.0	8.5	6.5	2.0	1.0	32
			9.0	6.5	—	—	32
21. iii. 32	34.0	32.0	10.5	9.5	1.0	0.5	29
			10.5	9.5	—	—	29
15. vii. 32	33.5	27.5	12.9	10.1	4.0	2.1	32
	41.2	—	17.3	—	—	—	—

Mouse tumours. Simultaneous measurements of the glucolysis, fructolysis and autoglycolysis of three different strains of mouse tumour are given in Table II. There is a great variability in metabolism of different mouse tumours of the same strain [Crabtree, 1929] which is reflected in the glucolysis figures given by us. It will be seen that none of the three mouse tumours attacks fructose anaerobically, even when the fructose concentration is raised to 0.6 %, for the differences between the fructolysis and autoglycolysis figures are in all cases of the same order of magnitude as the differences that we should expect to find between the autoglycolysis figures for different slices of the same tumour. It is interesting to note that the glycogen carcinoma does not fructolyse, for the two adult normal tissues which have large glycogen stores, namely muscle and liver, are the only ones which readily convert fructose into lactic acid, and it might have been supposed that some connection exists between fructolysis and glycogen-storage.

Rabbit tumour. Fructose is not converted into lactic acid by the Brown-Pearce rabbit tumour (Table II).

Fowl tumours. The Rous sarcoma provides very unsuitable material for metabolism experiments, as the material is heterogeneous and the recovery at the end of the experiment is difficult [*cf.* Crabtree, 1928]. It seems probable, however, from the figures in Table II, that this tumour can attack fructose anaerobically. Much better material is provided by the Mill Hill fowl fibrosarcoma No. 1, which shows a steady anaerobic fructolysis for at least 3 hours (Fig. 1 (*b*)). We have obtained no evidence that the spontaneous increase of fructolysis, which is observed with the Jensen sarcoma, occurs also in the Mill Hill tumour, even though the glucolysis of the two tumours is about the same, and the steady fructolysis of the Mill Hill tumour is of the same order of magnitude as the final steady fructolysis of the Jensen sarcoma. The relative fructolysis of the Mill Hill tumour in the second hour is about 30 %, thus differing little from that of the Jensen sarcoma.

The lactic acid formed by the Mill Hill tumour was estimated by Clausen's method, in the way previously described [Dickens and Greville, 1932, 1]. The results show the acid production in fructose to be a pure lactic acid fermentation. For example, in one experiment the preformed and total quantities of lactic acid estimated chemically were 0.22 and 1.07 mg. respectively, so that the lactic acid formed in the experimental period of 180 minutes was 0.85 mg. The simultaneous manometric readings gave 0.87 mg. of lactic acid.

Summarising the results obtained with tumours, we see that the ability to fructolyse is not possessed by all tumours, and that the different types of tumour—sarcoma and carcinoma alike—show great differences in their behaviour towards fructose.

FACTORS INFLUENCING FRUCTOLYSIS.

The effects of the addition of sodium fluoride, and of alterations of the fructose concentration, upon the anaerobic fructolysis of Jensen rat sarcoma have been studied, in order to obtain evidence as to whether the conversion of fructose into lactic acid is a similar process to the conversion of glucose into lactic acid by this tumour.

Effect of sodium fluoride. As the anaerobic fructolysis increases spontaneously in the first hour of the experiment, all measurements were made in the second hour, the fluoride being added after the vessels had been one hour in the thermostat and the spontaneous increases had occurred. Since it was necessary to use calcium-free Ringer solution, however, these increases were somewhat masked by the slight falling off in $Q_M^{N_2}$ which occurs in a prolonged anaerobiosis in the absence of calcium ions. The effect of fluoride on the second-hour glucolysis of the same tissue was simultaneously determined in the same way. The inhibitions produced by four different fluoride concentrations are shown in Fig. 2, in which a curve showing the effect of fluoride on the glucolysis of rat testis in the first hour [Dickens and Šimer, 1929] is given for comparison.

Fig. 2.

- Fig. 2. (1) Jensen rat sarcoma in glucose (2nd hour).
 (2) Jensen rat sarcoma in fructose (2nd hour).
 (3) Testis in glucose (1st hour).

Fig. 3.

- Fig. 3. (1) Jensen rat sarcoma in glucose.
 (2) Jensen rat sarcoma in fructose.
 (3) Rat liver in fructose [Rosenthal, 1931].

It appears from the observations of Dickens and Šimer [1929; 1930] that in the tissues examined the sensitiveness of the anaerobic glucolysis to fluoride runs roughly parallel with the magnitude of the anaerobic glucolysis in the

absence of inhibitor. The concentration of sodium fluoride necessary to produce 50 % inhibition of glycolysis for various tissues is given below together with the uninhibited glycolysis measured under the same experimental conditions; and it will be seen that the effect of fluoride on the anaerobic fructolysis of Jensen rat sarcoma in the second hour fits quite normally into the series. The effect of fluoride therefore does not suggest that in its conversion into lactic acid by the Jensen tumour, fructose proceeds by a route very different from that pursued by glucose.

Tissue	Substrate	Hour of exp.	$Q_M^{N_2}$	Concentration of NaF causing 50 % inhibition (mM)
Retina	Glucose	1st	60	<1
Jensen sarcoma	"	1st	22	1.3
Jensen sarcoma	"	2nd	21	2.0
*Chick embryo (4th day)	"	1st	17	6.0
Testis	"	1st	7.3	6.0
Jensen sarcoma	Fructose	2nd	6.7	9.0
Kidney	Glucose	1st	3	10.0

* Dickens and Greville (hitherto unpublished observation).

Fructose concentration. The anaerobic glycolysis of Jensen rat sarcoma in the second hour in glucose and in fructose was measured in Ringer solutions of different sugar concentrations, and the results of typical experiments are shown in Fig. 3. The velocity-sugar concentration curve for glucose agrees well with that given for Flexner-Jobling rat carcinoma by Warburg *et al.* [1924], and it will be seen that the glucose and fructose curves are similar in shape. In both cases the glycolysis does not increase much when the sugar concentration is raised above 0.2 %, and in both cases the substrate concentration at which half the limiting velocity is reached lies near 0.1 %. A curve showing the influence of fructose concentration on the anaerobic fructolysis of rat-liver in the second hour is also given for the sake of comparison in Fig. 3, the figures being taken from Rosenthal [1931]. The form of this curve is quite different from those of the Jensen rat sarcoma; the possible significance of this will be discussed later.

Spontaneous increase in fructolysis. We have made some observations on the occurrence of the spontaneous increase in fructolysis which happens with Jensen rat sarcoma during the first hour of the experiment. In these experiments the values of $Q_M^{N_2}$ in periods before and after the rise are denoted by *A* and *B* respectively, and the magnitude of the rise is expressed as a percentage by the quotient $100(B - A)/A$ [Rosenthal, 1930, 2]. The spontaneous increase occurs in the presence of phosphate, for in a Ringer solution containing both phosphate and bicarbonate an increase of 35 % was found when the necessary correction was made for carbon dioxide retention. In pure bicarbonate-Ringer, it was found from the experiments with varying fructose concentrations that the spontaneous rise is maximum when the fructose concentration is about 0.2 %; in 1 % fructose the increase is negligible. The

percentage increases with different sugar concentrations found in three different experiments are given below:

Fructose concentration %	Spontaneous increase of fructolysis (%)		
	$\frac{100 (B - A)}{A}$		
	(1)	(2)	(3)
0.1	+35	+27	- 2.5
0.2	+44	+48	+50
0.4	.	+13	+45
0.5	+ 7	.	.
0.6	.	+15	+20
0.8	.	- 2.5	.
1.0	+ 3	+ 9	.

The effect of the addition of sodium pyruvate on the spontaneous increase observed in Jensen rat sarcoma has already been reported [Dickens and Greville, 1932, 2], and is discussed below.

DISCUSSION.

The spontaneous increase in fructolysis observed in Jensen rat sarcoma was ascribed by Rosenthal [1930, 2] to the anaerobic formation and accumulation of an activator. This spontaneous activation, he considers, is analogous to the activation produced in liver tissue by a preliminary aerobiosis. Various differences, however, exist between the activation phenomena in the two tissues; the most important of these are as follows. Firstly, activation occurs anaerobically in tumour tissue, but only under aerobic conditions in liver. Secondly, the activated glycolysis falls off rapidly in liver, but continues practically constant in tumour. Lastly, whilst activation occurs in liver in the presence of any fermentable sugar, the activation phenomenon in tumour is readily seen only in the fructose metabolism. However, Rosenthal considers that these differences do not necessarily mean that the activation process is not similar in the two tissues, and that "soweit sich Abweichungen zeigten, konnten sie in ihrer Mehrzahl durch Unterschiede der verglichenen Gewebe im Gehalt an Aktivator bzw. zu seiner Bildung nötigen Substanzen und in der Geschwindigkeit der Aktivatorbildung erklärt werden." Some observations made by us [Dickens and Greville, 1932, 2] have led us to agree that the activation phenomena in liver and tumour are analogous. We have been able directly to demonstrate the spontaneous activation of the glucolysis in Jensen sarcoma, which Rosenthal had concluded must occur [Rosenthal, 1930, 2, footnote, p. 237]. Again, we found that the addition of $10^{-3} M$ sodium pyruvate to the Jensen rat sarcoma in fructose before the spontaneous increase had occurred caused an immediate increase in fructolysis, $Q_M^{N_2}$ thereafter remaining constant at about the value it would have reached by spontaneous activation, whilst addition of the pyruvate after the spontaneous increase had occurred had no effect at all on the fructolysis. Since Rosenthal [1932] has shown that sodium pyruvate produces an activation of the anaerobic

autoglycolysis and fructolysis of liver similar to that produced by preliminary aerobiosis, it certainly seems that activation in liver and tumour are similar processes. Rosenthal considers that in liver sodium pyruvate is not the activator; but whether in tumour tissue pyruvate can replace the activator, or is an intermediate substance in the chain of reactions whereby the activator is formed, or is even the activator itself, cannot possibly be decided from our present knowledge.

In the Mill Hill sarcoma we have been unable to demonstrate spontaneous activation of the fructolysis, and here pyruvate had no effect [Dickens and Greville, 1932, 2]. It may be that activation is extremely rapid, but as the rate of activation, according to Rosenthal, depends on the magnitude of the glycolysis, and the fructolysis of the two tumours is about the same, this seems unlikely. The possibilities remain that de-activation does not occur, or that the mechanism for spontaneous activation, even when pyruvate is supplied, is missing. We are not in a position to decide between these possibilities and explain why the Mill Hill and Jensen tumours behave so differently. Indeed, as we cannot explain why increase of fructose concentration, as shown earlier, reduces the apparent magnitude of the spontaneous increase, why activation occurs anaerobically in tumour but only aerobically in liver, and why the glycolysis falls off rapidly in liver, although this is prevented by increasing the sugar concentration, it is clear that much more work must be done before the activation phenomena become at all intelligible.

It does not seem improbable that in the Jensen sarcoma glucose and fructose are fermented by similar routes. In yeast it has been suggested that because of the uniformity of rate of fermentation of glucose and fructose, these sugars are probably fermented by the same enzyme, glucosylase [see Harden, 1932]. This possibility is strengthened by Dawson's demonstration [Dawson, 1932] that the phenomena of selective fermentation of glucose and fructose by living yeast may be explained on Michaelis's theory of enzyme affinity by the competition of substrates. In Jensen rat sarcoma the normal effect of fluoride found above and the observation of Rosenthal [1930, 2] that glyceraldehyde completely inhibits both fructolysis and glycolysis, suggest that the fermentation paths coincide at some stage between hexose and methylglyoxal, whilst the glycolysis-sugar concentration curves for the two sugars are similar to those which would be obtained if the fructose and glucose conversions were catalysed by the same or similar enzymes, and glucose had two or three times the affinity of fructose for the enzyme.

With the fructolysis of liver the situation is different and very complicated. The metabolism of surviving liver shows several striking anomalies. Liver is the only tissue known to be unable to convert glucose into lactic acid. It differs from the other adult normal tissues (except muscle) in converting fructose into lactic acid, and from tumours in its ability to glycolyse glyceraldehyde [Rosenthal, 1930, 2]. The extraordinary dependence of both aerobic and anaerobic metabolism on the state of nutrition, of the fructolysis on the time

of year, and of the anaerobic metabolism in general upon the presence of an activator which may be produced by preliminary aerobiosis [Rosenthal, 1929] or the addition of pyruvate, acetaldehyde or methylene blue [Rosenthal, 1932], shows that many different factors are operating to determine the glycolysis of any sample of liver tissue. It would therefore be dangerous to draw any definite conclusions from the fact that the fructolysis increases with the fructose concentration in quite an unusual way (Fig. 3). A possible explanation might be that increased fructose concentration, since it prevents the rapid fall of glycolysis with time, produces greater amounts of activator; but it seems to us that the fall of glycolysis may be due to causes other than the loss of activator. For not only does it occur both in the autoglycolysis and fructolysis, but it occurs equally in the activated glycolysis produced both by pyruvate and preliminary aerobiosis [Rosenthal, 1931; 1932]; moreover, after the falling off, Rosenthal [1931] could not restore the activation by a further aerobiosis. If, then, the effect of raising the sugar concentration does not produce activator, it may be that fructose has a very low affinity for the enzyme, so that a velocity equal to half the limiting velocity is reached only at a relatively very high substrate concentration. There is, however, one other possible explanation which we think should be borne in mind. In view of the fact that glucose is not glycolysed by liver, it is possible that the substrate of liver fructolysis is not the ordinary form *n*-fructose, but is some labile *h*-fructose which is in equilibrium with it in aqueous solution. Then the fructose concentration would have to be raised very considerably before the enzyme system became saturated with this labile sugar. Whatever the explanation, however, it must be conceded that liver fructolysis is of a type very different from the usual glycolysis.

Meyerhof's view, that the fructolysis of a tissue depends on the existence in that tissue of an initial phosphorylation stage, was discussed in the previous paper, and therefore no further reference to it is necessary here. It appears from the present paper that variations in the ability to fructolyse occur just as strikingly among the tumour tissues as among the embryonic tissues. The appearance of fructolysis in one tissue and its complete absence from another tissue of similar type, the great variability shown by the various tissues in their attack on fructose when their metabolism of glucose is similar, still await an explanation, which, when it is forthcoming, can hardly fail to clear up many obscure features of carbohydrate metabolism.

SUMMARY.

1. The anaerobic conversion of fructose into lactic acid by tumour and adult normal tissues has been studied.
2. The anaerobic attack of rat's retina, submaxillary and spleen on fructose is negligible, whilst kidney and testis show a slight attack. When these results are taken in conjunction with those obtained by other authors on brain, ~~nerve~~ ^{nerve}

and liver, it is seen that those adult normal tissues which convert glucose into lactic acid show little anaerobic attack on fructose, whilst liver, which cannot utilise glucose anaerobically, can under certain conditions readily form lactic acid from fructose.

3. The Jensen rat sarcoma and the Mill Hill fowl fibro-sarcoma No. 1 show a steady anaerobic fructolysis equal to about a third of the glucolysis. The Rous chicken sarcoma may also show some attack on fructose, but the other types of tumour examined (the Brown-Pearce rabbit tumour, two mouse carcinomas and one mouse sarcoma) lack the ability to convert fructose into lactic acid. There thus exists among the tumour tissues a variability in their behaviour towards fructose which is as pronounced as that found among the embryonic tissues.

4. The spontaneous increase in anaerobic fructolysis observed by Rosenthal in the Jensen rat sarcoma has not been observed in the Mill Hill tumour. Rosenthal's activator theory is discussed.

5. The effects of the addition of sodium fluoride and of alteration of substrate concentration upon the anaerobic fructolysis of Jensen rat sarcoma have been determined, and the possibility that glucose and fructose are converted into lactic acid by similar routes in this tumour is discussed.

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