Glucose Consumption by Transplanted Tumors in Vivo

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SUMMARY

The relationship between availability and utilization of glucose and production of lactate was studied in vivo in Walker carcinoma 256, Hepatoma 5123, and Fibrosarcoma 4966 transplanted in rats. The tumors utilized 0.96, 0.55, and 0.45 gm of glucose/hr/100 gm wet tumor weight, respectively, corresponding to 28%, 23%, and 32% of the amount supplied. About 35% of the glucose consumed was eliminated as lactate regardless of the tumor type. In normoglycemia, the amount of glucose consumed and glycylized was directly related to the glucose available which decreased per unit weight as the tumor size increased. During hyperglycemia, produced either by dextrose injections or diabetes, the tumors increased glucose utilization. The increase was maximum during the first few hours; then a "saturation" level was reached. When hyperglycemia was prolonged for several days, carcinomas and hepatomas consistently consumed about 4 more glucose; however, fibrosarcomas reduced their consumption by about 30%. Insulin did not improve glucose consumption of tumors either in normal or diabetic rats. Actually, the overall utilization was reduced because the plasma level of glucose in the host was lowered by insulin. Hypoglycemia or injections of 2-deoxy-n-glucose reduced glucose consumption, and in vivo the tumors were unable to compensate for this decrease by removing more glucose from the blood. The vascular walls of neoplastic vessels maintained a sharp concentration difference between glucose in plasma and in the interstitial fluid, with the fluid surrounding the neoplastic cells containing only a few mg percent of free glucose and practically all of the glucose passing through the vascular walls being rapidly consumed. During hyperglycemia the concentration difference disappeared and the vascular and interstitial compartments had about equal concentrations of glucose. Normo- or hypoglycemia restored the concentration gradient for glucose between the vascular and the interstitial compartment. The time needed to complete the restoration was longer after prolonged hyperglycemia. The regulation of the glucose transfer by the vascular wall of neoplastic vessels is postulated.

INTRODUCTION

Ever since glycolysis was suggested to be the outstanding biochemical characteristic of neoplastic tissue, the in vivo glucose consumption of tumors has been studied mainly with the purpose of finding whether the data obtained in vitro were applicable to the in vivo situation. Cori and Cori (7) observed that blood passing through a sarcoma growing in a chicken wing contained 23 mg % less sugar and 16.2 mg % more lactate than the blood which passed through the opposite normal wing. This finding was confirmed for tumors of different species (5, 22). Warburg found that the venous blood of Jensen sarcoma contained 57% less glucose than the arterial blood when the glycemia was 125 mg % (26). The consumption of glucose by the tumors, however, could not be measured because the blood flow was unknown.

The concept that in vivo neoplastic tissues required a large supply of glucose arose from the observation that large amounts of glucose were utilized by tumor slices in vitro (1). The same concept was strengthened by the finding that both Walker carcinoma and Novikoff hepatoma reduced the blood sugar level of alloxan-diabetic animals (10) and that the content (9) and the rate of deposition of liver glycogen after glucose ingestion (8, 11) was much reduced in tumor-bearing rats.

In the experiments reported here, the in vivo relationships among glucose availability, utilization, and glycolysis were studied. Three tumors which differed in structure and biologic properties were chosen, and the circumstances which influenced the ability of these tumors to remove glucose from the blood were examined. The experiments aimed at clarifying the in vivo mechanism of glucose supply to neoplastic cell populations.

MATERIALS AND METHODS

Animals and Tumors

Adult female rats (140 to 180 gm) which had been fed Purina laboratory chow diet since weaning age were used. The tumors studied were Walker Carcinoma 256 transplanted in Sprague-Dawley rats, random bred, NIH line, Hepatoma 5123, and Fibrosarcoma 4966 both in Buffalo/N adult rats, NIH inbred line (15).

Experimental Procedures

The in vivo measurement of glucose uptake by the tumor was based on an experimental system reported in a previous paper (15), and two types of procedures were used. In the first, glucose uptake was calculated from the blood flow and the arterial venous difference (A-V) in glucose content. The blood flow of the tumor was measured from the tumor vein in the abdominal cavity as previously described (15). In the second type of experiment, the interstitial fluid of the tumor was sampled with a micropore chamber, following a technic previously described (12), and the glucose uptake by the tumor was compared with the glucose concentration of this fluid. Ovarian and subcutaneous transplants of the three tumors studied were used in the experiments. The sampling procedure is summarized in Chart 1.

The precautions to be taken were reported previously (15).
P. M. Gullino, F. H. Grantham, and A. H. Courtney

CHART 1. Sampling procedure. Arterial blood was taken from the aorta with a catheter guided through the common carotid artery; venous blood was sampled from the abdominal portion of the tumor vein (ex-ovarian vein). Flow was measured as the amount of blood collected from the tumor vein by a syringe over a measured period of time. All of the blood passing through the tumor was flowing out of the ex-ovarian vein and sufficient suction was applied to ensure complete withdrawal from the vein kept empty of blood. The micro-pore chamber was present only in some of the ovarian transplants and used mostly with subcutaneous transplants. The walls of the chamber were formed by filters with pores small enough to let only the fluid surrounding the cells pass through (0.45 or 0.1 µ). This interstitial fluid was sampled with a catheter from the chamber incorporated by the tumor during growth (for more details see Ref. 12).

Treatment
The animals were anesthetized with urethan (1 gm/kg) (Merck Sharpe and Dohme, Rahway, N. J.) or pentobarbital sodium (25 mg/kg) (Pentosol, A. J. Buck and Sons, Washington, D. C.). Animals anesthetized with this last compound for more than 45 minutes showed an increase of the blood glucose level. Prolonged hyperglycemia of “normal” tumor-bearing hosts was produced by subcutaneous injections of 200 mg of dextrose.
Glucose Consumption by Transplanted Tumors in Vivo

In Vivo Consumption of Glucose by Neoplastic Tissues under Normal Conditions

For each tumor the blood flow and the decrease of glucose or the increase of lactate content of efferent as compared with afferent blood was measured. In parentheses, 95% confidence limits for the number of determinations listed in brackets in the first column. Host glucose levels from 135 to 160 mg per 100 ml plasma. Water content in gm per 100 gm of tumor: Walker carcinoma = 82.2, hepatoma = 80.0, fibrosarcoma = 84.1. Hemoglobin saturation from 80 to 95%. The range of variation which appears in Table 1 depended on various factors. The glucose available per unit weight varied inversely with the size of the neoplastic mass making it necessary to specify the weight range of the tumors studied when glucose consumption is determined in vivo. Another factor was the variability in the amount of glucose utilized or glycolyzed by the same tumor at different intervals of time. For example, when the glucose intake was examined in a group of Walker carcinomas, at 0.5, 1.0, and 24 hours, the variability reported in Table 2 was observed.

It seems reasonable to represent with an average figure the amount of glucose utilized and glycolyzed in vivo by each of the three tumors under normal conditions. Generally, both quantities were directly related to the amount of glucose available (Chart 2).

### TABLE 1

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Number of determinations</th>
<th>Tumor weight range (gm)</th>
<th>Glucose (gm/hr/100 gm)</th>
<th>Lactate eliminated (gm/hr/100 gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supplied</td>
<td>Utilized</td>
</tr>
<tr>
<td>Walker carcinoma</td>
<td>65</td>
<td>2.0-11.5</td>
<td>3.4</td>
<td>0.97</td>
</tr>
<tr>
<td>256</td>
<td></td>
<td></td>
<td>(3.2-3.9)</td>
<td>(1.16-0.77)</td>
</tr>
<tr>
<td>Hepatoma 5123</td>
<td>23</td>
<td>3.4-7.0</td>
<td>2.4</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.2-2.6)</td>
<td>(0.88-0.33)</td>
</tr>
<tr>
<td>Fibrosarcoma 4956</td>
<td>19</td>
<td>5.0-12.7</td>
<td>1.4</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.1-0.7)</td>
<td>(0.71-0.17)</td>
</tr>
</tbody>
</table>
P. M. Cullino, F. H. Grantham, and A. H. Courtney

The relationship between glucose available, utilized, and glycolyzed is shown in Chart 2. Each point represents one tumor. The glucose utilized and glycolyzed increased as the glucose available to the tumor augmented. The curves were drawn for Walker carcinomas, but hepatomas and fibrosarcomas behaved similarly. The difference in the amount of glucose available was due in part to the blood flow and in part to the level of glycemia.

2) The data in Table 1, however, suggest that the fraction of glucose utilized or glycolyzed may vary within a given tumor at various periods of time. In vivo, the supply was probably not the sole factor which determined the utilization.

The difference between the first and the second sample in Table 2 reflects not only the actual difference in glucose consumption or lactate production but also the errors of our sampling procedure (influence of anesthesia, shock of operation (25), effect of changes in blood flow, etc.), which could not be assessed. A relative large number of determinations were done in order to obtain a statistically reliable sample (Table 1).

Relationship between Uptake and Blood Level of Glucose

Hyperglycemia. Two variables were considered in these experiments, the level and the duration of glycemia. Three groups of determinations were performed. In the first, the host received one dose of dextrose intravenously and the glucose consumption of the tumor was measured about 10 minutes later. When the glycemia rose above 600 mg/100 ml plasma, the A-V difference in glucose content of tumors blood was unmeasurable for the majority of specimens. Only in about 15% of the cases could the uptake be evaluated, and it was always found to increase from 3- to 10-fold as compared with normoglycemia. When the dose of dextrose produced a hyperglycemia below 600 mg/100 ml plasma, the uptake of glucose increased but the values varied from just above that of normoglycemia to several times higher.

The first group of experiments showed that in vivo hyperglycemia invariably increased glucose uptake by the tumors. However, the procedure was not suited to measure the extent of this increase since a rise in glucose uptake due to accumulation of glucose in the interstitial space could not be excluded (17).

In the second group of experiments, a glycemia between 400 and 600 mg/100 ml plasma was maintained for 6-7 hours by repeated subcutaneous injections of dextrose in the host. Under these conditions, glucose consumption could be measured in the presence of a clear A-V difference and with enough time for equilibration of glucose in the interstitial fluid. Hepatomas showed increased uptake with the same relationship between glucose available and utilized as that obtained under normoglycemia (Chart 3). For periods of glycemia longer than 7 hours, however, the increased A-V difference disappeared, suggesting that the hepatoma's capacity to use such a large amount of glucose was decreasing with time. After 7 hours of hyperglycemia (above 400 mg/100 ml), carcinomas and fibrosarcomas consumed an amount of glucose roughly equal to the normoglycemic state although the scatter of values was larger. The slope of the utilization curve was shallower than normal (Chart 4) suggesting that there was not only a limit but also a decrease in the absolute extent of glucose utilization despite the large increase in availability.

In the third group of experiments, glucose uptake by the tumors was studied in diabetic hosts where the hypoglycemia was more uniform and could be maintained for days instead of hours. With a blood glucose level about twice that of normal and maintained for 7 days, carcinomas and hepatomas consumed...
Glucose Consumption by Transplanted Tumors in Vivo

TABLE 2
Glucose Utilization and Lactate Production by the Same Tumor at Two Different Intervals (Walker Carcinomas)

Glucose available and utilized and lactate eliminated were measured in the same tumor. First sampling at 0 time and second sampling at intervals of 0.5, 1.0, or 24 hours. In about half of the animals the glucose available and utilized and the lactate eliminated was rather similar at both intervals. In the remaining half there was a variation relatively independent from the glucose supply. Similar behavior was observed for hepatomas and fibrosarcomas.

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>Interval between samples (hr)</th>
<th>Glucose available (mmoles/hr/100 gm)</th>
<th>Glucose utilized (mmoles/hr/100 gm)</th>
<th>Glucose available (mmoles/hr/100 gm)</th>
<th>Glucose utilized (mmoles/hr/100 gm)</th>
<th>Lactate produced as % glucose utilized</th>
<th>Lactate produced as % glucose utilized</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First sampling</td>
<td>Second sampling</td>
<td>First sampling</td>
<td>Second sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose available (%)</td>
<td>Glucose utilized (%)</td>
<td>Glucose available (%)</td>
<td>Glucose utilized (%)</td>
<td>First sampling (%)</td>
<td>Second sampling (%)</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>14.0</td>
<td>5.3</td>
<td>30.0</td>
<td>3.2</td>
<td>47</td>
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<tr>
<td>2</td>
<td>0.5</td>
<td>2.5</td>
<td>0.8</td>
<td>32.0</td>
<td>1.8</td>
<td>44</td>
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</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>31.9</td>
<td>6.9</td>
<td>22.0</td>
<td>2.9</td>
<td>48</td>
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</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>45.0</td>
<td>7.3</td>
<td>16.0</td>
<td>4.0</td>
<td>29</td>
<td>29</td>
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<tr>
<td>5</td>
<td>1.0</td>
<td>22.3</td>
<td>5.3</td>
<td>24.0</td>
<td>9.4</td>
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<td>6</td>
<td>1.0</td>
<td>78.7</td>
<td>20.6</td>
<td>26.0</td>
<td>104.7</td>
<td>53</td>
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<td>7</td>
<td>24</td>
<td>33.3</td>
<td>8.4</td>
<td>25.0</td>
<td>32.5</td>
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<td>8</td>
<td>24</td>
<td>68.1</td>
<td>15.9</td>
<td>23.0</td>
<td>87.9</td>
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<td>9</td>
<td>24</td>
<td>55.9</td>
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<td>16.0</td>
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<tr>
<td>10</td>
<td>24</td>
<td>34.7</td>
<td>11.3</td>
<td>33.0</td>
<td>67.0</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>24.2</td>
<td>8.5</td>
<td>35.0</td>
<td>25.2</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Glucose 46% and 38%, respectively, more than in normoglycemia (Table 3). Fibrosarcoma, however, reduced glucose consumption by 30%, suggesting that the long-lasting hyperglycemia of the diabetic host was damaging the tissues.

Hypoglycemia. About 30 minutes after the intravenous injection of 16 units of insulin in normoglycemic rats, a depression of plasma glucose was initiated and progressed in the following 30 minutes until the plasma concentration of glucose was reduced to about one-half the starting level. During this period of intense utilization of glucose by the host tissues, all three tumors decreased glucose uptake. At one hour after insulin injection the average glycemia of the host was 80 mg/100 ml plasma, and the glucose uptake was 0.70, 0.40, and 0.28 gm/hr/100 gm wet tumor weight for carcinomas, hepatomas, and fibrosarcomas, respectively. The glucose utilized was proportional to the amount available as observed in normoglycemic animals (Chart 2). Thus it appeared that when the blood glucose decreased under the action of insulin, the tumors were unable to remove proportionally larger amounts of glucose from the plasma.

The inability of insulin to improve glucose uptake by the neoplastic cells was also found in diabetic rats. The plasma level of glucose varied in our animals from 293 to 442 mg/100 ml plasma before, and from 109 to 160 at one hour after 16 units of insulin. Glucose availability and utilization was compared for each tumor before and one hour after insulin. The overall consumption was reduced along with the level of blood glucose (Chart 5). The three tumors showed the same behavior.

A reduction of glucose uptake by Walker carcinomas was also
TABLE 3

Glucose Uptake by Tumors Growing in Diabetic Hosts

Diabetes produced by alloxan. Sampling at 7 days after onset of hyperglycemia. 12 animals each group. Values for normoglycemic hosts are given in parentheses (see Table 1). Carcinomas and hepatomas increased glucose consumption but fibrosarcomas used less glucose (±S.D.).

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Plasma glucose (gm/100 ml)</th>
<th>Glucose utilized (gm/hr/100 gm)</th>
<th>Lactate eliminated (gm/hr/100 gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker carcinoma</td>
<td>318 ± 19 (150)</td>
<td>1.42 ± 0.36 (0.97)</td>
<td>0.52 ± 0.15 (0.34)</td>
</tr>
<tr>
<td>Hepatoma 5123</td>
<td>301 ± 29 (150)</td>
<td>0.76 ± 0.34 (0.55)</td>
<td>0.24 ± 0.16 (0.18)</td>
</tr>
<tr>
<td>Fibrosarcoma 4956</td>
<td>249 ± 14 (150)</td>
<td>0.33 ± 0.12 (0.45)</td>
<td>0.14 ± 0.09 (0.15)</td>
</tr>
</tbody>
</table>

Glucose utilization by Walker carcinomas as related to increased supply. Utilization of glucose by a group of normoglycemic animals was compared with the utilization of another group in which the glucose available to the tumor was increased for 6 to 7 hours. Relative to the glucose available, the utilization decreased. The same behavior was observed in fibrosarcoma.

Regulation of Glucose Uptake from Blood

Plasma glucose passes through the vascular wall, the interstitial spaces and the cell membranes into the neoplastic cells. Since the amount consumed was always less than the quantity available, any or all of these structures could affect the transfer of glucose from plasma to cells. In order to study this process, the free glucose content of the interstitial fluid was determined in tumors and subcutaneous tissues of normo- and hyperglycemic animals.

In normoglycemic animals the free glucose content of the interstitial fluid of all three tumors was negligible (0-8 mg/100 ml) as compared with the normal subcutaneous fluid (80-100 mg/100 ml) (Table 4). This finding confirms previous data which showed that the normal subcutaneous cells live in a milieu rich in glucose while the neoplastic cells do not (12).

It should be pointed out that when glucose was added to the isolated interstitial fluid of tumors or normal subcutaneous tissue (1 mg/ml final concentration) and was incubated for 2 hours at 37°C, the concentration in the media remained unchanged. This indicated that the very low level of glucose in the interstitial fluid of tumors was not due to destruction by enzymes “leaked out” of the cells.
Glucose Consumption by Transplanted Tumors in Vivo

**Chart 5.** Glucose utilized by tumors in diabetic hosts before and after injection of insulin. Two values for each tumor: (a) during diabetes (∆) and (b) when hyperglycemia was corrected by insulin (●). No appreciable increase in glucose utilization after insulin injection; indeed hypoglycemia due to insulin produced a reduction of the glucose utilized by the tumors.

Since in normoglycemic animals the tumors very rapidly used all the glucose which passed from the plasma through the vascular walls into the interstitial fluid, a steep concentration difference was maintained by the vascular wall. This concentration gradient was modified by hyperglycemia. In animals injected with dextrose for 6-7 hours, the glucose concentration of the tumor interstitial fluid increased. However, if sampling of the fluid was delayed about 90 minutes after the last dextrose injection, the glycemia was usually below 300 mg/100 ml plasma and the interstitial fluid was again practically free of glucose (Table 4). This suggests that (a) several hours of hyperglycemia above 300 mg/100 ml plasma "saturated" the capacity of the neoplastic cells to use glucose, hence an accumulation in the interstitial fluid, (b) the increase of glucose concentration in plasma could augment the rate of passage across the vascular wall, and (c) the accumulation of glucose for a few hours did not impair the ability of the cells to use glucose, hence its rapid disappearance from the interstitial fluid as soon as glycemia returned to about 300 mg/100 ml plasma.

The concentration gradient for glucose between plasma and tumor interstitial fluid disappeared in 7-day-old diabetic rats. In these animals the interstitial compartment contained a large amount of free glucose, usually only slightly less than the vascular compartment. During insulin-induced hypoglycemia a decrease of glucose occurred simultaneously in both plasma and interstitial fluid (Table 5). However, even when blood glucose levels were lower than normal, free glucose disappeared from the interstitial fluid only after several hours. A quicker return to the normal gradient was observed at a more severe hypoglycemia (Rats 7 and 8, Table 5). A diagrammatic summary of the relationship in glucose concentration between vascular and interstitial compartments is reported (Chart 6). These data suggest the existence of a transfer system for glucose across the capillary wall.

**DISCUSSION**

In normoglycemic hosts the in vivo consumption of glucose by neoplastic tissues was found to be very high. Cerebral tissue is
Glucose consumption in vivo was found to be directly related to glycemia. Tumors were apparently unable to compensate for reduced blood glucose levels by more efficient removal of glucose from the afferent blood. In hyperglycemic hosts, the total consumption of glucose depended not only on the level of glycemia but also on its duration. During the first hours of increased supply, tumors used more glucose than later. A plateau was eventually reached where the glucose consumption was maximal. After 7 days at this level, carcinomas and hepatomas were still consuming glucose at a rate higher than normal, but fibrosarcomas had reduced the uptake below that of normoglycemia, perhaps indicating damage to the cell population. Hyperglycemia is known to damage cells in vitro (11) and to depress tumor growth in vivo (8).

The regulation of glucose transfer from the vessels into the neoplastic cells was partially clarified by the comparison between glucose content of plasma and interstitial fluid under various levels of glycemia. In vivo the neoplastic cells are in contact with a fluid containing only a few milligrams of glucose. The difference between plasma and interstitial fluid was about 140 mg/100 ml for the 3 tumors. It appeared that all the glucose passing through the vascular wall was rapidly utilized by the neoplastic cells. That plasma concentration was one of the factors regulating the passage of glucose across the vascular wall, was shown by the increased or decreased accumulation of glucose in the interstitial space following changes in plasma glucose level. However, plasma concentration alone does not explain all the observations. In the carcinomas, hepatomas, and fibrosarcomas, the vascular spaces were related as 1.0:0.5:0.1 (14), the blood flow per unit of time and weight, as 1.0:0.6:0.5 and the glucose consumption as 1.0:0.6:0.5. Fibrosarcomas, for instance, consumed the amount of glucose as carcinomas but received the volume of blood through a vascular system that of carcinomas. Since carcinomas and fibrosarcomas were transplanted into the ovary, and it is known (13) that the vascular net of tumors is furnished by the host, both tumor types should have initially had the same vascular system. Differences in the rate of glucose consumption which developed during growth cannot only be due to different concentrations of blood glucose since in normoglycemia the glucose levels are fairly uniform. The data reported here suggest that the vascular wall is an important factor in regulating the in vivo uptake of glucose by tumors.

Glucose uptake from the blood seems to be different in normal cell populations of the subcutaneous tissue than in neoplastic cells transplanted in the same area. The subcutaneous interstitial fluid always contained a large amount of free glucose, and it seems obvious that in such an environment the plasma membrane of the cell would regulate the glucose uptake. If the neoplastic cells were present, however, the free glucose available was rapidly used and the transfer system of the vascular wall became the rate-limiting structure. Under these circumstances it is not surprising that in vivo insulin had no enhancing effect on glucose uptake by tumors. When plenty of free glucose was available to the neoplastic cells, as in diabetic animals, the transfer across the cell membranes and the consumption was already at the maximal levels.
Glucose Consumption by Transplanted Tumors in Vivo

**CHART 6.** Summary of experimental data indicating the role played by the vascular wall in the glucose uptake by Walker carcinoma. The neoplastic tissue is presented as a three-compartment system: cells, interstitial space, vessels. Under normal conditions about 150 mg of glucose were present per 100 ml of plasma passing through the tumor, yet the free glucose content of the tumor interstitial fluid (TIF) was negligible. The utilization of glucose under these conditions was 0.97 gm/hr/100 gm wet tumor, about 28% of the glucose supplied by the blood stream (upper dark section of the scheme). Repeated injections of dextrose maintained the glycemia to about 600 mg/100 ml plasma for 6-7 hours. At this time the free glucose of the TIF was always detectable in various amounts. However, as soon as the injections were suspended and the plasma glucose decreased below 300 mg/100 ml, free glucose disappeared from TIF (central section of the scheme). In 7-day diabetic rats, free glucose content of TIF was about 300 mg/100 ml, only 10 to 30% lower than the plasma level. Utilization increased to 1.42 gm/hr/100 gm wet tumor, but decreased from 28 to 19% of the supply. Rapid depression of glycemia by insulin produced, within 2 hours, similar depression of glucose concentration in TIF. However, free glucose did not disappear rapidly from TIF as one would have expected from the data of 6-7 hours of dextrose hyperglycemia. Only after 24 to 48 hours of normo- or hypoglycemia did the concentration gradient for glucose reappear (lower section of the scheme). The regulation of the glucose transfer by the vascular wall of neoplastic vessel is postulated.

The utilization of glucose was usually about 1/10 that of the supply. If this were a limiting factor in growth, an increased consumption of glucose should have probably enhanced the growth rate since it was found (2) that an impairment of glucose utilization by 2-deoxy-d-glucose reduced the tumor growth. However, the opposite was found to be true: the tumors grew less well in hyperglycemic hosts when consuming more glucose than normal. If the supply of glucose was adequate for the metabolic needs of the tumors, it remains an open question whether growth alone can justify the large glucose consumption.
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Glucose Consumption by Transplanted Tumors in Vivo

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