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Blood Glucose Levels and Gluconeogenesis in Animals Bearing Transplantable Tumors

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SUMMARY

A correlation between the capacity of tumor-bearing animals to maintain normal glucose levels and the stimulation of gluconeogenesis from noncarbohydrate sources has been established. Gluconeogenesis was shown to counterbalance the tendency toward hypoglycemia caused by tumors in mice with Crocker sarcoma and Guelstein 22a hepatoma, and in rats with Zajdela ascites hepatoma. Mobilization of liver and muscle glycogen reserve failed to ensure normal glucose levels in rabbits with Brown-Pierce carcinoma.

The enhancement of endogenous glucose formation from ^{14}C-labeled amino acids in the tumor-bearing host depended upon the response to glucocorticoids of the tissues involved in gluconeogenesis. Mice with Ehrlich ascites carcinoma developed severe hypoglycemia that increased with tumor growth. There was no enhancement of gluconeogenesis in these animals.

A prolonged stress imposed on such mice or the administration of large doses of cortisol was found to stimulate gluconeogenesis and elevate the blood glucose concentration to a normal level. A reduced responsiveness of the host's tissues to glucocorticoids is regarded as a manifestation of the systemic action of the tumor on distant organs.

INTRODUCTION

It has been shown previously that a tumor growing in the body behaves as a trap for glucose and acts as a powerful hypoglycemic factor imposing a strain on the host's ability to maintain normal blood glucose levels (2, 19, 22). Such properties of malignant tumors are determined by a gap between an extremely high potential rate of glucose consumption by cancer cells and the real rate, limited by a relatively slow glucose influx from the host. Such a difference causes an imperceptibly low glucose level in the tumor tissue and surrounding medium (8, 14, 18) and maintains the cancer cells in a state of "glucose hunger" *in vivo*.

Owing to an enormous gradient between the concentration of glucose in the blood vessels surrounding the tumor and the tumor tissue itself, the latter takes priority over normal tissues in terms of glucose consumption (22). One of the results is an elevated mobilization of glycogen from the liver and skeletal muscle of the host and a reduction in glycogen deposition.

Despite the tendency toward hypoglycemia in the host caused by the tumor, normal blood glucose concentrations have been observed in most (but not all) tumor-bearing animals and patients. This fact indicates that the tumor growing *in vivo* forces the host to depend on gluconeogenesis from noncarbohydrate compounds to maintain its blood glucose levels.

It is surprising that no data on gluconeogenesis from amino acids and lipids in tumor-bearing animals can be found in the literature. In this paper we discuss our studies of the correlation between the dynamics of blood glucose levels in tumor-bearing animals as a result of tumor development and the intensity of gluconeogenesis.

MATERIALS AND METHODS

Animals. Male albino mice belonging to no particular line (random) and C3HA mice (20 to 22 g) were used. Albino mice were inoculated with 0.3 ml of Ehrlich ascites carcinoma cell suspension i.p., or with 1 ml 20% homogenate of solid Crocker sarcoma s.c.; Guelstein 22a hepatoma was also transplanted s.c. (1 ml 20% homogenate) into C3HA mice.

White random (nonbred) male rats (150 to 200 g) were inoculated i.p. with 0.3 ml of Zajdela ascites hepatoma. One ml of 20% suspension of Brown-Pierce carcinoma cells was transplanted into one of the testes of rabbits (2.5 to 3 kg).

To follow the dynamics of glycemia in Ehrlich carcinoma-bearing mice that were starved overnight, as well as that in all the other experimental animals, the concentration of glucose in the blood was determined daily for 8 days. Blood sugar levels in the ascites fluid were measured after transplantation, beginning at Day 5. At the same time intervals, glucose concentration in the blood was assayed in intact animals.

A separate group of intact and Ehrlich carcinoma-bearing mice was forced to swim in water at 17-19° for 15 min daily, suspended by the fold of the nape, or kept immobilized for 1 hr on Day 8 after transplantation (stress). After 8 days, these mice were decapitated and glucose concentration was determined in the blood and ascitic fluid. The life-span of animals bearing Ehrlich carcinoma, Crocker sarcoma, Guelstein hepatoma, Zajdela hepatoma, and Brown-Pierce carcinoma was 10 to 12, 25 to 27, 25 to 27, 5 to 6, and 28 to 32 days, respectively.

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Labeled Compounds Used. Specific activities (in parentheses) are expressed in mCi/mmole: L-tyrosine-^{14}C (2.58), glycine-1-^{14}C (1.46), and L-alanine-^{14}C (2.58). The sources of labeled compounds were as follows. Tyrosine and glycine were from the office "Isotope," Moscow, U. S. S. R.; alanine was from Czechoslovakia. All the compounds except glycine were uniformly labeled. The activity of newly formed glucose-^{14}C was expressed in counts/min/ml or 100 ml of blood serum, and in counts/min/g or 100 g of tissue, wet weight. To minimize the isotopic dilution of labeled amino acids, the experimental animals were starved 14 to 18 hr prior to use.

Analytical Methods. The concentration of glucose in the blood and ascitic fluid was determined enzymatically by means of a glucose oxidase-peroxidase procedure (15). Gluconeogenesis was studied independently in mice and rats *in vivo* in different experiments by means of 2 procedures that measured labeled glucose derived from radioactive precursors. In the 1st method, after paper chromatography of the protein-free eluate from Amberlite IR-112 and IRA-410 (7), 0.1 ml of the eluate was applied to FN-15 paper (German Federal Republic). This was subjected to ascending chromatography in a mixture of pyridine:acetone:*n*-propyl alcohol:NH_4OH (density, 0.880): 0.5% EDTA (60:10:18:9:3) (16, 17). This technique separated sugars from organic phosphorus compounds and amino acids. The more specific method developed by Friedman *et al.* (6) was used with a slight modification for determination of glucose derived from radioactive glycine and alanine.

Radioactive liver glycogen, derived from labeled glucose precursors, was isolated according to Good *et al.* (12). The glycogen was dissolved in hot water and then put directly on filters made of FN-15 chromatography paper to measure the radioactivity, thus avoiding the acid hydrolysis step.

RESULTS

A progressive decrease in the blood glucose of rabbits inoculated with Brown-Pierce carcinoma was noted over the entire period of observation. The original blood glucose level in intact rabbits was 63.8 ± 3.5 mg/100 ml blood. By Days 10, 20, and 30 of tumor growth, these levels dropped to 58.8 ± 2.0, 41.1 ± 2.9, and 38.1 ± 3.0, respectively. A concomitant depletion of liver and skeletal muscle glycogen in tumor-bearing rabbits was also observed (Table 1).

By Day 30, the concentration of liver glycogen was found to be reduced to 5% of its original value and by Day 20, that of muscle glycogen was found to be reduced 10% of its original value. As previously shown in tumor-bearing rats and mice (23), the only reason for such a depletion in the host's glycogen reserve was its increased mobilization to compensate for the losses caused by the excess consumption of glucose by the tumor.

As to the extent of tumor dissemination (the number and diameter of tumor-lesions in the lung, liver, kidney, diaphragm, peritoneum, large intestine, mesentery, and omentum, measured on autopsy and expressed in arbitrary units), the total values correlated strictly with the progression of hypoglycemia (1). These observations confirmed previous data (22).

A similar correlation between the progression of hypoglycemia and tumor-growth was found in mice bearing Ehrlich ascites carcinoma. The concentration of glucose in the blood of intact mice was as high as 90.8 ± 5.4 mg/100 ml. Within the 1st 4 days after transplantation of the tumor, normal blood glucose concentrations were observed. From then on, however, blood sugar levels started to decrease progressively (Chart 1) to a level of 54.9 ± 5 mg/100 ml by the 8th day. Four animals survived 11 days after inoculation, and the average value for the concentration of glucose in the blood was 45.2, ranging from 35.0 to 55.5.

Hypoglycemia in tumor-bearing mice, progressing from the 5th to the 8th day, was accompanied by an increase in the volume of ascitic fluid (1.5 to 10.6 ml) and in the number of ascites cells (2.8×10^8 to 7.7×10^8 per animal); the high consumption of glucose by these cells was not counterbalanced by an elevation of endogenous glucose production.

As seen in Chart 1, the intensity of glucose formation from tyrosine-^{14}C, glycine-^{14}C, and alanine-^{14}C (not shown) in such mice did not exceed that in control animals.

When intact mice were exposed to prolonged stress known to cause hyperfunction of the adrenal cortex, a marked stimulation of gluconeogenesis from tyrosine-^{14}C was observed.

The mice bearing Ehrlich carcinoma behaved differently under identical conditions. The increase in endogenous glucose production was significantly less pronounced (Table 2). In these tumor-bearing animals, gluconeogenesis in the liver proved to be less sensitive to the action of hormones. The results of the experiments, when cortisol was administered directly into the animals, support the above conclusion. It is apparent (Chart 2), that mice with Ehrlich carcinoma failed to respond to cortisol by an adequate stimulation of gluconeogenesis. This was assessed by measuring both liver glycogen and glucose, as well as blood glucose. On the contrary, the response of Crocker sarcoma-bearing mice (which were able to maintain the normal blood glucose levels) to the hormone was found to be close to that of control animals.

Nevertheless, stress, which provided a stimulus stronger than hypoglycemia, enhanced gluconeogenesis to an extent sufficient to maintain normal glucose levels in mice with

Table 1

Depletion of liver and skeletal muscle glycogen reserves in rabbits in the course of the growth of Brown-Pierce carcinoma

Rabbits	Concentration of glycogen (g/100 g, wet wt)	
	Liver	Muscle
Intact	2.96 ± 0.44[a] (7)[b,c]	0.310-0.537 (3)
Tumor-bearing		
10th day	0.84 ± 0.34 (5)	0.333 (3)
20th day	0.81 ± 0.14 (5)	0.031-0.062 (6)
30th day	0.16 ± 0.05 (5)	

[a] Mean ± S.E.

[b] Numbers in parentheses, number of animals.

[c] Differences for liver are statistically significant at the 0.001 probability level.

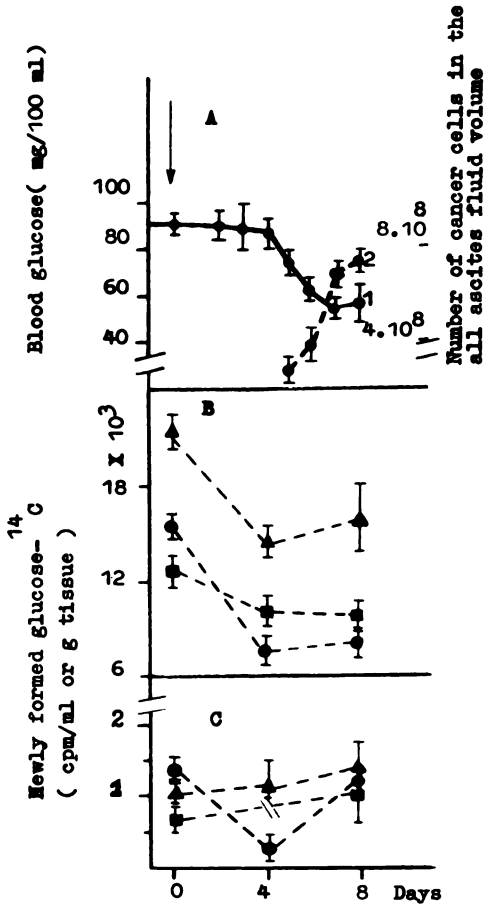

Chart 1. Dynamics of blood glucose and gluconeogenesis in mice with Ehrlich carcinoma. *A*, *Curve 1*, blood glucose levels (5 to 11 mice were killed daily). *Curve 2*, number of cancer cells. The cells from 6 to 7 mice were counted daily in a counting chamber. *B* and *C*, gluconeogenesis. Glucose-^{14}C derived from tyrosine-^{14}C was isolated by paper chromatography and glucose-^{14}C that originated from glycine-^{14}C was separated by the glucose oxidase method (4). Intact and tumor-bearing mice were given 30 μCi, 1.0 ml glycine-^{14}C (*B*) or 30 μCi, 1.0 ml tyrosine-^{14}C (*C*). The animals were killed 1 hr after administration of the isotope. *Points*, mean values for 5 to 7 mice; *arrow* denotes the day after tumor transplantation; ●, blood; ▲, liver; ■, kidney. Mean values ± S.E. are incorporated into this diagram and the ones that follow.

Ehrlich carcinoma by the 8th day of tumor development (Table 3) whereas, in untreated tumor-bearing mice, blood sugar levels dropped drastically (Chart 1).

We should like to stress the point that on measuring the amounts of the radioactive glucose in Ehrlich carcinoma cells *in vivo* 1 hr after tyrosine-^{14}C was administered to the animal, one could see clearly how avidly the cancer cells trapped the glucose produced by the host, especially under stress conditions. Then the figure, corresponding to newly formed glucose accumulated in the cancer cells, increased by 400%, as compared with that in similar cancer cells from untreated tumor-bearing mice (Chart 3).

In contrast to the mice with Ehrlich carcinoma, animals with Crocker sarcoma had no decrease in the concentration of blood glucose during the entire period of tumor development. At the same time, gluconeogenesis was found to be stimulated to a significant degree at the 20th day after transplantation, with tyrosine-^{14}C as a glucose precursor (Chart 4).

This stimulation coincided with a substantial rise in blood glucose levels up to 115 ± 6.1 *versus* 90.8 ± 5.4 mg/100 ml of blood in intact mice ($p < 0.01$). A similar stimulation of gluconeogenesis from tyrosine-^{14}C was observed in mice with Guelstein 22a hepatoma (Chart 5).

The regularity with which stimulation of gluconeogenesis occurred in mice bearing the Crocker sarcoma and Guel-

Table 2

Hepatic gluconeogenesis in mice bearing Ehrlich carcinoma in response to various kinds of stress

The tumor-bearing animals were tried for gluconeogenesis on the 8th day after transplantation. Treatments 1 and 2, stress for 1 hr; in Treatment 3, control and tumor-bearing animals were forced to swim for 8 days in 17-19° water within 15 min every day.

Intact and tumor-bearing mice were given 30 μCi, 1.0 ml tyrosine-^{14}C. In Treatment 1 and 2, the isotope was administered at the start of stress, in Treatment 3, it was administered at the moment the animals stopped swimming. All the animals were sacrificed 1 hr after the labeled precursor was injected.

Glucose-^{14}C, derived from tyrosine-^{14}C, was isolated by paper chromatography, and its radioactivity was expressed in counts/100 sec/g liver.

Treatment	Mice		
	Control	Tumor-bearing	*p*
1. Immobilization	3270 ± 513	990 ± 94	<0.01
2. Suspension by the fold of the nape	4420 ± 470	1430 ± 68	<0.01
3. Swimming	6450 ± 303	2500 ± 560	<0.01

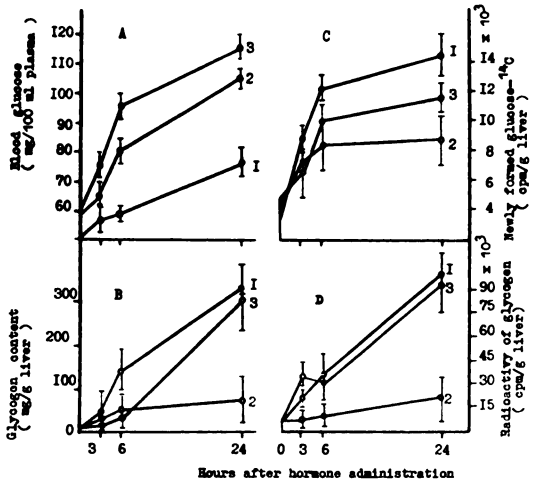

Chart 2. Gluconeogenic response of normal and tumor-bearing mice to cortisol; *A*, blood glucose levels; *B*, changes in glycogen content in liver; *C*, glucose formation from uniformly labeled alanine-^{14}C in liver. The radioactive precursor introduced into the animals in succession (2.5 μ Ci/mouse/day); *D*, dynamics of glycogen synthesis from glycine-^{14}C in liver as revealed by the radioactivity of glycogen. *1*, control; *2*, mice with Ehrlich carcinoma 8 days after transplantation; *3*, mice with Crocker sarcoma 20 days after transplantation. Each *point* of the curves corresponds to a mean value obtained on 15 (*A*) and 5 (*B*, *C*, *D*) animals. Starting from the moment the isotope was introduced, the animals starved for 18 hr (12). At zero time, cortisol, 5 mg/mouse, was given.

Table 3

Blood glucose levels in mice bearing Ehrlich carcinoma under various experimental conditions

Group 1: control and tumor-bearing animals, the latter 8 days after transplantation; Group 2: animals are as in Group 1, but 5 mg of cortisol was given each mouse daily over 8 days; Group 3: animals as in Group 1, but after swimming in 17–19° water for 15 min daily for 8 days. All mice were sacrificed at Day 8, 5 to 6 hr after the last treatment.

When p was calculated, the experimental groups were compared to the animals of Group 1.

Mice	Control	p	Tumor-bearing	p
1. Untreated	90.8 ± 5.4[a] (15)[b]		54.9 ± 5.0 (8)	<0.001
2. Cortisol	57.9 ± 15.2 (6)	N.S.	70.8 ± 8.7 (12)	<0.05
3. Swimming	66.1 ± 2.1 (6)[c]	0.01	81.2 ± 9.2 (12)	<0.05

[a] Mean ± S.E.

[b] Numbers in parentheses, number of animals.

[c] In control animals 5 to 6 hr after they stopped swimming, blood sugar level dropped, whereas in tumor-bearing mice it turned out to be higher as compared with their untreated counterparts. This phenomenon may be due to a diminished glucose tolerance in tumor-bearing animals (see Ref. 1).

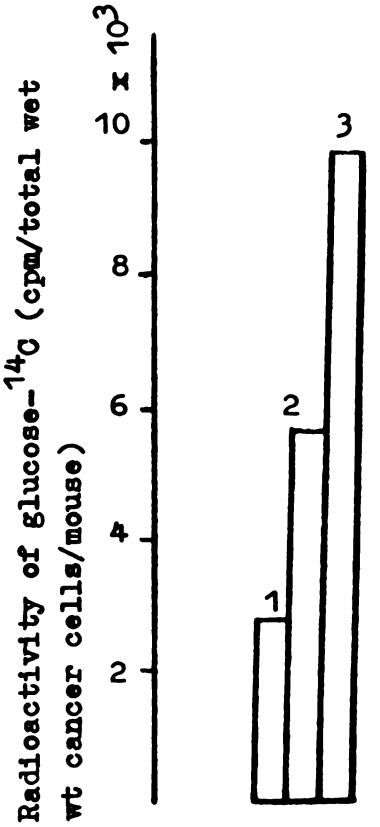

Chart 3. The *in vivo* accumulation of newly formed glucose by Ehrlich ascites carcinoma cells under stress conditions. *1*, untreated tumor-bearing mice 8 days after transplantation. *2* and *3*, mice as in *1*, but immobilized or swam, respectively. All the animals were given 30 μCi, 1.0 ml tyrosine-^{14}C, sacrificed 1 hr thereafter, and glucose-^{14}C was then isolated by paper chromatography. *Bars*, mean values for 6 mice.

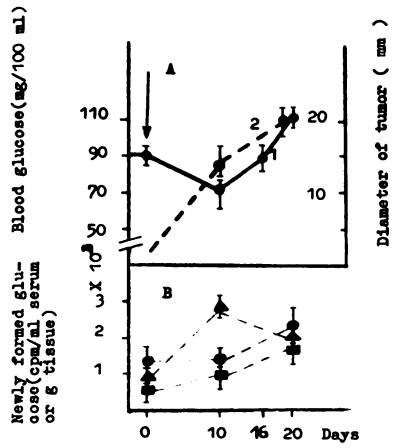

Chart 4. Dynamics of blood glucose and gluconeogenesis in mice with Crocker sarcoma. Designations and conditions as in Chart 1. Glucose-^{14}C, derived from 30 μCi, 1.0 ml tyrosine-^{14}C, was isolated by paper chromatography. Diameter of the tumor was measured as described (24).

stein 22a hepatoma was confirmed in the experiments carried out on the rats with Zajdela hepatoma (Chart 6). Normoglycemia was maintained in the host throughout the entire period of tumor development, owing to an enhanced glucose production (as high as 2.8-fold) measured by the use of tyrosine-^{14}C as a glucose precursor.

When the mice bearing Crocker sarcoma were given daily injections of glucose (10 mg/g of body weight), within 20 days a statistically significant hyperglycemia, 139 ± 3.7 mg glucose per 100 ml blood, was observed.

Hyperglycemic mice displayed a marked reduction of gluconeogenesis in the liver by a factor of 1.3, and in the kidney by 1.7, in comparison with nontreated tumor-bearing mice. In the latter, the blood levels of newly formed glucose were 3 times as high as in hyperglycemic animals.

DISCUSSION

The major finding of the present paper is the conclusion that enhancement of gluconeogenesis (at least partly influenced by the adrenal cortex) is to be regarded as one of the principal mechanisms counterbalancing a consistent tendency toward hypoglycemia in tumor-bearing animals.

The correlation between the maintenance of normoglycemia and the stimulation of gluconeogenesis from noncarbohydrate sources has been shown in mice with Crocker sarcoma and Guelstein 22a hepatoma, and in rats with Zajdela hepatoma.

In the case of Crocker sarcoma, despite the large size of the developing tumor, even slight hyperglycemia was noted.

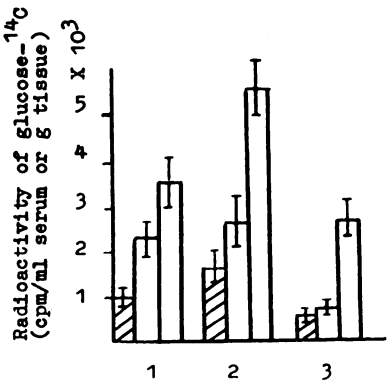

Chart 5. Gluconeogenesis in mice with Guelstein 22a solid hepatoma. Glucose^{14}C was isolated by paper chromatography; 30 μCi tyrosine-^{14}C, 1.0 ml/mouse, exposed to the isotope 1 hr. ▩, control; □, tumor-bearing animals; *1*, blood; *2*, liver; *3*, kidney. *First and 2nd open columns*, 10 and 20 days after transplantation, respectively.

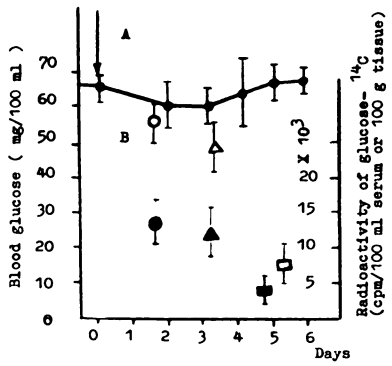

Chart 6. Blood glucose levels (*A*) and gluconeogenesis (*B*) in rats with Zajdela hepatoma. Glucose-^{14}C was isolated by paper chromatography; 200 μCi, 1.0 ml tyrosine-^{14}C/rat; exposed to the isotope 1 hr. Animals were sacrificed at the 4th day after transplantation. ○, △, and □, control animals; ●, ▲, and ■, tumor-bearing rats. Designations as in Chart 1.

Thus, gluconeogenesis in the host seems to be stimulated to a greater extent than is needed. A similar phenomenon may be underlying hyperglycemia, sometimes detected in patients with malignant neoplasms (5).

Our observations concerning the stimulation of gluconeogenesis in tumor-bearing animals are in line with the data on the enhanced activity of gluconeogenic enzymes in the liver of tumor-bearing animals (10). This is in agreement with Greengard *et al.* (9) who reported an elevation of liver tryptophan pyrrolase and tyrosine transaminase activities in tumor-bearing animals, and a reduction of the enzyme levels after adrenalectomy (11, 13). When animals bearing the same tumor that caused a marked stimulation of gluconeogenesis were "presaturated" with glucose for the duration of the experiment, no extra production of endogenous glucose was evidenced.

Indeed, the amount of labeled glucose circulating in the blood of the tumor hosts presatured with cold glucose was found to be one-third of that in the nontreated mice bearing Crocker sarcoma (13,510 and 39,500 cpm, respectively), whereas the total amount of glucose (both labeled and nonlabeled) in the blood of the former group of mice increased only from 17.3 to 20.9 mg. Therefore, the reduction of glucose-specific activity in their blood cannot be attributed to isotope dilution and influence the validity of our interpretation of the results concerning newly formed glucose.

We did not assess the glucose-turnover rate, but the fact that no increase in the labeling of glucose in the blood, liver, and kidney was observed in mice with Ehrlich carcinoma developing a severe hypoglycemia lends support to our interpetation of the changes in the radioactivity of glucose after the administration of amino acids, as an index of the intensity of gluconeogenesis.

We regard the inability of these mice to maintain normal blood sugar levels as a consequence of reduced sensitivity of the tissues involved in gluconeogenesis to a stimulation of glucocorticoids. Several lines of evidence support this idea. (*a*) When mice with Ehrlich carcinoma were subjected to stress (Table 2), or given cortisol, they formed less endogenous glucose from radioactive amino acids (tyrosine-^{14}C, alanine-^{14}C, glycine-^{14}C) than healthy control animals under identical conditions (Chart 2, *B*, *C*, and *D*).

As a result, the increment in blood glucose levels (Chart 2*A*) in response to cortisol treatment was shown to be significantly less pronounced when compared with similarly treated control mice. (*b*) A marked stimulation of gluconeogenesis in mice bearing Ehrlich carcinoma could be elicited only by large amounts of the hormones either produced by the host's adrenal cortex (extensive stress) or administered exogenously (Ref. 3; see also Table 3).

The ability of the Ehrlich carcinoma to reduce responsiveness of the host's tissues, affecting gluconeogenesis, may reflect a systemic action of the neoplasm on the distant organs.

In Crocker sarcoma-bearing mice that maintained normal blood glucose levels, the response to cortisol proved close to those characteristic of control animals.

The behavior of rabbits bearing Brown-Pierce carcinoma deserves special attention. These animals were shown to develop severe hypoglycemia that correlated with the intensity of tumor growth and its dissemination (see above). The study of endogenous glucose production from tyrosine-^{14}C in these rabbits (4) revealed some enhancement of gluconeogenesis in the liver, but its level was reduced in the kidney. However, the stimulation of gluconeogenesis in these tumor-bearing animals, in general, was obviously insufficient, since the concentration of radioactive glucose in the blood was either equal to or significantly lower than that of intact control rabbits. They maintained a normal blood insulin level (data not shown), measured by a radioimmunoassay. However, in such rabbits, glucose intolerance, increasing sharply from the 10th to 30th day after transplantation, could be observed after both a single and a repeated glucose load (2). The response to the glucose tolerance test became normal, provided the animals were presaturated with glucose by daily injections from the 1st to the 30th day of inoculation (21). The same treatment (see above) reduced enhanced gluconeogenesis in mice bearing Crocker sarcoma.

Many questions remain to be elucidated. For instance, no data are currently available as to the capacity of various malignant tumors to produce glucose themselves. Observa-

tions concerning the potential activity of the enzymes participating in gluconeogenesis in many Morris hepatomas provide no information as to whether the glucose production from noncarbohydrate compounds can actually proceed in the tumor, even if it preserves some of the gluconeogenic enzymes. Experiments are now underway in this laboratory to clarify these questions.

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