The experimental production of ascites tumors in mice was first reported by Lowenthal and Jahn (8) following the intraperitoneal injection of a brei prepared from the solid Ehrlich mouse carcinoma. The ascites tumor is a suspension of free and homogeneously distributed tumor cells in the ascites fluid of the peritoneal cavity. The tumor is readily transmissible and infects and kills essentially 100 per cent of the animals (6). The survival time is proportional to the number of cells injected and is highly reproducible for a given inoculum (7, 8). Recent in vitro studies (1@) demonstrated that small amounts of glucose stimulated the oxygen consumption of ascites tumor cells, while large concentrations had an inhibitory effect. This influence of glucose levels suggested that it might be of interest to investigate the reactions of animals with naturally occurring and induced hyperglycemia to ascites tumors. Such a study was made possible by the availability of mice with hereditary obesity and hyperglycemia (obob gene) (10) and the production of alloxan diabetes in mice. Under each of the two conditions of diabetes there was slower growth of ascites tumor and a prolonged survival of the animals.

MATERIALS AND METHODS

Twenty-seven obob animals, eleven obese (40–80 gm.) and sixteen control litter-mates (20–32 gm.), were employed in this part of the experimentation. The animals were 5–7 months of age, and each of the two groups contained about equal numbers of males and females. Blood glucose levels were determined in seven of the obese animals, by the Somogyi method (14) and with Nelson’s color reagent (13), and were found to be 200–548 mg. per cent.

The alloxan diabetic mice were 2–4-month-old male and female C57BL mice weighing 17–23 gm. Diabetes was produced (4) by the subcutaneous administration of 400 mg/kg of alloxan (Eastman) to mice fasted 48 hours. The alloxan was given over a 3-day period in daily doses of 100, 100, and 100 mg/kg. During this period a 5 per cent glucose solution was offered the animals to protect against the early hypoglycemic phase. A diabetic state was determined by qualitative analysis of the urines with Benedict’s reagent and quantitative microanalyses of tail blood (13, 14). The 28 diabetic mice were used for tumor experimentation within 1–4 weeks of treatment with alloxan.

All animals were kept in cages with screened bottoms and allowed free access to water and Purina Laboratory Chow. Food intakes were observed to be unchanged during the first several days after the injection of tumor and then gradually dropped to near zero levels in the terminal state.

The ascites tumor, 0.3 ml. with the obob animals and 0.2 ml. with the C57BL mice, was injected intraperitoneally. The donor animal for the obob mice was a Swiss mouse bearing the Ehrlich ascites carcinoma, while the donors for the C57BL mice were Ehrlich ascites tumor-bearing C57BL mice. Thus far in our studies no morpho-

The authors are indebted to Dr. H. N. Christensen, Department of Biochemistry, Tufts Medical School, Boston, for the gift of an ascites tumor-bearing animal.
logical, chemical, or metabolic differences have been observed in this ascites carcinoma grown in various strains of mice, although certain cyclic changes in the tumor have been observed even within a given strain of mouse.

Duration of survival of the mice was noted to the nearest half day. It was observed in other studies with the carcinoma (15), that the amounts of tumor produced in the alloxan diabetic mice were considerably less than in the nondiabetic mice. Although it was not possible to quantitate the amount of tumor in the obese mice, the material in the obese appeared to be less and of a more viscous nature than that in the control mice.

RESULTS

The obese animals survived, on the average, 4.6 days longer than the nonobese litter-mates. The survival times, with the standard deviations of the two groups, are shown in Table 1. Probability tests show that the differences noted between obese and control thin mice are highly significant (P < 0.01).

Similarly, the alloxan diabetic mice survived, on an average, 2.0 days longer than the nondiabetic controls. The survival times, with the standard deviations of the two groups, are shown in Table 1. Probability tests show that the differences noted here are also highly significant (P < 0.01). The picture here is complicated, but in favor of an even larger significant difference, because of occasional deaths of the control (diabetic) animals due to the diabetes. This is difficult to evaluate, so there has been no attempt to consider it in the calculations; however, it makes more certain the longer survival of the diabetic-tumor animals.

It is of interest that the glucose content of the ascites tumor from nondiabetic mice was low and constant at 2-5 mg/100 ml (mg. per cent), while the glucose content of the tumor from alloxan diabetic animals ranged up to 34 mg. per cent. In one instance the glucose content of the tumor from an obese-hyperglycemic mouse was 138 mg. per cent, and at the same time the blood glucose of the animal was 548 mg. per cent. As indicated in Table 2 the presence of a tumor in the animals lowers their blood glucose levels. This would be expected from the rapid rate of glucose utilization by the tumor cells (12).

### TABLE 2

<table>
<thead>
<tr>
<th>Glucose Content of Tumor (mg. per cent)</th>
<th>Duration of Survival (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alloxan diabetic</td>
<td>15</td>
</tr>
<tr>
<td>Controls</td>
<td>20</td>
</tr>
<tr>
<td>Obese-hyperglycemic</td>
<td>8</td>
</tr>
<tr>
<td>Nonobese litter-mates</td>
<td>18</td>
</tr>
</tbody>
</table>

* t-test = P < 0.01.

### DISCUSSION

The obese-hyperglycemic syndrome has been described in a number of reports (9-11). These hereditarily obese animals manifesting this genetic characteristic are overweight, show an increased rate of carcass and liver lipogenesis from C14-labeled acetate even when underfed or fasted, and are usually hyperglycemic in spite of high pancreatic content of insulin. High blood glucose levels can be elicited by a single injection of growth hormone in the obese mouse but not in the nonobese animals, which have normal blood sugar levels. These obese mice are very much more sensitive to external traumas (infections, posthemorrhoidal treatments, changes in diet, etc.) than are the nonobese animals (5, 10). When the weight of the obese animals is decreased by underfeeding to normal or subnormal levels, fat is preferentially retained at levels several times the normal.

Waxler, Tabar, and Melcher (16) observed that goldthioglucose obesity was associated with an earlier appearance of spontaneous mammary carcinoma and a shorter duration of survival, as compared with un.injected animals or with goldthioglucose-treated mice which did not become obese. However, it has been demonstrated (9, 10) that this type of obesity is metabolically different from the obese-hyperglycemic type. Animals with goldthioglucose obesity exhibit increased lipogenesis only to the extent that they are allowed to overeat. Their blood glucose is normal and is not raised by growth hormone treatment (11).

Dunning, Curtis, and Friedgood (2) found with alloxanized rats that the diabetes did not delay or prevent the onset of benzpyrene-induced sarcomas. Similarly, Sarcoma 37 grew as fast in alloxan diabetic rats as in nondiabetic animals (1). However, Goranson, Botham, and Willms (3) found...
that the transplanted hepatoma (Novikoff) reduced the level of blood sugar in the rat; the successful tumor takes were reduced to 57.5 per cent; the tumor weights were reduced to 38 per cent of the controls; and, in some instances, alloxan injected into tumor-bearing animals caused complete regression of the tumor.

It is of interest that preliminary observations (15) with the tumor cells from the alloxan diabetic mice indicated a slower rate of metabolism of added acetate and an increased rate of alanine decarboxylation than by the tumor cells from non-alloxan diabetic mice. With these in vitro experiments the presence or absence of glucose does not appreciably influence the altered metabolism of acetate or alanine. Thus, the influence, per se, of high blood sugar seems less likely as a causative agent; yet it still is not ruled out. The reduced oxidative metabolism of the tumor cells in vitro in the presence of amounts of glucose in excess of about 20 mg. per cent (19) may very well have an effect on the rate of growth of the tumor cells. These studies are being pursued in an attempt to determine the reasons for the slower rate of tumor growth and the prolonged survival of the host mice.

SUMMARY

1. Mice with the hereditary obese-hyperglycemic syndrome survived significantly longer than control nonobese animals when given injections intraperitoneally of Ehrlich mouse ascites carcinoma cells.

2. C57BL mice with induced alloxan diabetes survived significantly longer than the control non-diabetic mice when injected intraperitoneally with Ehrlich mouse ascites carcinoma cells.

3. The results are discussed in light of the fact that the hereditarily obese-hyperglycemic mice have an increased rate of lipogenesis from acetate even when food intake is limited and show hormonal imbalance; and in view of the preliminary findings that the Ehrlich mouse ascites tumor cells from alloxan diabetic mice have a lowered acetate metabolism and an increased alanine decarboxylation.

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Influence of the Hereditary Obese-Hyperglycemic Syndrome and of Alloxan Diabetes on the Survival of Mice with Ehrlich Ascites Carcinoma

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