Pregnancy, Tumor Growth, and Liver Regeneration

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We have previously reported observations on tumor growth in partially hepatectomized rats. These studies were undertaken to investigate the extent to which two rapidly growing tissues might compete for metabolic requirements for increased anabolic processes. In the case of tumor growth in the presence of regenerating liver after partial hepatectomy, no evidence for such competition was found; in fact, the growth of certain tumors was significantly enhanced without simultaneous impairment of liver regeneration (18). The present report deals with similar observations on fetal growth and liver regeneration and on fetal growth in the presence of transplanted tumors.

MATERIALS AND METHODS

Pregnancy and liver regeneration.—Rats of the Sherman strain (Barkbridge Farms, N.J.) were mated between 6 and 7 P.M. The next morning, at 9:00 A.M., the animals were separated, and vaginal smears were examined for the presence of sperm. If positive, this day was recorded as day 1 of pregnancy. Occasionally, although rarely, an animal did not conceive, despite a fertile mating as evidenced by the presence of sperm in the vagina.

Partial hepatectomy was performed under ether anesthesia by the technic of Higgins (12), by which 67 per cent of the liver is removed. Control animals were subjected to a “sham operation,” in the course of which the liver was brought outside the abdomen and subjected to manipulation. In both the partially hepatectomized and the sham-operated animals, the uterus was inspected at operation to confirm the presence of pregnancy. This was particularly important in those experiments in which partial hepatectomy was performed early in pregnancy, at a time when the fetuses were not detectable by abdominal palpation.

Comparison of the fetal weights after spontaneous delivery would involve certain difficulties. Before a litter would be discovered, varying amounts of milk might have been ingested. Moreover, variation in the length of gestation (21–23 days) might cause differences in fetal weight. Consequently, all animals were killed on the 20th day of pregnancy by exsanguination under light ether anesthesia. The following weights were recorded: body, liver, uterus (full), fetuses plus placenta, and fetuses alone. Furthermore, the number of dead fetuses was noted as well as the number of resorption sites, consisting of varying amounts of placental remnants without amniotic sacs or fetuses. Liver regeneration was calculated on the basis of the weight of the portion of the liver excised at operation and that of the liver mass found at autopsy, according to the formula of Canzanelli et al. (5).

Three groups of rats and their respective controls were studied. Group I was operated upon (partial hepatectomy) on the 8th day of pregnancy and each of the 20th; Group II was operated upon the 17th day and killed on the 20th; Group III was operated upon the 8th day and killed on the 16th. All animals received a stock diet (Purina Dog Chow).

The influence of the protein content of the diet was studied in one experiment, in which partial hepatectomy was performed on the 8th day of pregnancy and the fetuses harvested on the 20th day. Two levels of protein feeding (casein) were employed, 16 per cent and 64 per cent, in diets reported previously (21). Groups of pregnant rats subjected to “sham operation” only, and fed the two diets, served as controls.

One group of animals hepatectomized on the 17th day and killed on the 20th received daily subcutaneous injections of 5 mg. of progesterone and 1 µg. of estrone, beginning on the day of operation.

Pregnancy and growth of transplanted tumors.—Mating, establishing the presence of sperm in the vagina, and sacrificing on the 80th day were carried out in the manner described above. Three transplantable tumors were employed: (a) a lymphosarcoma (Murphy), grown in Wistar rats; (b) a hepatoma, originally developed in A X C rats by Dr. H. Morris (Nat. Cancer Institute) by feeding diacetylaminofluorene; and (c) the Walker 256 tumor, grown in Sprague-Dawley rats. The Wistar and Sprague-Dawley rats were obtained from Barkbridge Farms, N.J. The A X C rats were at first generously supplied by Dr. H. Morris; later they were bred for us at Barkbridge Farms, N.J., from breeders obtained from Dr. Morris.

Tumor inoculation was performed by subcutaneous injection of a suspension of tumor cells; the hepatoma was inoculated on the 4th, the lymphosarcoma on the 11th day of pregnancy. Two series were studied with the Walker 256 tumor, with inoculation on the 6th and 12th days, respectively. In each of the three strains, two control series were employed: (a) tumor-bearing, nonpregnant rats (injected with the same cell suspension as the pregnant animals) and (b) tumor-free, pregnant rats. In addition, a group of normal female rats (non-pregnant, tumor-free) from each of the three strains was sacrificed. At autopsy, the body weight, liver weight, tumor weight, weight of the pregnant uterus and of the fetuses were obtained. Liver weights were recorded both as actual weight and as percentage of body weight. It appeared preferable to express liver weight as the percentage of total body weight rather than of carcass weight (body weight minus tumor, or pregnant uterus, or both), because the increased liver size

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probably bears some relation to the metabolic needs of the total tissue mass.

RESULTS

In the first experiment (Table 1), partial hepa-
tectomy was performed on the 8th day of preg-
nancy, and the animals were killed on the 20th
day. Fetal survival was severely impaired: com-
plete resorption of the products of gestation oc-
curred in four of thirteen pregnancies; in the
other nine animals there were many resorption
sites which showed only placental remnants. The
mean number of fetuses per pregnancy was 3.4,
as against 9.8 in the sham-operated pregnant
control animals. Growth of the surviving fetuses
was impaired, as evidenced by a mean fetal weight
of 1.9 gm. in the partially hepatectomized animals,
as against 2.2 gm. in the pregnant controls. Re-
generation of the liver, over the 12-day period,
was significantly enhanced in the pregnant ani-
mals (92.7 per cent as against 64 per cent in the
hepatectomized nonpregnant controls).

In the second experiment (Table 1), partial
hepatectomy was performed on the 17th day of
pregnancy, and the animals were killed on the 20th
day. Complete resorption occurred in none of the
twelve pregnancies, but numerous partial resorp-
tion sites were evident. Consequently, the mean
number of surviving fetuses per pregnancy was
5.0, as against 9.8 in the nonhepatectomized preg-
nant controls; significant impairment of fetal
growth was evident, the mean fetal weight being
1.6, as against 2.2 in the pregnant controls. At
autopsy, ascites was present in four of the twelve
hepatectomized pregnant animals. Liver regenera-
tion did not differ significantly from that in the
nonpregnant hepatectomy controls.

In the third experiment (Table 1), in which
partial hepatectomy was performed on the 19th
day and the animals killed on the 15th day,
exposure to the regenerating liver was for the
same time as in Group 2, but earlier in pregnancy,
at a time when the fetal growth rate is relatively
slow. Of fourteen pregnancies in partially hepa-
tectomized rats, in this group all fetuses were
dead and partially macerated in three, and in
five others there were placental remnants in addi-
tion to live fetuses. The number of surviving
fetuses did not differ from that of sham-operated
pregnant controls, but the mean fetal weight was
significantly less in the partially hepatectomized
animals (0.16 gm. as against 0.19 gm.). Ascites

<table>
<thead>
<tr>
<th>Exper. procedure</th>
<th>Group</th>
<th>No. of animals</th>
<th>Mean no. of fetuses</th>
<th>Mean fetal wt. (gm.)</th>
<th>Liver reg. (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatect. 8th day, autopsy 20th day</td>
<td>Preg. contr.</td>
<td>7</td>
<td>9.8</td>
<td>$2.25 \pm 0.31$</td>
<td>64 ±1.7*</td>
</tr>
<tr>
<td></td>
<td>Hepatect. contr.</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatect. hepatect.</td>
<td>13±‡</td>
<td>3.4</td>
<td>1.90 ± 0.2</td>
<td>92.7 ± 8.1 P &lt; 0.01</td>
</tr>
<tr>
<td>Hepatect. 17th day, autopsy 20th day</td>
<td>Preg. contr.</td>
<td>7</td>
<td>9.8</td>
<td>$2.35 \pm 0.31$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatect. hepatect.</td>
<td>12‡</td>
<td>5.0</td>
<td>1.60 ± 0.1 P &lt; 0.05</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Hepatect. hepatect. est. and progest.</td>
<td>18</td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Preg. hepatect. est. and progest.</td>
<td>5±§</td>
<td>4.7</td>
<td>1.80 ± 0.19</td>
<td>60</td>
</tr>
<tr>
<td>Hepatect. 12th day, autopsy 15th day</td>
<td>Preg. contr.</td>
<td>10</td>
<td>9.6</td>
<td>0.19 ± 0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatect. hepatect.</td>
<td>13</td>
<td>10.2</td>
<td>0.16 ± 0.02 P &lt; 0.02</td>
<td>45.8</td>
</tr>
</tbody>
</table>

* Standard error.
† 4/13 complete resorption.
‡ 4/10 ascites.
§ 3/5 ascites.

Influence of ovarian hormones (Table 1).—One
group was subjected to partial hepatectomy on
the 17th day and was autopsied on the 20th
day of pregnancy. Beginning on the day of opera-
tion, each rat received, by subcutaneous injection,
1 µg. of estrone and 5 mg. of progesterone daily.
As indicated in Table 2, treatment with these
ovarian hormones had no significant influence
on the number of surviving fetuses or the fetal
weight. The mean values for liver regeneration
were slightly higher in the hormone-treated group,
but the difference is not significant statistically.

Influence of high-protein diet (Table 2).—Com-
parison of the effects of partial hepatectomy in
pregnant rats fed a 16 per cent protein diet
with those fed a 64 per cent protein diet reveals
that the high-protein diet not only failed to im-

TABLE 1

PARTIAL HEPATECTOMY IN PREGNANT RATS

<table>
<thead>
<tr>
<th>Exper. procedure</th>
<th>Group</th>
<th>No. of animals</th>
<th>Mean no. of fetuses</th>
<th>Mean fetal wt. (gm.)</th>
<th>Liver reg. (per cent)</th>
</tr>
</thead>
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<td>$2.25 \pm 0.31$</td>
<td>64 ±1.7*</td>
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<td></td>
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<td>1.60 ± 0.1 P &lt; 0.05</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Hepatect. hepatect. est. and progest.</td>
<td>18</td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Preg. hepatect. est. and progest.</td>
<td>5±§</td>
<td>4.7</td>
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</tr>
<tr>
<td>Hepatect. 12th day, autopsy 15th day</td>
<td>Preg. contr.</td>
<td>10</td>
<td>9.6</td>
<td>0.19 ± 0.03</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>45.8</td>
</tr>
</tbody>
</table>

* Standard error.
† 4/13 complete resorption.
‡ 4/10 ascites.
§ 3/5 ascites.
prove, but actually further impaired, fetal survival after heparatectomy. Complete resorption occurred in five of six pregnancies (83 per cent) in rats fed 64 per cent protein, and in only two of seven (29 per cent) in animals fed 16 per cent protein. The latter figure is identical with that obtained in the rats fed stock diet (Purina Dog Chow).

No damaging effects of the high-protein diet were observed in the nonheparatectomized pregnancy controls. There was no significant difference in either the mean number of fetuses per pregnancy, the mean fetal weight, or the liver weight (in per cent of body weight) in the pregnant animals fed 16 per cent protein, 64 per cent protein, or stock Purina Dog Chow diets.

### TABLE 2

**PARTIAL HEPALETECTOMY IN PREGNANT RATS**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. animals</th>
<th>Diet, per cent prot.</th>
<th>Mean no. of fetuses</th>
<th>Mean fetal wt. (gm.)</th>
<th>Liver reg. (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preg. contr.</td>
<td>6</td>
<td>16</td>
<td>8.8</td>
<td>2.12</td>
<td>99 Compl. resorp. in 2/7 (29 per cent)</td>
</tr>
<tr>
<td>Preg. hepatect.</td>
<td>7</td>
<td>16</td>
<td>4.7</td>
<td>2.02</td>
<td>99 Compl. resorp. in 2/7 (29 per cent)</td>
</tr>
<tr>
<td>Preg. contr.</td>
<td>6</td>
<td>64</td>
<td>7.7</td>
<td>2.16</td>
<td>97 Compl. resorp. in 5/6 (83 per cent)</td>
</tr>
<tr>
<td>Preg. hepatect.</td>
<td>6</td>
<td>64</td>
<td>1.3</td>
<td>2.17</td>
<td>97 Compl. resorp. in 5/6 (83 per cent)</td>
</tr>
<tr>
<td>Preg. contr.</td>
<td>9*</td>
<td>25†</td>
<td>9.8</td>
<td>2.25</td>
<td>92.7 Compl. resorp. in 4/13 (50 per cent)</td>
</tr>
<tr>
<td>Preg. hepatect.</td>
<td>13*</td>
<td>25†</td>
<td>3.4</td>
<td>1.90</td>
<td>92.7 Compl. resorp. in 4/13 (50 per cent)</td>
</tr>
</tbody>
</table>

* From Table 1.

† Purina Dog Chow.

### TABLE 3

**TUMOR GROWTH IN PREGNANT RATS**

<table>
<thead>
<tr>
<th>EXPER. PROCEDURE</th>
<th>GROUP</th>
<th>NO. ANIMALS</th>
<th>Wt./fetus (gm.)</th>
<th>PER CENT OF BODY WT.</th>
<th>TUMOR (gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma in AXC rats, tu. inoculated on 4th day, autopsy on 20th day</td>
<td>Tumor</td>
<td>10†</td>
<td>7.0</td>
<td>2.14 ± 0.05 †</td>
<td>8.2</td>
</tr>
<tr>
<td>Lymphosarcoma in Wistar rats, tu. inoculated on 12th day, autopsy on 20th day</td>
<td>Tumor</td>
<td>15‡</td>
<td>9</td>
<td>2.18 ± 0.1 ‡</td>
<td>11.2</td>
</tr>
</tbody>
</table>

* Means ± standard errors of means.
† Difference statistically not significant.
‡ In one pregnancy (9.1 per cent) fetuses were dead and partly resorbed. Two further animals are excluded because of multiple congenital malformation, including single uterine horn.
§ In one of these fetuses dead.
|| P of difference <0.01.

### TABLE 4

**TUMOR GROWTH IN PREGNANT RATS**

<table>
<thead>
<tr>
<th>EXPER. PROCEDURE</th>
<th>GROUP</th>
<th>NO. ANIMALS</th>
<th>Wt./fetus (gm.)</th>
<th>PER CENT OF BODY WT.</th>
<th>TUMOR (gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tu. inoculated on 6th day, autopsy on 20th day</td>
<td>Tumor</td>
<td>13</td>
<td>12.8</td>
<td>4.4 ± 0.14</td>
<td>57.8 ± 8.49</td>
</tr>
<tr>
<td>Tumor</td>
<td>25†</td>
<td>9.3</td>
<td>2.35 ± 0.09</td>
<td>14.1</td>
<td>4.31 ± 0.03</td>
</tr>
<tr>
<td>Controls</td>
<td>6</td>
<td>9.5</td>
<td>2.35 ± 0.13</td>
<td>10.4</td>
<td>3.81 ± 0.14</td>
</tr>
<tr>
<td>Tu. inoculated on 12th day, autopsy on 20th day</td>
<td>Tumor</td>
<td>14</td>
<td>9.1</td>
<td>3.4 ± 0.15</td>
<td>6.49 ± 1.37</td>
</tr>
<tr>
<td>Tumor</td>
<td>15</td>
<td>10.2</td>
<td>2.39 ± 0.06</td>
<td>11.2</td>
<td>3.6 ± 0.10</td>
</tr>
<tr>
<td>Controls</td>
<td>6</td>
<td>9.5</td>
<td>2.35 ± 0.13</td>
<td>10.4</td>
<td>3.8 ± 0.14</td>
</tr>
</tbody>
</table>

* Standard error of mean.
† In five of these pregnancies (82 per cent) there were additional dead fetuses or resorption sites.
‡ P of difference <0.05.
Pregnancy and tumor growth.—The pertinent findings are summarized in Tables 3 and 4. In no instance did the presence of a growing tumor affect the mean number of fetuses or the mean weight of the individual fetuses. This was equally true of animals bearing small tumors (lymphosarcoma, hepatoma, Walker 256, second series), and of those bearing large Walker tumors. However, there were some dead fetuses or resorption sites in five of 23 (22 per cent) pregnancies in animals bearing the large Walker tumors (Table 4). In the animals bearing the small Walker tumors (Table 4) and in those bearing the small lymphosarcoma (Table 3), intrauterine fetal death occurred only occasionally, as was the case also in normal pregnant rats. Dead fetuses or resorption sites were observed in eight of nineteen (42 per cent) A × C rats bearing small hepatomas.

The mean weights of the tumors of pregnant animals did not differ significantly from those of nonpregnant animals in any of the experimental groups.

The liver weight was greater in all pregnant animals than in normal, nonpregnant controls. The livers of pregnant, tumor-bearing animals showed a further weight increase over that induced by pregnancy alone, regardless of the size of the tumors, with the exception of the hepatoma-bearing A × C rats—in the latter, the presence of a tumor was associated with no further increase of liver weight. In two groups (lymphosarcoma, large Walker tumor) there was an increase of not only the absolute liver weights but also the relative liver weights (percentage of total body weight).

DISCUSSION

Influence of regenerating liver and of tumor growth on pregnancy.—Fetal growth and survival are severely impaired following partial hepatectomy. Certain observations suggest that this effect is not due merely to unsuccessful competition of the fetus with the regenerating liver for the metabolic pool of amino acids. Nelson and Evans (15) reported death of all fetuses in rats fed a protein-free diet, survival occurring, however, when estrone and progesterone were administered during the period of protein deprivation. In the present study, administration of these hormones did not improve fetal growth or survival, and no beneficial effect was produced by substituting an isocaloric 64 per cent protein diet for the stock 16 per cent protein diet.

In contrast to its deleterious influence on fetal growth, partial hepatectomy is followed by actual enhancement of certain growth processes: partial hepatectomy in one member of a parabiotic pair is followed by stimulation of mitotic activity in the liver of the intact parabiont (8, 6); growth of certain transplanted tumors is enhanced by partial hepatectomy (18), as are corneal mitosis and the compensatory hypertrophy of the kidney following unilateral nephrectomy (17). In this connection, a comparison of the effects of regenerating liver with those of a transplanted tumor on fetal growth and survival is of importance. Bly et al. reported various degrees of fetal damage in pregnant rats bearing the Walker 256 tumor (1). In none of our experiments with tumor transplants in pregnant animals was there as severe an impairment of the fetuses as occurred in the partially hepatectomized pregnant rat. This is equally true in experiments in which the tumor reached only moderate size (2–6 gm.) and those in which the mean tumor weight was 54 gm. The synthesis of tissue in this amount would appear to involve a greater demand on the metabolic pool than the synthesis of about 3–6 gm. of liver tissue (depending on the length of the regeneration period in different experiments). On the other hand, whereas the total amount of tissue formed during the experimental period is greater in the case of large tumors, the rate of tissue synthesis per unit time may well be higher in the case of regenerating liver, at least during certain phases of liver regeneration. However, the presence of a growing tumor did influence the fetuses to some extent. This was not reflected in the mean weight of surviving fetuses, which in no instance differed from that of the controls, whereas the growth of surviving fetuses was severely impaired following partial hepatectomy. In spite of the identical mean fetal weights, there were 5/20 (25 per cent) litters with a mean fetal weight of less than 2 gm. in the Sprague-Dawley rats bearing large Walker tumors, as against 1/7 (14 per cent) in the pregnancy controls in this strain. Possibly the study of a larger number of animals would show a decrease in mean fetal weight.

The identical mean numbers of surviving fetuses per pregnancy in all groups suggest the absence of any lethal effects. Nevertheless, resorption sites and dead fetuses were found in five of twenty pregnant Sprague-Dawley rats bearing large Walker tumors; there was a single resorption site in one of thirteen animals bearing the smaller Walker tumors; this is no more than was found in normal pregnancy controls. In the Wistar rats bearing small lymphosarcomas, fetal death occurred only in one out of fifteen pregnancies. Fetal death was more frequent in the A × C rats bearing the hepatoma, even though these tumors were small.
Resorption sites or dead fetuses were present in 8/19 (42 per cent) pregnancies. This may be due to specific qualities of this tumor or to a greater vulnerability of the fetuses of this strain.

It is possible that the growing liver tumor might have requirements similar to those of regenerating liver and therefore exert effects on the fetus similar to those produced by the latter tissue.

In certain respects, the livers of pregnant animals (pr), and of animals bearing large tumors (tu) exhibit similar changes, e.g., increased weight (pr 2, 4, 19; tu 23, 24), decreased glycogen content (pr 4, tu 25), and increased water content (pr 4; tu 22). In the pregnancy liver there is an increase of RNA "in excess" of protein (4); in the liver of tumor-bearing animals the RNA content is increased (14), but there are no data on the comparative simultaneous increase of protein. On the other hand, there are significant differences between the pregnancy liver and the liver of tumor-bearing animals; e.g., decrease of catalase activity, characteristic of the latter, is not present in the former (10).

It has been suggested that those changes which occur in the liver both in pregnancy and in the tumor-bearing animal should be regarded as "homeostatic," i.e., a response of this organ to the metabolic demands of a rapidly growing tissue (9). The specific demands of the growing tissue being met by these liver changes are not known. It appears probable from our experiments that none of the factors common to both fetal growth and tumor growth can be involved in the impairment of fetal survival and growth following partial hepatectomy, since tumor growth in the partially hepatectomized rat is not only not similarly impaired, but is actually stimulated (18).

Mider (8) and others have shown that the nutritional and metabolic conditions of the host are altered significantly when the tumor weight reaches 10 per cent or more of the body weight of the host. This would not necessarily be true for the pregnant animal, in which metabolic and nutritional requirements are different from those of nonpregnant animals. Whereas it might be anticipated that small tumors (1–5 per cent of the host's body weight) had little influence on fetal growth and development, it seems significant that large tumors (Walker 256) ranging in weight from 29 gm. to 102 gm. (mean, 54 gm.) permitted almost normal growth and development of the fetuses. Many of these tumors are close to the stage at which the host succumbs, and several pregnant rats bearing these large tumors did die before reaching the 20th day of pregnancy and were therefore excluded from the tabulation.

If the liver changes in pregnancy and those in tumor-bearing animals are, in part at least, "homeostatic" in nature, representing a response to the metabolic demands of the host, the fact that the weight increase of the liver of the tumor-bearing pregnant rat exceeds that of the pregnancy controls suggests that the liver can meet the double demand. A study of the chemical composition of these livers will be of interest. Insofar as conclusions based on liver weight alone are valid, this may have a bearing on the fact that tumor growth and fetal growth are mutually compatible under the conditions of our experiments.

It is of interest that the above statements apply to small lymphosarcomas and to the Walker 256 tumor but not to the hepatoma. With this tumor, there was no difference in liver weights, either absolute or in percentage of total body weight, between pregnant and pregnant tumor-bearing animals. The size of these tumors was small but of the same order of magnitude as the lymphosarcoma.

Influence of pregnancy on tumor growth.—Reported data on tumor growth in pregnant animals are contradictory. In many instances, growth of transplanted tumors is reported to be retarded during gestation and considerably increased after parturition and during lactation (11, 13, further ref. in 13); however, acceleration of tumor growth during pregnancy has been reported (Bogomolek, cited in 13). Bly et al. (1), in a study of the Walker 256 tumor in pregnant rats, found impairment of tumor growth in some instances, fetal death in others, and some tumor growth and some impairment of fetal growth and survival in certain animals. In the present experiments there was no difference in tumor size in pregnant and in nonpregnant animals. In view of the fact that different authors studied different tumors and different species and strains (rats and mice) it can only be stated that the effects are not uniform or consistent. In the experiments of Homburger and Tregier with mouse Sarcoma 180, even sterile mating caused tumor regression but led to increased tumor growth if the tumor was implanted 24 hours before mating (13). This implicates possible hormonal factors in addition to possible metabolic factors operating in the pregnant, tumor-bearing animal. In none of the present experiments was the tumor implanted before mating, a time relationship which seemed most conducive to tumor regression during ensuing pregnancy in Homburger's experiments (13). The tumors...
were implanted on the 4th, 6th, and 12th day of pregnancy, respectively, as indicated in the tables. Different results might possibly have been obtained if tumor-bearing animals had been mated; such studies are in progress.

Influence of pregnancy on liver regeneration.—
Regeneration of the liver following partial hepatectomy in the pregnant animal does not differ from that in nonpregnant controls during a 72-hour period of regeneration. However, after 12 days, the weight attained by the regenerating liver in the pregnant rat significantly exceeds that in the nonpregnant hepatectomized control. In view of the facts that only wet weight was determined and that no analysis of the chemical composition of the liver was performed, this observation cannot be fully explained at present. However, there is information indicating that the composition of the regenerating liver differs appreciably during the first 4 days of regeneration from that at later stages. Price and Laird have shown that the protein content of the liver cells decreases after an initial slight rise on the 1st day, reaching a minimum on the 4th day, and increasing subsequently (20). On the other hand, the DNA content is higher on the 1st and 2d days, decreasing thereafter to only slightly elevated levels (16, 20). It is possible that the observed late increase of liver weight in pregnant, partially hepatectomized rats is related to the “protein phase” of liver regeneration.

SUMMARY
Partial hepatectomy in the pregnant rat caused death of many fetuses and impaired growth of surviving fetuses. This damaging effect upon the fetus was not alleviated by feeding a high-protein diet nor by administration of estrone and progesterone. In the pregnant rat, liver regeneration is influenced by pregnancy, regardless of whether the experiment was designed to yield small or large tumors. The growth of large Walker tumors had a slight damaging effect on the fetuses, whereas even small hepatomas caused fetal death or fetal resorption. This could be owing to a specific quality of this hepatoma or to a particular vulnerability of the fetus in the A × C rat, in which this tumor is grown.

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Pregnancy, Tumor Growth, and Liver Regeneration

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