Metabolic Adaptations in Rat Hepatomas

IV. Regulation of Threonine and Serine Dehydrase*

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SUMMARY

The enzyme(s) threonine dehydrase (TDH) and serine dehydrase (SDH) were assayed in several hepatomas to determine the level in chow-fed, nonadrenalectomized and high protein-fed, nonadrenalectomized and adrenalectomized animals. The capacity of the hepatomas to respond to the high protein stimulus varied from tumor to tumor and also, with one tumor, was dependent on the presence of adrenocorticosteroids. The effect of portal vein ligation on the capacity of hepatic tissue to respond with increased TDH and SDH to a high protein diet was studied, and the results were related to the dietary effects seen in hepatomas. The variable enzyme patterns are discussed in relation to the possibility that there may be “multiple pathways” by which a normal cell may become malignant.

The induction of hepatomas having enzyme profiles closely resembling normal liver (4, 6, 13) has provided a useful tool for the study of some mechanisms controlling the levels of specific enzymes involved in amino acid metabolism (9, 10, 12), in both normal and neoplastic tissue. In the first paper in this series (12) data on the effect of dietary protein content on tryptophan pyrrolase (TPO), threonine dehydrase (TDH), and serine dehydrase (SDH) in tumor and host liver of Morris 5128 hepatomas were presented. The first paper (12) also showed that Hepatoma 5123 growing in adrenalectomized animals had much lower levels of serine and threonine dehydrase than did tumors in nonadrenalectomized animals. The finding that these enzymes in the 5123 were affected by dietary and hormonal influences (12) opened the door to the study of the control of enzyme levels in other “minimal-deviation hepatomas” (10) in which comparisons with normal liver seemed justifiable. From these studies it might then be possible to draw certain tentative conclusions concerning primary or secondary effects of the neoplastic change on some control mechanisms in liver. A partial realization of this program comprises the major portion of this paper.

In the consideration of the previous effects of dietary protein on Hepatoma 5123 the question arose whether the difference of blood supply of the tumor and liver could account for the lack of induction of the enzymes studied. The liver normally has a dual blood supply consisting of portal blood, rich in materials absorbed from the gastrointestinal tract, and also arterial blood by way of the hepatic arteries. The tumor, however, as a consequence of being implanted intramuscularly or in the subcutaneous tissues, has only an arterial blood supply. To study these variables, animals were subjected to ligation of a branch of their portal vein (16), and the effect of hormonal and dietary manipulations on the level of these enzymes was determined in the intact and ligated lobes of the liver.

MATERIALS AND METHODS

The tumor-bearing animals used in these experiments were of two strains. All tumors except the Reuber H-35 (14) were carried in Buffalo strain rats obtained from the National Cancer Inst-

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stitute. The Reuber H-35 tumor was carried in ACI/N inbred animals also obtained from the National Cancer Institute. The animals used for the portal vein ligation experiments were Holtzman males obtained from the Holtzman Company of Madison, Wisconsin. The tumors were either subcutaneous or intramuscular in location. Some of the tumors were carried at the McArdle Memorial Laboratory, although the majority of the tumors were injected into animals by Dr. H. P. Morris at the National Cancer Institute and were then shipped to the McArdle Memorial Laboratory when the tumors were palpable.

Diets.—The animals were shifted to high protein diets and maintained on the diets ad libitum for varying lengths of time. The 91 per cent protein diet was made up as described previously (12) and was fed as a powder. The animals were maintained in suspended wire-bottomed cages and prior to the start of the high protein diet were maintained on Rockland Rat Chow diet. All animals were killed by cervical dislocation, and the livers were rapidly excised and placed in cold 0.154 M KCl. A 20 per cent homogenate in 0.154 M KCl was then made with the use of the Ultra-Turrax Homogenizer (Janke and Kunkel KG., Staufen i., Br., Germany). Tumors, after careful dissection, were also prepared for assay in this way. Whole homogenate or 100,000 X g supernatant (S8) was used for the assay depending upon what other enzymes were also being run on the specific sample. The dehydrase activity of both the S8 and the homogenate was identical in every case examined.

Enzyme assays.—The enzyme assays for TDH and SDH were reported in an earlier paper (11) and are modifications of the technics of Sayre et al. (15). The modified assay included the addition of pyridoxal phosphate to the reaction mixture at a concentration of 1 X 10^-4 M (Assay #1). This technic gave apparent linearity with enzyme amount and was used for all the tumor and host liver assays. During later work, however, when attempts were made to purify TDH from normal rat liver and tumor, it was found that the pH optimum and the Michaelis constants for both TDH and SDH were much higher for the rat enzyme than those reported for the sheep enzyme (or enzymes) on which the original assay by Sayre et al. (15) was based (3). Because of these findings a modified assay utilizing a higher substrate concentration (0.1 M threonine or serine) and higher pH (0.1 M phosphate buffer, pH 8.0, Assay #2) was used for the later studies on normal liver and on lobes with their portal vein ligated. Assay #2 gave values 6-8 times greater than the previous assay (#1) but did not alter the relative values. All tumors and host livers were assayed by method #1, and the ligated and intact lobes were studied by method #2. The keto acids produced by the deamination of threonine (a-ketobutyrate) and serine (pyruvate) were assayed by the method of Friedeman and Haugen (1) in both Assay #1 and Assay #2. The resultant color was read at 440 mµ in a Beckman DU spectrophotometer, and the μmoles of ketoacid produced per gram of wet tissue per hour was calculated from a standard curve utilizing a-ketobutyrate and pyruvate at known concentrations.

Adrenalectomy and portal ligation.—In all studies where adrenalectomized animals were used bilateral adrenalectomy was performed by the Endocrine Research Laboratories, Madison, Wisconsin. The animals were given 0.9 per cent NaCl in their drinking water and a chow diet for 7 days before dietary or hormonal manipulation was begun. The portal ligations were performed in the authors' laboratory under ether anesthesia (16), and at the time of sacrifice the portal vein was injected with a suspension of India ink in normal saline to insure that the ligated lobe did not receive collateral venous circulation. Sections of the ligated lobe were compared with normal liver as to morphology by histological section. No marked differences were noted. There was a low mortality rate from the procedure, and a certain number of the ligated lobes underwent necrosis, probably because of accidental ligation of the hepatic artery in addition to the regional branch of the portal vein. Only grossly and microscopically viable tissue was used for enzyme assay.

Chemicals.—L-Threonine, L-serine, and pyridoxal phosphate were obtained from the California Corporation for Biochemical Research. 2,4-Dinitrophenylhydrazine was obtained from Matheson, Coleman, and Bell. Cortisone acetate was used as a saline suspension under the trade name Cortone Acetate, a product of Merck, Sharp and Dohme Co.

RESULTS

Previous studies (12) on Hepatoma 5128, sublines A and D, had shown a higher level of TDH when the tumor was implanted in female than when implanted in male hosts. This result was not found for any of the tumors studied here; thus, re-

1 The addition of 1 X 10^-3 M disodium ethylenediaminetetraacetate to the final reaction mixture was found to increase the activity of both TDH and SDH twofold, although this further modification of the assay was not used for any of the enzyme determinations in this paper.

2 The technical assistance of Mr. Robert Westphal in performing the ligations is gratefully acknowledged.
TUMOR NO. THREONINE DEHYDRASE ACTIVITY. Chow diet.

Table 1
THREONINE DEHYDRASE ACTIVITY OF HOST LIVER AND TUMOR OF CHOW-FED AND HIGH PROTEIN-FED RATS BEARING MINIMAL-DEVIATION HEPATOMAS*

<table>
<thead>
<tr>
<th>Tumor no.</th>
<th>Tumor activity</th>
<th>High protein diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Host liver</td>
<td>Tumor</td>
</tr>
<tr>
<td>7800</td>
<td>6; 4; 4; 0; 0; 0</td>
<td>81; 25; 24; 18; 16</td>
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<tr>
<td>7793</td>
<td>78; 8; 8; 6; 2</td>
<td>374; 364; 535; 286; 118</td>
</tr>
<tr>
<td>7316</td>
<td>6; 4; 4; 3</td>
<td>46; 48; 50; 15</td>
</tr>
<tr>
<td>7794</td>
<td>48; 48; 46; 32; 9; 9</td>
<td>5; 2; 2; 0; 0; 0</td>
</tr>
<tr>
<td>7795</td>
<td>6; 6; 2</td>
<td>50; 47; 34</td>
</tr>
<tr>
<td>H-35</td>
<td>98; 71; 58; 36; 18</td>
<td>68; 10; 0; 0; 0</td>
</tr>
<tr>
<td>7888C</td>
<td>65; 23; 23</td>
<td>3; 0; 0</td>
</tr>
</tbody>
</table>

* All values are individual determinations of liver or tumor homogenates by Assay #1 as described in the text. Results are given as mmoles of a-ketobutyrate produced per gram of wet tissue per hour. Values for normal liver of male Holtzman rats on chow diet were 0.84, with a mean of 26 (nine animals). Values for normal liver of male Holtsman rats on a high protein diet for 7 days was 1330—1720, with a mean of 1525 (two animals). Individual values were used in all tables because of the rather marked variation in some of the values, both of host liver and tumor.

High protein diet in tumor-bearing animals.—The hepatomas studied included the Reuber H-35, Morris 7888C, 7816, 7800, 7793, 7794, and 7795. The levels of TDH in the host livers and tumors under the various dietary and hormonal conditions are presented in Tables 1–6. The present study was designed to continue the work which was done with Hepatoma 5123 (18). This included the comparison of the levels of the enzymes in chow-fed and high protein-fed tumor-bearing animals. In addition, since adrenalectomy of the host caused a fall in the TDH and SDH levels of Hepatoma 5123, the response of host liver and other minimal-deviation hepatomas to dietary and hormonal stimuli was studied in adrenalectomized hosts.

The data for the TDH levels of host liver and tumor of chow-fed and high protein-fed hormonally intact animals are given in Table 1. Of the tumors studied, the one with the highest level in the chow-fed animals was the 7793. Three tumors had medium levels of the enzyme (7800, 7816, and 7795), and three tumors (7288C, 7794 and H-35) usually gave very low values. These data (excluding data on the 7288C) were also presented in an earlier paper (11) and are used here for comparison. When the animals bearing these tumors were fed a high protein diet (Table 1), the host livers of all except one animal responded with elevations of TDH, although to a lesser extent than tumor-free animals. Five of the tumors (7288C, 7816, 7794, 7793, and H-35) did not have elevations of TDH.
nine high protein-fed animals responded to this diet with increased levels of SDH. The failure of two host livers to respond to the stimulus may relate to the fact that these livers were fatty at the time the animals were sacrificed. The levels of SDH attained in the host livers on a high protein diet reached levels from one-tenth to one-half the maximum values which could be obtained when the same diet was fed to normal rats for the same length of time (Tables 1 and 2).

Effect of adrenalectomy.—Because of the previous observation that Hepatoma 5128 lost its high TDH when the host animals were adrenalectomized, the levels of TDH and SDH were studied in adrenalectomized animals bearing the 7800 tumor. Both TDH and SDH were found to be lower in the adrenalectomized chow-fed animals. When adrenalectomized animals bearing the 7800 tumor were fed a high protein diet, neither the TDH or SDH were increased in the tumor (Tables 3 and 4).

The 7794 tumor was also studied after adrenalectomy and adrenalectomy plus a high protein diet. The adrenalectomy produced decreases of TDH in three of four animals (Tables 1 and 3). When the adrenalectomized animals were fed a high protein diet, however, two tumors had levels of TDH approaching the levels seen in the chow-fed controls (Table 3). The SDH of the six tumors in animals fed a high protein diet also had variable levels of this enzyme, with two out of six in the range of the tumors in chow-fed nonadrenalectomized animals (Table 3). Host livers of these adrenalectomized animals (Table 4). Two of the three values of TDH in the cortisone-treated animals were also higher than the levels seen in chow-fed rats with adrenal glands intact. Animals bearing the 7288C hepatoma, which had shown no TDH or SDH activity in the chow-fed nonadrenalectomized animals, were also adrenalectomized and given injections of cortisone acetate 2.5 mg. twice daily for 7 days. The tumor from the cortisone-treated animals also failed to show measurable levels of TDH and SDH (Table 4).

Effect of portal vein ligation.—Because of the difference between the blood supply of the liver and tumor, experiments were carried out to study enzyme induction in hepatic tissue not supplied with portal blood. The questions to be answered were as follows: (a) Would a high protein diet induce TDH and SDH in normal liver if it were supplied

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**Table 2**

<table>
<thead>
<tr>
<th>Tumor no.</th>
<th>Chow diet</th>
<th>High protein diet</th>
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<tbody>
<tr>
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<td>Host liver</td>
<td>Tumor</td>
</tr>
<tr>
<td>7800</td>
<td>5; 5; 5</td>
<td>28; 15; 14</td>
</tr>
<tr>
<td>7794</td>
<td>68; 47; 48; 18</td>
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<tr>
<td>7795</td>
<td>10; 9; 9</td>
<td>9; 7; 5; 1</td>
</tr>
<tr>
<td>H.S5</td>
<td>168; 62; 76; 28; 14</td>
<td>68; 3; 0; 0; 0</td>
</tr>
<tr>
<td>7288C</td>
<td>66; 29; 28</td>
<td>3; 2; 0</td>
</tr>
</tbody>
</table>

*All values are individual determinations of liver or tumor homogenates by Assay #1 as described in the text. Results are given as amoles of pyruvate produced per gram of wet tissue per hour. Values for normal livers of male Holtzman rats on a chow diet were 4—123, with a mean of 38 (seven animals). Values for normal liver of male Holtzman rats on a high protein diet for 7 days were 960—1400, with a mean of 1200 (two animals).† These values are for a later transplant generation of tumor than those utilized for the TDH assay, and failure of this enzyme to parallel the TDH may reflect the selection of new cell types in the later generation.
only by arterial blood? (b) If the ligated lobe would respond to high protein in intact animals, would it also respond in the ligated lobe of adrenalectomized animals? It was felt necessary to answer these questions to allow interpretation of the results in tumors of animals fed high protein diets. The results of these experiments are shown in Charts 1–2. Chart 1 shows the effect of feeding a high protein diet for 5 days to animals with the branch of the portal vein to one lobe ligated. (Assay #2 was used for this study, giving approximately 6–8 times larger values than with Assay #1.) The TDH of the lobe with intact portal circulation appeared to increase almost linearly for the first 4 days of feeding, with a plateau being achieved at about 5 days (Chart 1). The total increase in enzyme activity was approximately 17X above control levels in the intact lobe. The ligated lobe started at a somewhat lower level (50 μmoles/gm liver/hr) and increased for about 3 days after the diet was started, but it then leveled off and did not increase further. The total increase in enzyme

### TABLE 3

**THREONINE DEHYDRASE ACTIVITY OF HOST LIVER AND TUMOR OF ADRENALECTOMIZED CROW-**

**FED AND HIGH PROTEIN-FED RATS BEARING MINIMAL-DEVIATION HEPATOMAS***

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Crow Diet</th>
<th>Host liver</th>
<th>Tumor</th>
<th>High protein diet</th>
<th>Host liver</th>
<th>Tumor</th>
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<tbody>
<tr>
<td>7800</td>
<td>4; 4; 2; 0</td>
<td>17; 8; 6; 0</td>
<td>408; 70; 272</td>
<td>9; 7; 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7793</td>
<td>3; 0; 6</td>
<td>101; 5; 0; 0</td>
<td>486; 336; 370; 274; 10</td>
<td>329; 191; 47; 87; 77</td>
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<td></td>
</tr>
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</table>

* All values are individual determinations of liver or tumor homogenates by Assay #1 as described in the text. Results are given as μmoles of α-ketoacid produced per gram of wet tissue per hour.

### TABLE 4

**THREONINE AND SERINE DEHYDRASE ACTIVITY OF HOST LIVER AND OF 7316 AND 7288C HEPATOMAS OF ADRENALECTOMIZED AND CORTISONE-TREATED ADRENALECTOMIZED RATS MAINTAINED ON CHOW DIETS***

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Control</th>
<th>Host liver</th>
<th>Tumor</th>
<th>Cortisone, 5 mg/day for 7 days</th>
<th>Host liver</th>
<th>Tumor</th>
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<tbody>
<tr>
<td>7816</td>
<td>28; 18; 1; 0</td>
<td>88; 9; 3; 1</td>
<td>34; 33; 13</td>
<td>191; 142; 33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7288C</td>
<td>42; 29; 7</td>
<td>0; 0; 0</td>
<td>104; 78; 33</td>
<td>0; 0; 0</td>
<td></td>
<td></td>
</tr>
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</table>

* All values are individual determinations of liver or tumor homogenates by Assay #1 as described in the text. Results are given as μmoles of α-ketoacid produced per gram of wet tissue per hour.
activity in the ligated lobe was approximately 10 X.

Chart 2 shows the level of the enzyme SDH in the intact and ligated lobes of the animals on a high protein diet. This enzyme very closely paralleled the levels of TDH in both the intact and ligated lobes, with an approximately 17-fold increase of enzyme activity per gram of tissue in the intact lobe and a tenfold increase of enzyme activity above control levels in the ligated lobe.

This experiment was repeated with adrenalectomized animals. These animals were maintained on a high protein diet for 3 days, and results similar to those of the nonadrenalectomized animals were obtained. Table 5 shows that the TDH of the intact lobe had increased 100-fold, whereas the ligated lobe increased only 20-fold. These data also show the SDH response in the intact and ligated lobes of the same animals with a response approximately 10 X greater in the intact as compared with the ligated lobe. These results would indicate that, although the stimulus for the induction of these enzymes in a portion of liver not supplied by portal blood may be less than for the intact liver, the dietary protein will induce the enzymes in the ligated lobe, albeit to a lesser extent than in the intact liver. The lower level of the enzyme in the ligated lobe could be explained on the basis of early induction of the enzyme in the normal liver, which then acts as a filter to decrease the amount of the supposed inducer, threonine, reaching the peripheral circulation. This would also hold true for the enzyme serine dehydrase and

<table>
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<th>TABLE 5</th>
<th>THREONINE AND SERINE DEHYDRASE ACTIVITY OF LIVER LOBES WITH INTACT AND LIGATED PORTAL VEIN AFTER ADRENALLECTOMIZED ANIMALS WERE FED A HIGH PROTEIN DIET FOR THREE DAYS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOBE</td>
<td>CONTROL</td>
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<tr>
<td></td>
<td>Threonine dehydrase</td>
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<tr>
<td>Intact</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Ligated</td>
<td>40 ± 10</td>
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<tr>
<td></td>
<td>Serine dehydrase</td>
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<tr>
<td>Intact</td>
<td>50 ± 10</td>
</tr>
<tr>
<td>Ligated</td>
<td>50 ± 10</td>
</tr>
</tbody>
</table>

* Assay #2 was used for all determinations. Values are expressed as μmoles of α-ketoacid per gram liver per hour ± S.D. A minimum of three animals was used under each condition.
its substrate serine. In support of this theory, it was previously shown by Peraino (8) that the portal vein level of threonine is higher than the peripheral level 1.5 hours after the tube feeding of casein to the rat. These results suggest that, since the stimulus from a circulating amino acid to a subcutaneous hepatoma would be less than to normal liver because of its blood supply, one would hardly expect it to have an induced level of enzyme comparable to that of intact liver.

DISCUSSION

It was hoped that the use of the minimal-deviation hepatomas, differing as little as possible, biochemically, morphologically, and functionally from their specific cell of origin, would be the most logical tool to help distinguish in at least one case the primary alterations responsible for biologic malignancy from changes secondary or unrelated to the malignant transformation.

Although five of the tumors discussed in this paper were produced by similar conditions of carcinogen feeding (5125, 7800, 7798, 7794, 7795) in the laboratory of one of the authors (H.P.M.), the methods of the production of the other tumors varied considerably as to the carcinogen used, the dose used, and the feeding schedule (4, 14). Because of the variability seen in these tumors and because of the different conditions of tumor induction, one of the important questions to be answered is whether the differences observed among tumors reflect differences inherent in carcinogenesis and illustrating multiple pathways by which a cell can become malignant or whether these differences reflect stages of progression through which each tumor passes on its way to becoming a "multiple-deviation" tumor (7). The data presented in this paper would tend to support the "multiple pathways" possibility, since several of these tumors have proved to be moderately stable through several transplant generations and, even after explant into tissue culture and subsequent transplant into animals, have remained identifiable as far as their enzyme pattern was concerned (2). Also, there are difficulties in studying the second possibility, since changes in tumor enzyme patterns and growth rates may reflect the selection of some cell type which was already present in the early transplant generations and thus would not necessarily mean a change in the original predominant cell type. We felt that a systematic study of minimal-deviation hepatomas as a group might answer this question. From the data presented in this paper some preliminary conclusions may be suggested.

Previous work (11) in this laboratory indicated that the levels of a series of enzymes involved in amino acid metabolism varied widely from tumor to tumor, and the pattern was not duplicated in any of the different tumors studied. Some of this diversity has also been found in this same series of tumors when they were studied in regard to their patterns of response to a high protein diet, adrenalectomy, and adrenalectomy plus a high protein diet. The data in the present paper illustrate examples of (a) a tumor (7800) which responded with an increase in TDH to an elevation of dietary protein in an animal with normal adrenal function but which did not respond to a high protein diet after adrenalectomy; (b) a tumor (7793) which may have responded to a high protein diet in the adrenalectomized animal; (c) a tumor (7816) which did not respond to a high protein diet with an elevation of TDH or SDH but did have increased levels of both enzymes after treatment with large doses of cortisone for 1 week after adrenalectomy; and (d) four tumors (7794, 7795, and H-35) with low levels of TDH and SDH in the chow-fed intact animal which did not respond to a high protein diet even in the intact animal.

These tumors represent several of the possible combinations of deranged control mechanisms as far as these enzymes are concerned. The individuality of this series of minimal-deviation tumors can be illustrated by categorizing the TDH levels as low, medium, or high and noting the changed levels produced by shifting from chow diet to high protein diet. On this basis the hepatomas in Table 1 shift as follows: medium/high, high/high, medium/medium, low/low, and medium/low. The H-35 is not included in this series.

Previous work (9, 10) had indicated that one possible common denominator of altered control mechanism in the minimal-deviation tumors was an inability of the enzyme tryptophan pyrrolase to respond to substrate induction in the adrenalectomized animal. It was felt that TDH also showed this inability to respond to dietary induction as represented by a high protein diet in the adrenalectomized animal. However, the variable response of the 7793 hepatoma with an elevation of TDH in the adrenalectomized animal on a high protein diet raises the possibility that this enzyme may respond to dietary control in at least one of these tumors. Further studies are under way to clarify this point.

The experiments reported on the effect of ligation of a branch of the portal vein on the induction of TDH and SDH by a high protein diet indicate that the failure of a hepatoma to respond to a high protein diet is a valid observation. The differences
between the blood supply of the liver and of the tumor would offer a possible explanation for the differences in enzyme levels seen in normal liver and tumor, except that the tumors are not consistent in the direction or magnitude of the enzyme alterations, and the differences in enzyme level must, therefore, reflect basic differences in the hepatomas themselves.

The data that have been accumulated up to this time would indicate that the tumors known as “minimal-deviation hepatomas” form a spectrum of neoplasms, each differing from the other as far as enzyme level and control of enzyme levels is concerned. The data suggest that carcinogenesis may be a random development of molecular changes, some of which lead to a cell that is able to divide independently of host control mechanism, but all of which, at least in the hepatomas thus far studied, lead to some aberration in mechanisms controlling enzyme levels in the initiated tumor cell. This suggestion does not indicate anything about the mechanisms or sites of these changes at this time, and it is still an open question whether a common denominator may be found.

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REFERENCES

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