ROLE OF COENZYMES AND SUBSTRATES IN ENZYME INDUCTION

DR. DOUGHERTY raised an important point regarding the possibility that some of the enzyme activity alterations may not reflect variation in enzyme amount but may simply reflect rate-limiting changes in the availability of a cofactor.

DR. PITOT said that this was not true in his experiments because the enzymes were always assayed in the presence of an excess of their respective cofactors. DR. DOUGHERTY suggested that it would be a valuable approach to explore whether the enzymes discussed may respond through variations in the cofactor content at the cellular level. DR. PITOT answered that to his knowledge that experiment has not yet been done.

DR. KENSLER inquired whether there is a general rule of reciprocal relationship between a number of enzymes in liver neoplasms. DR. PITOT explained, “I didn’t mean to imply that with all the enzymes that were discussed there is a reciprocal relationship in the liver. This relationship of Zwischenferment and threonine dehydrase was discovered by Dr. Bottomley in our laboratory working with Dr. Potter and myself. We were interested in seeing whether the reciprocity of these two enzymes was present in hepatocellular carcinomas. You will have noticed, however, there was one exception. We do have one tumor, the Morris 7800, in which the threonine dehydrase is inducible but not the Zwischenferment.”

“When the tumor-bearing hosts were adrenalectomized, then almost without exception the threonine dehydrase of all the neoplasms dropped virtually to the Y axis, that is, almost to zero.”

DR. NICHOL drew attention to problems arising from the term “induction” as applied to mammalian cells. He emphasized the lack of complete evidence whether in mammalian cells we deal with an actual induction or whether the process really involves a repression. He stressed that in using the term “substrate” we are really referring to small molecules or drugs; indeed this is a drug effect because the inducing doses of tyrosine and tryptophan are quite toxic to the animal. In view of this, he felt that “substrate induction” is not a completely correct term and pointed out the advisability of clarifying our concepts in this respect and finding other suitable terms.

DR. ROSEN stressed the importance of the finding that tyrosine transaminase was increased in Morris hepatoma 5123. In connection with this, he mentioned that adrenalectomy does not affect the activity of hepatic tyrosine transaminase. However, the liver becomes greatly sensitive to corticosteroid induction of this enzyme. He was able to decrease this sensitivity to normal by treating adrenalectomized rats with deoxycorticosterone. He suggested that it would be of interest to inject hepatoma-bearing animals with deoxycorticosterone to see whether or not the high levels of tyrosine transaminase would decrease in the hepatoma. DR. Rosen also referred to experiments with Dr. Nichol in which they were able to block the induction of tryptophan pyrrolase when growth hormone was administered simultaneously with cortisol. He interpreted this phenomenon as the channeling away of amino acids in the liver into structural protein, interfering with the pool available for the synthesis of the inducible enzyme.

DR. PARDEE referred to his talk in which he outlined that there were two kinds of mechanisms for the increased amount of enzyme in a cell: (a) The conversion of an enzyme already present to an active form; for instance, the combination of tryptophan pyrrolase with its hematin cofactor. (b) New enzyme formation; e.g., more tryptophan pyrrolase molecules are produced. These two mechanisms can operate simultaneously, producing an increased amount of enzyme, and they do not have to be exclusive processes (1–8).

DR. NICHOL pointed out that in relation to the substrate specificity of induction it must be kept in mind that tryptophan and related compounds are very effective in inducing tyrosine transaminase. He mentioned that Dr. Rosen recently showed that a number of indoles are capable of inducing tyrosine transaminase in adrenalectomized ani-
mals. Therefore, he suggested that in a sense, although amino acids are not drugs, it may be preferable to look at this as a drug action rather than as an amino acid effect.

Dr. Weber referred to the fact that the International Enzyme Commission recommended a standard nomenclature in this field, and it might be in order to examine the applicability of the discussed concepts to the recommendations of the Commission (6).

Dr. Parks drew attention to the consideration that structural specificity must play a crucial part in the induction mechanisms.

Dr. Pardee referred to concepts well established in bacteria which indicated that an enzyme inducer does not have to be a substrate for the enzyme. However, the inducer is usually quite similar to the substrate in structure. It is thought that the inducer acts at a site on the enzyme different from the site where the substrate combines. From this point of view it may be useful for the enzyme if in some cases the inducers are completely different from the substrate. Thus, it is believed that enzymes may have structural sites for substrate combination and regulatory sites for regulation.

**ROLE OF ENZYME DEGRADATION IN ENZYME SYNTHETIC PROCESSES**

Dr. Werkheiser posed the question whether we pay enough attention to another possible aspect of enzyme production apart from the synthetic processes. He was wondering whether under certain circumstances in the mammalian cells the rate of destruction of enzymes may not be the critical rate-limiting aspect.

Dr. Pardee felt that this may be extremely important under certain circumstances, since the increases occurring under induction are usually very temporary and generally the enzyme disappears rapidly, which cannot be owing to simple dissolution.

Dr. Weber referred to results pertinent to the problems raised by Dr. Werkheiser. In long-term starvation experiments it is assumed that enzyme breakdown processes dominate over synthetic processes. Under starvation in normal rats it was shown that during a 6-day fast, liver enzyme activities could be classified into three groups according to their relation to the declining nitrogen content in the liver. In the first group were enzymes which were preferentially maintained (glucose-6-phosphatase, fructose-1,6-diphosphatase). In the second group were enzymes which decreased essentially parallel to the depletion of hepatic nitrogen level (phosphoglucomutase, phosphohexose isomerase, lactic dehydrogenase). In the third group were enzymes which were preferentially depleted to a level markedly under the declining nitrogen content (glucose-6-phosphate and 6-phosphogluconate dehydrogenases) (11). The operation of hormonal factors in this process was indicated by the fact that in hypophysectomized rats all examined liver enzyme activities and nitrogen content were depleted to the 6-day fasting level in 24 hours (13). It is possible that in the hypophysectomized, fasted rats one may be studying the rate of enzyme breakdown which may be completely unopposed by effective synthetic processes. These experimental arrangements are brought to attention as technics for studying enzyme breakdown aspects of the turnover of enzyme population (12).

Dr. Pitot commented that "with respect to what Dr. Werkheiser has said, we are very conscious of the importance of this concept since, if these inducers are merely acting to stop the degradation of the enzyme, then we are not studying enzyme induction in the modern sense.—I think Francis Kenney has shown in a very excellent paper (5) that this is not true in the case of tyrosine transaminase.

"This enzyme may be induced as much as 25-fold in 5 hours by hydrocortisone administration. If hydrocortisone merely acts to block enzyme degradation, then one must postulate in the steady state in noninduced animals an enzyme turnover with a half-life of only a few minutes. In fact, however, from the decay rate of the induced enzyme as well as by the elegant immunochemical technics of Kenney, the half-life of the enzyme has been found to be 3–4 hours. In addition, from Kenney’s data, it is possible to say that induction of tyrosine transaminase is the result of an increased rate of enzyme synthesis. The kinetics of tryptophan pyrrolase induction are very much like that of tyrosine transaminase, and it is thus probable that this too represents an increased rate of enzyme synthesis. The dietary induction of enzymes that we mentioned shows kinetics similar to that of bacterial enzyme induction. This may be due to the fact that the inducer (hydrolyzed casein) is present constantly during the period of study, much like the situation in unicellular organisms where the inducer is constantly in the environment during enzyme induction."

**FEEDBACK AND OTHER CONTROL MECHANISMS**

Dr. Pardee, referring to Dr. Pitot's examples that tumors seem to lack some of the control mechanisms of normal tissues, wished to add another example. He referred to the work of Dr.
Siperstein, who showed that in normal tissues cholesterol prevents its own synthesis (8). He mentioned a personal communication of Dr. Siperstein regarding mouse, rat, and human tumors which also lacked the control of cholesterol synthesis by cholesterol.

DR. BURCHENAL inquired whether there are instances of a loss of negative feedback in tumors additional to that discovered by Dr. Siperstein as referred to by Dr. Pardee. Dr. Pitot answered that "as I mentioned in the manuscript, to my knowledge, and somebody can correct me on this, there are only three possible examples of negative feedback that have been studied in hepatomas, and in all three cases the feedback is normal in the tumor. But in the case of repression in the liver, Dr. Siperstein's is the only example that I know of that has been studied in hepatomas.

"We are presently interested in studying enzyme repression in renal tumors since in the rat, Walker has shown that creatine biosynthesis is repressed in the kidney of the rat by dietary creatine. Do renal carcinomas also exhibit defective enzyme repression?"

DR. BURCHENAL asked for a definition of the difference between repression and negative feedback. Dr. Pitot answered, "Repression involves a cessation of synthesis of the enzyme, whereas negative feedback affects the activity of the enzyme."

DR. FREI said that, since the feedback inhibition and repression seem to operate in many synthetic pathways, the question arose whether folic acid metabolism may be subject to such endogenous regulatory influences.

DR. WEBER suggested that this was a good possibility. It is a matter of speculation, but it is likely that automatic feedback mechanisms should be operating in nucleic acid metabolism in mammalian organisms which would exert very strong, genetically influenced limits on metabolic processes. Obviously, transient metabolic conditions such as diet alterations should not affect nucleic acid metabolism, whereas these temporary processes should meet with rapid response in the field of carbohydrate and lipid metabolism.

DR. ANDERSON asked Dr. Pardee to comment on the relation of sub-units of aspartic transcarbamylase to the activity of these enzymes in Dr. Pardee's bacterial studies.

DR. PARDEE explained that aspartic transcarbamylase is made of four sub-units which can be reversibly dissociated by a variety of treatments. The sub-units are still active as enzymes, but they are no longer subject to feedback inhibition. The normal feedback inhibition in the cell does not dissociate the enzyme into sub-units. He suggested that there is something in addition to feedback inhibition that is also involved in this problem.

DR. KENSLER reported that methotrexate and 6-mercaptopurine prevented the induced increase in tryptophan pyrrolase activity, but not that of benzpyrene hydroxylase activity. He suggested that some of the chemotherapeutic agents may have an important role in interfering with adaptive enzyme formation.

DR. HOLLAND brought up the same type of fundamental question which Drs. Frei and Burchenal referred to previously regarding the nature of endogenous compounds which can affect either by repression or negative feedback the intermediary metabolism in mammalian tissues. He was especially interested whether any of these compounds might be used for the purpose of achieving chemotherapeutic effects. Dr. Pardee said that feedback inhibitors have been identified, but very little is known about the nature of repressors.

ENZYMATIC AND METABOLIC ALTERATIONS IN LIVER TUMORS OF DIFFERENT GROWTH RATES WITH SPECIAL REFERENCE TO GLUCONEOGENESIS

DR. PARKS asked whether the fact that even the most differentiated hepatomas are unable to deposit glycogen in appreciable amounts is also reflected in an inability of the tumor to carry on gluconeogenesis. Does the absence of important liver carbohydrate functions have any relation to the extent of differentiation in the Morris tumors?

DR. WEBER: "In answer to Dr. Parks' question and in reference to the paper of Dr. Pitot I would like to comment on the behavior of gluconeogenic mechanisms and on correlation of gluconeogenesis and other biochemical parameters in liver tumors of different growth rates.

"To facilitate the discussion, some of our recent investigations in liver neoplasms of different growth rates are summarized in Table 1 (14). A tumor spectrum is shown in this table in which the rat hepatic neoplasms are arranged in order of increasing growth rates, starting with 5123-D and ending with the most rapidly growing tumor in this series, the Novikoff hepatoma. The transplantation time, as expressed in months necessary between transplantation of tumors, is given, and the length of growth is indicated in days between tumor inoculation and the killing of the rat for biochemical investigation of the tumor (14).

"The tendency towards decrease and total loss of glucose-6-phosphatase and fructose-1,6-diphosphatase, which are rate-limiting enzymes in glu-
coneogenesis, is observed in tumors of increasing growth rates. Current work in my laboratories also revealed marked decreases in aldolase and malic dehydrogenase activities, and preliminary results indicate that phosphoenolpyruvate carboxykinase is also absent in the rapidly growing hepatic neoplasms. The lesions in these key enzyme activities are also reflected in the failure of gluconeogenesis in these tumors as shown by isotope methods (9).

"The data on gluconeogenic enzymes and other enzymes of carbohydrate metabolism are pertinent to the theme of this Conference, since these studies tend to show that the enzyme activities and metabolic parameters can be classified according to their relation to the growth rate of the hepatomas. Such information is important from the standpoint of designing, as well as evaluating, chemotherapeutic weapons. Three classes can be set up: 1, enzymes and parameters which show correlation; 2, those which do not correlate; and 3, those which are decreased or increased in all or most of the hepatomas in the spectrum.

In Table 2 is presented a classification of enzymes and metabolic factors according to their relation to growth rate in liver neoplasms. This table summarizes our studies during the past three years on the behavior of certain strategic parma-

**TABLE 1**

**COMPARISON OF CARBOHYDRATE ENZYME ACTIVITIES IN THE AVERAGE CELL OF NORMAL LIVER AND HEPATOMAS OF DIFFERENT GROWTH RATES**

Data are expressed in percentages of the values of the respective normal livers which are taken arbitrarily as 100%.

<table>
<thead>
<tr>
<th>Hepatomas:</th>
<th>Normal</th>
<th>5153-D</th>
<th>7800</th>
<th>H-35</th>
<th>7888-C</th>
<th>7988-B</th>
<th>5984-A</th>
<th>5685</th>
<th>Novikoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellularity</td>
<td>100</td>
<td>94</td>
<td>107</td>
<td>188*</td>
<td>217*</td>
<td>83</td>
<td>77</td>
<td>104</td>
<td>130*</td>
</tr>
<tr>
<td>Homogenate nitrogen</td>
<td>100</td>
<td>58*</td>
<td>76*</td>
<td>66*</td>
<td>37*</td>
<td>63*</td>
<td>53*</td>
<td>56*</td>
<td>50*</td>
</tr>
<tr>
<td>Supernatant nitrogen</td>
<td>100</td>
<td>73*</td>
<td>90</td>
<td>65*</td>
<td>38*</td>
<td>77*</td>
<td>75*</td>
<td>63*</td>
<td>50*</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>100</td>
<td>58*</td>
<td>18*</td>
<td>50*</td>
<td>42*</td>
<td>&lt; 2*</td>
<td>&lt; 1*</td>
<td>&lt; 2*</td>
<td>&lt; 1*</td>
</tr>
<tr>
<td>Fructose-1,6-diphosphatase</td>
<td>100</td>
<td>30*</td>
<td>57*</td>
<td>18*</td>
<td>96*</td>
<td>11*</td>
<td>21*</td>
<td>25*</td>
<td>7*</td>
</tr>
<tr>
<td>Phosphoglucomutase</td>
<td>100</td>
<td>15*</td>
<td>21*</td>
<td>39*</td>
<td>20*</td>
<td>69*</td>
<td>43*</td>
<td>7*</td>
<td>22*</td>
</tr>
<tr>
<td>Phosphohexose isomerase</td>
<td>100</td>
<td>66*</td>
<td>70</td>
<td>62*</td>
<td>24*</td>
<td>77</td>
<td>126*</td>
<td>54*</td>
<td>80*</td>
</tr>
<tr>
<td>Lactic dehydrogenase</td>
<td>100</td>
<td>85*</td>
<td>185*</td>
<td>&quot;50&quot;</td>
<td>&quot;23&quot;</td>
<td>75*</td>
<td>82*</td>
<td>15*</td>
<td>18*</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>100</td>
<td>92</td>
<td>1988*</td>
<td>503*</td>
<td>1508*</td>
<td>751*</td>
<td>312*</td>
<td>900*</td>
<td>900*</td>
</tr>
<tr>
<td>6-Phosphogluconate dehydrogenase</td>
<td>100</td>
<td>50*</td>
<td>252*</td>
<td>61*</td>
<td>250*</td>
<td>48*</td>
<td>32*</td>
<td>32*</td>
<td>32*</td>
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<tr>
<td>Transplantation time (months)</td>
<td>2.5</td>
<td>2.1</td>
<td>2.0</td>
<td>1.5</td>
<td>1.6</td>
<td>0.94</td>
<td>1.0</td>
<td>0.56</td>
<td>0.25</td>
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<tr>
<td>Per cent</td>
<td>100</td>
<td>84</td>
<td>80</td>
<td>80</td>
<td>64</td>
<td>38</td>
<td>40</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Length of growth (days)</td>
<td>60-90</td>
<td>85</td>
<td>73</td>
<td>53</td>
<td>41</td>
<td>41</td>
<td>24</td>
<td>18</td>
<td>5-7</td>
</tr>
</tbody>
</table>

* Statistically significant difference when compared with normal values.

**TABLE 2**

**CORRELATION OF CERTAIN INTERMEDIARY METABOLIC FACTORS WITH GROWTH RATE IN HEPATOMAS**

The results collected to date are grouped from the point of view of definite trends which fit into one of the three categories. The direction of the trend for a parameter is indicated by an arrow showing whether it increased (†) or decreased (⊥) with the increasing growth rate.
ometers and enzymes characterizing carbohydrate metabolism as well as results on the incorporation and oxidation of amino acids and levels of nitrogen (10, 14).

"Such a correlation points out that in an analogy to symptoms and signs of the same disease, there are marked variations in individual cases from the subclinical through the moderately mild to the full-blown case where most or all symptoms and signs are present. Therefore, in agreement with general medical experience, enzymatic alterations and behavior of metabolic pathways such as gluconeogenesis can be best interpreted in the framework of a spectrum of tumors of different growth rates such as shown in Table 1. Many of the important symptoms and signs do not show up clearly under subclinical conditions of a disease. The same consideration refers to enzymatic and metabolic lesions in slowly growing tumors where some of the deviations may be minimal and thus may or may not show up to a sufficient extent to permit correct evaluation.

"The comparisons given in Tables 1 and 2 show in which direction the symptoms and signs of liver neoplasia are manifested at the molecular level, through the mild case of 5123-D to the full-blown case of the Novikoff tumor. These studies demonstrate that the operation of gluconeogenesis is incompatible with liver neoplasia; it is present only in traces and is usually completely wiped out in the hepatomas examined to date.

"I may add to these studies carried out in rodent tumors that our recent results in a human primary hepatoma are in complete agreement with the findings described in the rat."1

DR. JOHNSON suggested that it would be valuable to study the effect of glucagon on the series of hepatomas of different growth rates discussed by Dr. Weber. DR. JOHNSON referred to the work of Dr. C. H. Best and his associates (7), who reported that this hormone appeared to show some antitumor effect on the Walker tumor and on the Novikoff hepatoma. DR. JOHNSON also saw this effect in a number of mouse tumors (4) and inquired whether this has been investigated in the rat hepatomas of different growth rates.

DR. WEBER answered that he recently discussed with Dr. Harold P. Morris the various projects being carried out with the Morris tumors, and it appears that this has not been done yet.

DR. WARWICK referred to the important question of whether any of these hepatomas in the series of liver tumors of different growth rates represents a homogeneous cell population. Furthermore, he raised the question whether the subsequent transplantations of these neoplasms caused any alteration in the cellular population and biochemistry of the original tumor picture.

DR. POTTER referred to studies in his laboratories in which some of these hepatomas were allowed to grow in tissue culture, and when these tumors were retransplanted to rats they exhibited a more rapid growth rate than in previous transplantations. It appears that the chromosome number remained constant, and the cells have apparently retained some enzymes which seem to be liver markers.

DR. PARKS wanted to know whether reinjection of the tissue-cultured tumor cells into rats resulted in any changes in tissue morphology and in enzymatic make-up.

DR. POTTER emphasized that when tissue-cultured tumor cells were put back into animals they grew more rapidly. He referred to the table Dr. Weber showed (Table 1) which had enzyme studies on Morris hepatoma 5123-t.c., which is the result of the culturing of the original 5123-D. Thus, in the series Dr. Weber showed, we have the enzyme picture of a "fast-growing tumor variant which is an offspring of one of the slow-growing variants. This way the comparison becomes more meaningful."

DR. WELCH emphasized that it is an important point that a certain correlation between purine degradation and the growth rate of tumors can be demonstrated.

DR. HOLLAND suggested that it would be most useful to obtain information on the relative rate of purine synthesis in tumors of different growth rates.

DR. BERTINO emphasized the point that among the difficulties involved in studying enzyme induction in mammalian liver is the fact that there is more than one cell population present. He referred to the work of Dr. Werkheiser, who showed that in studies with methotrexate disappearance the data were compatible with a concept that one type of hepatic cell turns over very rapidly, whereas another type of liver cell turns over very slowly.

He also raised the point that although we frequently say that cancer cells are unable to regulate themselves the clinicians doing chemotherapy are constantly faced with the problem that the neoplastic cells are able to adapt very easily to whatever is done to them. Therefore, it appears that they can adapt their metabolic pattern.
DIFFERENTIATION AND DEPENDENCY IN LIVER TUMORS

DR. WARWICK referred to work in the Chester Beatty Institute where scientists were able to induce kidney tumors in hamsters with estrogen, but these primary tumors could only be transplanted provided that additional estrogen was given to the animals. However, after several transplant generations the level of estrogen necessary could be decreased, and finally the tumor was capable of growing without the hormone. This finding probably shows an example of the process of selection in an established tumor.

DR. PITOT said that “this brings up a very interesting question in these highly differentiated liver tumors; that is, are they in fact ‘dependent’ tumors? The fact that they do grow, although not as well, in both the adrenalectomized and hypophysectomized animal would argue against this possibility, however. With reference to Dr. Warwick’s earlier remark, if one can say that the chromosome population of the tumor gives us some index as to its homogeneity, then for at least 10 or 15 transplant generations the Morris 5123 hepatoma has remained essentially homogeneous with a chromosomal mode of 42, the normal diploid complement for the rat.”

DR. FISCHER asked whether any single cell injections from this tumor have ever been carried out in rats. DR. PITOT answered “No.”

DR. SEGALOFF pointed out that the term “dependency” requires careful definition, since in his opinion this is one of the most misused terms. For instance, the fact that the transplantable hepatomas are not markedly affected in their growth rates when grown in hypophysectomized or adrenalectomized animals is not a case where dependency can be invoked. In this regard it is important to keep in mind that under certain circumstances adrenalectomized or hypophysectomized rats may die in a matter of hours. In view of these considerations the investigators should carefully clarify their own particular usage of the word “dependency.”

DR. PITOT said that “My terminology was patterned after that of Dr. Furth, and by his definition these tumors are not dependent. The discrepancy appears to lie in the definition of terms which may be a function of the individual investigator.”

DR. WEBER added that adrenalectomized and hypophysectomized rats can be well maintained for weeks provided that they are given food. However, these animals are unable to withstand starvation and, as Dr. Segaloff implied, the basic homeostatic failure becomes manifest and the animals expire in hypoglycemia, convulsions, and coma. It has been suggested that the failure of the hypophysectomized and adrenalectomized, fasted rats to maintain blood sugar level is the consequence of a failure in the synthetic mechanisms of the gluconeogenic enzymes (11, 13).

DR. BURCHENAL wondered whether the word “dependent” as employed a great deal by investigators and clinicians interested in carcinoma of the breast is used in its correct sense.

DR. SEGALOFF pointed out that it has been said that carcinoma of the breast is dependent on estrogens; however, what we really know is that some of them are responsive to castration. Very few of them actually can be shown to progress more rapidly with estrogen administration. He emphasized that it is possible to make some of the breast carcinomas regress by giving large amounts of estrogen to premenopausal women with advanced breast cancer so that the picture is very confused indeed.

SUMMING UP

DR. WEBER suggested that Dr. Potter might be kind enough to make a comment on the current status of the tumor problem in the present context since Dr. Potter has been very closely associated with the progress of this field for more than 20 years.

DR. POTTER said that “In the particular context in which we are speaking, I think it is important to say that the minimal deviation tumors, not just the liver tumors but the minimal deviation tumors in general, probably represent one end of a spectrum. In terms of tumor progression these tumors can progress to multiple deviation tumors, and from the standpoint of chemotherapeutic approaches we are concerned with neoplasms all along the line of the spectrum. With the minimal deviation tumors we may be able to utilize some of the normal controls in studying chemotherapeutic approaches. However, as these tumors progress to multiple deviations, then we are confronted with the possibility of using some of the deletions as an actual help and attacking point in chemotherapy. On the other hand, from the standpoint of understanding the mechanism of carcinogenesis, I feel very strongly that the most valuable information comes from those tumors which represent a minimal deviation from a normal cell that can be identified.

“So I think that the concept of tumor progression in terms of enzymatic lesions is a concept that should be with us at all times in the field of carcinogenesis as well as in the field of chemotherapy.”

DR. WEBER: “At this time I would like to ex-
press my thanks to Drs. Pitot and Pardee and to the members of the Conference for their fine contribution to the lively and productive discussions.

"Since I happen to be the last one to speak here, it is fitting that I use this opportunity on behalf of all of us to express our highest appreciation to Dr. Jack Milder and his committee for the foresight in planning this very timely Conference. Dr. Milder should be congratulated for all the fine things he has achieved, including the mailing of all the transcripts of the papers before the Meeting, as well as looking after the Conference in a most efficient way. Finally, our highest appreciation to the American Cancer Society for their support of this most useful Conference and for the arrangements they have made for its success."

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Summary of Informal Discussion on Basic Concepts in Neoplasia

George Weber


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