Chapter VII

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The aim of the investigations incorporated in this thesis was to obtain comparative data on the nutritional and metabolic characteristics of normal and neoplastic rat liver with regard to the requirement and metabolism of glucose and amino acids and to determine therefrom the metabolic changes that take place during the transformation of normal liver to neoplastic tissue. In order to ascertain that any changes observed are not due to differences between fast-growing and other tissues, comparative data were obtained on newborn, and regenerating liver as well.

The subjects of the investigation were albino rats and the transformation to neoplastic liver was achieved by 3'-methyl-4-dimethylaminoazobenzene feeding for a period of about six months. The tissue culture technique was used for the study of nutritional characteristics. Explants of normal, neoplastic, newborn, and regenerating liver were maintained in vitro in synthetic medium and studies made of the changes in the composition of the culture fluid with regard to glucose, keto and lactic acids, and amino acids, with the progress of cultivation. The differences observed with regard to nutritional

characteristics were followed up by investigating the presence of corresponding differences in the enzyme make-up of the tissues.

Glucose was found to be released into the medium by explants of normal, and regenerating liver and to be removed from the medium by those of newborn and neoplastic liver. The hypothesis that this difference may be due to the greater amounts of glycogen found to be initially present in the former was not borne out by additional data obtained on fasting liver which was also found to release glucose into the medium inspite of its very low glycogen content. The two groups of tissues were also found to differ with regard to lactic acid production and the ratio of lactic acid to keto acid produced. Further, newborn liver was found to utilize glucose and produce lactic acid at a much faster rate than neoplastic liver. The differences observed were considered as suggestive of underlying differences in carbohydrate metabolism.

Investigations on enzymes concerned with the production and utilization of glucose in the four tissues studied showed the neoplastic tissue to differ from the other tissues studied in that the activities of phosphorylase, phosphoglucomutase, glucose-6-phosphatase,

and fructose-1,6-diphosphatase are greatly reduced in this tissue while the specific activity of glucose-6-phosphate dehydrogenase is found to be somewhat increased. It would thus appear that the enzymes which channel glucose-6-phosphate into release or storage are greatly reduced in neoplastic liver whereas those which channel it into glycolysis are atleast maintained if not increased. Further, inspite of its nutritional similarity to newborn liver, neoplastic liver was found to differ from the same in its enzyme make-up except with regard to phosphorylase. The results thus point to the biochemical uniqueness of neoplastic liver among the tissues studied and to some distinguishing characteristics between normal, newborn, and regenerating liver.

Studies of changes in the amino acid composition of the medium showed that neoplastic cultures differ from the others with regard to threonine which is removed from the medium by this tissue and is released into the medium by the other tissues studied. Differences were also observed in the rate of utilization of arginine and glutamine, the former being utilised at a slower rate, and the latter, at a faster rate, by neoplastic cultures. Some differences were also noticed with regard to the utilization of other amino acids such as alanine, aspartic acid, tyrosine + tryptophane.

Follow up studies on some of the related enzymes in these tissues showed a marked decrease in neoplastic liver in the activities of arginase, glutamine synthetase, glutamyltransferase, and glutamic-pyruvic transaminase. The differences observed would appear to account for the differences previously pointed out with regard to the utilization of arginine and glutamine.

The interesting observation was made that newborn liver was closer to neoplastic liver than normal liver in regard to these enzymes although it was found to show a nutritional similarity to the latter. The two tissues were, however, found to show quantitative differences, the enzyme levels in newborn liver ranging from •3 to 7 times those in neoplastic liver.

Thus, the present studies point to considerable differences between normal and neoplastic liver with regard to several nutritional and metabolic characteristics. The view that the same represent basic metabolic changes during carcinogenesis is strengthened by the absence of similar differences between normal and fast-growing liver tissues. Incidentally, the studies point to the potentiality

of the tissue culture technique as a tool for a study of nutritional characteristics and for the biochemical characterization of different tissues, and underline the essential interrelatedness of nutritional and metabolic characteristics.