# Meetings

## Hepatomas

In 1935, Sasaki and Yoshida showed that liver tumors were induced in rats fed chemical carcinogens. At a symposium on hepatomas held in Philadelphia, 19–20 May 1967, under the sponsorship of the Fels Research Institute, Temple University School of Medicine, new information resulting from an upsurge of interest in liver tumors stimulated by the development of the so-called "minimal deviation" hepatomas was presented. These tumors were developed in inbred rats by Harold P. Morris of the National Cancer Institute, by feeding them very low dosages of various chemical carcinogens, primarily derivatives of 2-aminofluorene. They can be transplanted in the rat strain of origin, and many of them resemble the parenchymal liver cell in many biological and chemical properties. Thus, they provide a system in which the differences between neoplastic cells and the cells of origin may be successively eliminated, permitting, perhaps, the discovery of a relatively small number of enzyme alterations essential to neoplastic transformation. These tumors together with other types developed by Morris and others, make available a spectrum of neoplastic cell types whose wide range of growth rates provides an experimental system for study of some of the biochemical bases of growth rate.

The symposium was opened by Dr. Morris who described the induction, transplantation, growth rates, and histology of the 38 hepatoma strains now carried by serial transplantation. The growth rates, in terms of time between successive transplantations, range from 0.5 to 10 months. These tumors vary from the slowly growing, highly differentiated types which resemble parenchymal liver cells to rapidly growing, poorly differentiated types which deviated greatly from the cell of origin.

Van R. Potter described the "minimal deviation" concept, as applied to the Morris hepatomas, in terms of a hypothetical tumor in which there has occurred a minimal number of alterations required for conversion of a normal liver cell to a neoplastic cell. He emphasized that while none of the Morris hepatomas can be classified as minimal, on the basis of morphology, growth rate, or enzymatic makeup, continuing research is providing information on which of the available hepatoma strains are the least deviated from parenchymal liver cells. However, as he pointed out, new and more favorable strains may become available in the future. A feature of the hepatomas is their loss of responsiveness to the feedback controls that are effective in regulating enzyme synthesis in adult liver after dietary and diurnal variation, while individuality is expressed as wide qualitative and quantitative differences in enzyme activity.

George Weber emphasized the importance of correlating growth rate with enzyme activities. Using a series of Morris hepatomas he showed decreased activities of key gluconeogenic enzymes; decreases in catabolic enzymes of purines, pyrimidines, and amino acids; and increased activities of anabolic enzymes with increasing growth rate.

The remaining papers were limited to 15-minute presentations and covered biological properties, nucleic acids, carbohydrate and fatty acid metabolism, amino acids, proteins, and control mechanisms.

Using 38 transplantable rat hepatoma lines carried in hosts of the opposite sex to facilitate identification of host and tumor cell karyotypes, Peter Nowell found that only eight hepatomas (7800, 7794A, 9098, 9108, 9121, 9618A, 9618B, and 9633B) had the normal chromosome number of 42, and only two (9618A and 9633B) had both normal number and completely normal appearance. Evidence for progression with continued transplantation was clear from data on four separate strains originally derived from hepatoma 5123, one of which (5123C) had up to 95 chromosomes by the 56th transplant generation, while 5123 A, B, and D had 46, 46, and 45 chromosomes, respectively.

In another study, Isaka of the Sasaki Institute, Tokyo, found a rough correlation between DNA content and chromosome number of individual ascites hepatoma cells, except ascites hepatoma AH3683, which was hypodiploid and had an increased amount of DNA. Odashima (Sasaki Institute) summarized the work on the development of 50 different lines of Yoshida's ascites hepatoma. Survival times were 10 to 15 days in most cases. Most ascites hepatomas occurred as "hepatoma islands" of less than 20 cells, but in AH-H35tc2 islands of 50 to 100 cells were common.

Neubert (Berlin) reported that mitochondria of hepatoma cells have higher concentrations of DNA, DNA polymerase, and DNA-dependent RNA polymerase than normal liver cells and these increases seemed to be correlated directly with growth rate. Two fractions of DNA polymerase have been found, the level of peak I in hepatomas and liver paralleling growth rate (Ono, Tokyo). Nishizuka (Kyoto) described experiments on a chromatin-associated enzyme from rat liver which splits out nicotinamide from nicotinamide adenine dinucleotide to form a polymer of adenosine diphosphate ribose. Nicotinamide adenine dinucleotide pyrophosphorylase was also localized in rat liver and hepatoma chromatin, and its activity was inversely correlated with growth rate, while the new enzyme seemed unaffected. Busch reported that in Morris hepatoma 9618A and other hepatomas with normal chromosome numbers the base compositions of the newly synthesized nucleolar RNA differed markedly from those of normal or regenerating liver.

Drews studied the messenger RNA of three Morris hepatomas including No. 9121 by means of hybridization competition experiments and suggested that the hepatomas contained no novel mRNA and, in fact, contained fewer species of mRNA than normal liver nuclei. Whereas normal liver cytoplasm contained about one-third of the nuclear RNA species, the rapidly growing hepatoma cytoplasm appeared to contain all the varieties found in the

nucleus, while the cytoplasm of hepatoma 9121 behaved like normal liver.

In the session on carbohydrates and fatty acids, Gullino described work with hepatomas implanted in rat ovaries to permit sampling of afferent and efferent blood in vivo. He found a reversed Pasteur effect: anaerobiosis resulted in a lowered glucose consumption and lactic acid production. Devlin reported that, whereas liver mitochondria catalyze both an intra- and extramitochondrial $\beta$-hydroxybutyrate dehydrogenase, the hepatoma mitochondria had only the intramitochondrial activity. The enzyme seemed to be significantly lower in all hepatomas than in normal liver. Weinhouse has found that in homogenates of the well-differentiated hepatomas lactate production was low and respiratory phosphorylation was not diminished. Intermixing of particulate and supernatant fractions from hepatomas with different glycolytic capacity made it clear that glycolysis could be regulated by the intensity of mitochondrial respiration. Fractionation of several enzymes by electrophoresis or column chromatography established that the highly differentiated hepatomas possessed enzymes characteristic of adult liver while the poorly differentiated hepatomas had enzymes characteristic of nonhepatic or fetal tissue. Fatty acid oxidation and synthesis in Morris hepatomas 5123C, 7793, 7795, and 7800 occurred but was insensitive to the nutritional state of the host, in contrast to normal liver (Abraham). Cholesterol synthesis was impaired in host liver presumably caused by cholesterol deposition, but in the tumors the rate was up to ten times that of normal liver (Ofner).

In the final session Wu reported that glutamine synthetase is present in some Morris hepatomas and is almost lacking in others. Cortisol induced the enzyme in the hepatomas to a much greater extent than in normal or regenerating liver. Rechcigl measured rates of catalase synthesis and degradation in hepatomas and in host liver. In one example, the catabolic rate was 2.4 percent per hour in both hepatoma and host liver, whereas the synthetic rate was 0.92 and 3.88 unit/g per hour, respectively, showing that the catalase concentration in the hepatoma was determined by decreased synthesis rather than by increased degradation. Sorof presented the latest findings on the $h_2$ soluble proteins of liver which bind liver carcinogens and inhibit cell replication in tissue culture. Evidence was presented linking the relevant properties of the $h_2$ proteins with arginase activity. Pitot reported new findings on the glucose repression of serine dehydrase synthesis with immunochemical techniques. Repression of enzyme synthesis was demonstrated in liver but in none of the hepatomas that were studied.

Although none of the studies demonstrated a molecular defect universally present in all hepatomas (such as the total loss or unique presence of an enzyme or individual regulatory protein, membrane component, or regulatory target) several appeared to be approaching this goal. While some investigators were discouraged by the many enzyme patterns that were evidently compatible with the neoplastic process, others were encouraged by the thought that many laboratories were now concentrating on experimental tumors that could be characterized by growth rate, karyotype, activities of a large number of enzymes, and responses to enzyme regulation. It appeared that although many of these hepatomas were nearly normal with respect to glycolysis, karyotype, and enzymes characteristic of normal liver, some showed drastic alterations in certain enzyme activities, and none of them appeared to be normal with respect to their response to normal controls. Many more strains of hepatoma need to be compared; hopefully the essential changes can be separated from nonessential changes, and one or more hepatomas with a minimum of molecular alterations will be discovered. Meanwhile, the multiplicity of enzyme patterns provided a sobering realization that cancer chemotherapy, lacking guiding principles, faces tremendous obstacles until key targets can be identified.

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## Calendar of Events—November

### National Meetings

*5–8.* National **Agricultural Chemicals** Assoc., 34th annual mtg., Palm Springs, Calif. (National Agricultural Chemicals Assoc., 1145 19th St., NW, Washington, D.C. 20006)

*5–8.* American Society of **Plastic and Reconstructive Surgeons**, annual mtg., New York, N.Y. (P. Randall, ASPRS, 2850 Sixth Ave., Suite B, San Diego, Calif.)

*5–9.* American **Nuclear** Soc., Chicago, Ill. (O. J. Du Temple, Executive Secretary, American Nuclear Soc., 244 E. Ogden Ave., Hinsdale, Ill. 60521)

*5–10.* American Soc. of **Agronomy**, Washington, D.C. (Executive Secretary, 677 S. Segoe Rd., Madison, Wis. 53711)

*5–10.* **Crop Science** Soc. of America, Washington, D.C. (Executive Secretary, 677 S. Segoe Rd., Madison, Wis. 53711)

*5–10.* **Soil Science** Society of America, Washington, D.C. (Executive Secretary, 677 S. Segoe Rd., Madison, Wis. 53711)

*6–8.* **Applied Superconductivity**, conf. and exhibition, Austin, Tex. (G. D. Cody, Publicity Chairman, RCA Laboratories, Princeton, N.J. 08540)

*6–8.* **Ground-Water Hydrology**, natl. symp., San Francisco, Calif. (M. A. Marino, % AERA Hq., 1201 16th St., NW, Washington, D.C. 20006)

*6–8.* **Speech Communication and Processing**, annual conf., Cambridge, Mass. (G. Cushman, 555 Huntington Ave., Boston, Mass.)

*6–8.* **Weather Forecasting**, conf., Fort Worth, Tex. (K. C. Spengler, American Meteorological Soc., 45 Beacon St., Boston, Mass.)

*6–9.* Interstate **Postgraduate Medical** Assoc. of North America, annual mtg., Chicago, Ill. (R. T. Ragatz, Box 1109, Madison, Wis.)

*7–9.* **Automatic Support Systems for Advanced Maintainability**, 1967 symp., Clayton, Mo. (D. L. Reed, Box 4124, Jennings Station, St. Louis, Mo. 63136)

*7–9.* **Reliability Physics**, 6th symp., Los Angeles, Calif. [A. Coppola, Publicity Chairman, RADC (EMERS), Griffis AFB, New York 13440]

*8–10.* Eastern **Analytical** Symp., New York, N.Y. (E. G. Brame, Jr., Elastomer Chemistry Dept., duPont Experiment Sta., Wilmington, Del. 19898)

*8–10.* American **Water Resources** Assoc., 3rd annual conf., San Francisco, Calif. (A. A. Stone, International Engineering Co., 74 New Montgomery St., San Francisco 94105)

*8–11.* **Respiratory Therapy**, 4th annual conf., Boston, Mass. (M. J. Nicholson, 6 Beacon St., Suite 620, Boston 02108)

*9–11.* **Gerontological** Soc., Inc., 20th annual mtg., St. Petersburg, Fla. (Mrs. M. Adler, 660 S. Euclid St., St. Louis, Mo.)

*10.* **Laboratory Animal in Gerontologic Research**, symp., St. Petersburg, Fla. (R. H. Yager, Natl. Acad. of Sciences–Natl. Research Council, 2101 Constitution Ave., NW, Washington, D.C.)

*11–12.* American Acad. of **Psychotherapists**, annual conf., Warrenton, Va. (H. Rockberger, Conference Chairman, 44 South Munn Ave., East Orange, N.J. 07017)

*11–15.* American Soc. for **Cell Biology**, 7th annual mtg., Denver, Colo. (M. J. Moses, Box 2982, Duke Univ. Medical Center, Durham, N.C. 27706)

*12–17.* American Soc. of **Mechanical Engineers**, winter annual mtg., Pittsburgh, Pa. (A. B. Conlin, Jr., 345 E. 47 St., New York 10017)

*13–15.* **Industrial Diamond** Revolution, technical conf., Columbus, Ohio (Con-