

radioactivity of  $^{67}\text{Ga}$  both in tumor and in normal livers. These results indicated that  $^{67}\text{Ga}$  was highly concentrated in lysosomes.

The light mitochondrial fractions were treated by various procedures to disrupt the lysosomes gradually. Marker enzyme of lysosomes (acid phosphatase) was activated stepwise at the same rate of solubilization of  $^{67}\text{Ga}$  from lysosomes. So it is conclusive that  $^{67}\text{Ga}$  was contained in lysosomal granules.

Cytosol of tumor tissue accumulated not only the highest counts of  $^{67}\text{Ga}$  ( $36.3 \pm 2.5\%$  of all accounts), but also the highest activity of lysosomal marker enzyme (acid phosphatase) ( $41.6 \pm 1.7\%$  of all activities) And the correlation coefficient between

the two activities ( $^{67}\text{Ga}$  and acid phosphatase) was 0.97. From this result, it is clear that most counts of lysosomes move into cytosols through subfractionation probably because lysosomes of tumors are liable to break and move into cytosols.

Similar results were also obtained in case of normal rat livers. The highest counts of  $^{67}\text{Ga}$  and relative radioactivity were found out in light mitochondrial fraction. The fact that accumulation mechanism of  $^{67}\text{Ga}$  exists in lysosomal fraction, is more clear than in case of tumor tissue. From these observations we must not discuss the accumulation mechanism without saying lysosomal function of tumors.

### **Effects of Cold Gallium on Cultured Cancer Cells: A Biological Approach to the Study of Mechanisms of Gallium Tumor Affinity**

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In spite of its clinical usefulness, the mechanisms of  $^{67}\text{Ga}$  tumor affinity remains controversial. The present investigations were undertaken in order to obtain an insight into this problem by studying probable biological effects on cultured mammalian cancer cells of cold gallium.

#### **Results:**

1. EM3A mouse mammary cancer cells were shown capable of extracting  $^{67}\text{Ga}$  from the surrounding culture medium when they were exposed to the radioelement during the logarithmic growth period.
2. Cold, nonradioactive gallium was found quite less toxic to the cells than the x-rays as studies by the colony formation technic.
3. The biological effectiveness of gallium on the

logarithmically multiplying cells was evidenced by plateau formation, reduced growth rate, reduced saturation density, development of locomotion and phagocytic function as well as morphological maturation. Similar morphological changes were observed in B-16 melanotic and amelanotic melanoma cells of C57B1 mouse origin, too. These changes appear to suggest an attainment of reduction in malignancy of these cells and their phenotypic acquisition of the normal cell morphology and function.

4. The rat ascitic hepatoma cells, AH 7974F, are free cells of malignancy and cell membrane negative charge much greater than their sibling cell line, AH 7974, an island-former. An

in vitro cellular uptake of  $^{67}\text{Ga}$  of AH 7974F was greater than that of AH 7974, indicating a membranous localization of the gallium, cold or radioactive, in the malignant cells.

#### Conclusions:

The gallium adsorption on the cell membrane,

an essential phenomenon, and subsequent blockade of the membrane function would lead to the phenotypic normalization of the cancer cells. This event appears to be the fundamental and discriminating mechanisms of tumor affinity of gallium.

### **Ga-67 Binding Patterns in Tumor and Rapidly Growing Tissues**

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In respect to the relationship between Ga-67 uptake and tumor growth, we studied the tumor bearing rat with 4 different kind of experimental tumors, Yoshida sarcoma, AH130, AH7974, and Sato's lung cancer, as well as normal and partially hepatectomized regenerating liver of rat. After I.V. injection liver and solid tumors were excised, homogenized and centrifuged at 105,000G for 60 min. Subcellular fractionation was carried out on aliquot. The result indicated that there were characteristic high uptake of Ga-67 radioactivity in lysosomal fraction. However, no higher uptake was found in tumor lysosomes than normal, as

reported by Hayes and others. The 105,000 G supernatant was fractionated through Sephadex-6B, and the protein and radioactivity eluate was counted. The result indicated that there was no correlation between tumor growth, cellular growth, and eluate patterns as was reported by Matsuzawa et al. These results supported our findings on unincreased Gallium uptake in regenerating liver, and undecreased uptake in tumors treated either with X-ray or with chemotherapy.<sup>(1) (2) (3)</sup>

(1) Orie: *Strahlentherapie* **144**: 192 (1972)

(2) Hill & Wagner: *JNM* **15**: 818 (1974)

(3) Gams et al: *JNM* **16**: 231 (1975)

### **Red Cell $^{86}\text{Rb}$ Uptake in Benign and Malignant Breast Tumors**

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The both of cation Rb and K are often very nearly interchangeable,  $^{86}\text{Rb}$ , with its half-life of 18.7 days, is certainly a more convenient isotope

to use, than is  $^{42}\text{K}$ , with its short half-life of 12.7 hours.

The present study compared the RBC  $^{86}\text{Rb}$