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^{67}Ga-UPTAKE IN THE REGENERATING RAT LIVER

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Gallium-67-citrate accumulation in the regenerating liver of the partially (67%) hepatectomized rat was measured 4 hr after surgery and 8 hr following injection of the tracer. After 24 hr, the weight of the remaining liver increased 57.3 ± 7.6 (s.e.) % compared with the corresponding portion of the liver of a sham-operated control rat. The ratio of ^{67}Ga uptake per gram liver in the partially hepatectomized rat to that in the paired control animal was 0.99 ± 0.08 (s.e.). These findings suggest that ^{67}Ga uptake is not related to hepatic cell proliferation associated with regeneration.

In 1969 Edwards and Hayes first observed that ^{67}Ga-citrate accumulated in soft-tissue malignant tumors and permitted their detection by scintiscanning (*1*). Subsequently other workers have demonstrated the clinical usefulness of ^{67}Ga scintiscanning as an aid in the differential diagnosis of a wide variety of primary and metastatic malignancies (*2–5*). Although ^{67}Ga scanning is now becoming an established diagnostic technique, the pathophysiologic processes responsible for gallium accumulation are poorly understood.

We postulated that ^{67}Ga accumulation might be related to the rapid cell proliferation that characterizes regeneration and repair. To test this hypothesis, we performed experiments in rats subjected to partial hepatectomy. Following partial hepatectomy, the remaining liver tissue undergoes rapid cell proliferation and growth (*6,7*).

METHODS

The first set of experiments was designed to obtain information regarding the time after injection at which ^{67}Ga concentration is maximum. Gallium-67 (supplied carrier-free by Diagnostic Isotopes, Inc.) diluted with 0.008 *M* sodium citrate (pH 7.83) to give a dose of 10 μCi (2.5×10^{-7} μ*M* of ^{67}Ga) in 0.3–0.4 cc was injected intravenously into male Wistar rats. The rats were sacrificed at 6, 12, 24, and 48 hr following injection. The livers were then weighed and counted in a well counter between 50 and 350 keV. Sufficient counts were obtained to yield a relative standard deviation of less than 1%. The percent of injected activity per gram of liver in each of four rats was averaged for each time interval, except at 48 hr where three rats were used.

To assess the possibility of significant colloid formation in our tracer solutions, 2 ml of ^{67}Ga-citrate solution, prepared in the usual manner, was dialyzed against 500 ml of 0.008 *M* sodium citrate. By 6 hr, with three changes of the 0.008 *M* sodium citrate solution, 87.7% of the radioactivity was removed, and by 24 hr, with four changes, 99.4% was removed.

In the second set of experiments, one member of each of seven pairs of rats was anesthetized with 10–15 mg of pentobarbital and partially hepatectomized by resecting the left lateral and median lobes according to the method of Higgins and Anderson (*8*). The second member of each pair served as a sham-operated control; the animals were anesthetized and their abdomens were opened but no liver was removed. In all animals, 16 hr following surgery, 10 μCi of ^{67}Ga-citrate was injected through the tail vein. The ^{67}Ga-citrate was prepared as described for the experiments in Set 1. Eight hours after injection,

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the rats were sacrificed, livers removed and rinsed with 0.9% saline. The tissue was then blotted on a paper towel, weighed, and counted as described above. The entire liver of the control rat was weighed; the left lateral and median lobes were then cut away, and the remaining liver weighed (hereafter referred to as "remaining liver") for comparison with the corresponding portion of the experimental liver.

The mean weight of all rats was 235 gm. Animals were given access to tap water and Purina rat chow throughout.

RESULTS

The results of the first set of experiments are summarized in Fig. 1. The vertical lines represent ±1 s.e. of the mean. The activity at 8 hr is 88% of maximum. The difference in uptake at 12 and 48 hr was of borderline significance ($p < 0.05$). None of the other uptake values differed significantly from one another. The mean liver uptake at 24 hr, expressed as percent of injected activity, is 8.71 ± 1.26 (s.d.) and is somewhat greater from the mean uptake of 6.71% reported by Popham, et al (*9*).

The results of the second set of experiments are presented in Table 1. Partial hepatectomy resulted in a highly significant increase in weight of the remaining lobes of the liver. The remaining liver of the experimental animals was 37.5–97.8 (mean 57.3) percent heavier than the remaining liver of the control member of the pair. However, despite the unequivocal stimulation of growth, a significant increase in ^{67}Ga uptake was not observed. The mean ratio of percent of injected activity per gram liver in experimental animals to that of the paired controls was 0.99 ± 0.21 (s.d.).

DISCUSSION

The rate of cell proliferation in the regenerating liver is probably near maximal at 24 hr. Grisham, using male Wistar rats, found that the maximum rate of hepatocyte DNA synthesis, as calculated from autoradiographs following administration of ^{3}H-thymidine, occurred at 20 hr after partial hepatectomy. The maximum percent of cells mitosing appeared at 26 hr (*6*). Weinbren estimated maximum mitotic rate at 28 or 29 hr (*7*). Gallium was given 16 hr following hepatectomy in order to permit the animals to recover from surgery while still allowing sufficient time for most of the hepatic uptake to occur before sacrificing.

The present results are of interest in light of the findings of other investigators. Bichel and Hanson demonstrated increased ^{67}Ga accumulation by hyperactive bone marrow of mice subjected to bleeding (*10*). Furthermore, there appears to be greater

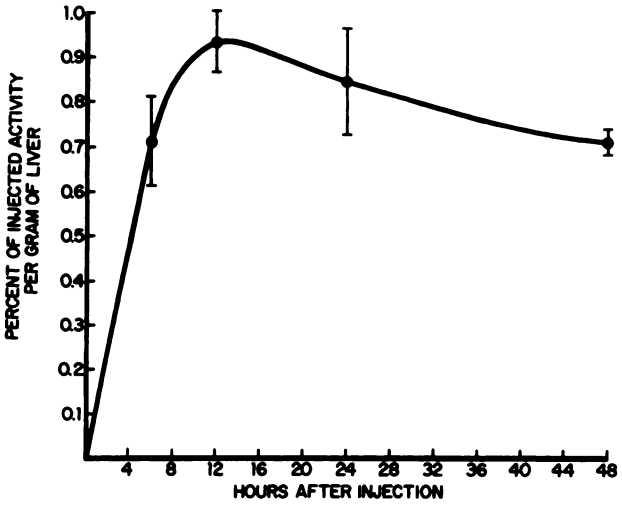

FIG. 1. Percent injected activity per gram liver, as function of time after injection, shows maximum uptake of tracer at 12 hr and 88% of maximum at 8 hr. Vertical lines represent ±1 s.e. of mean.

TABLE 1. COMBINED RESULTS FOR PARTIALLY HEPATECTOMIZED AND CONTROL ANIMALS, RESPECTIVELY*

	Hepatectomized	Control
Remaining liver wt (gm)	4.28 ± 0.39	2.77 ± 0.49
Percent dose per gm liver	0.92 ± 0.20	0.96 ± 0.25
Percent dose in liver	—	8.49 ± 1.72
Percent dose in remaining liver	3.90 ± 0.73	2.58 ± 0.57

* mean ±1 s.d.

^{67}Ga uptake in viable tumors compared with necrotic tumors (*11*) and in transplanted animal tumors during their rapid-growth phase compared with the same tumors in their plateau or slow-growth phase (*10,12*).

Our findings argue against the hypothesis that ^{67}Ga uptake is a function of the rate of hepatic cell proliferation per se.

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