

## Liver Scanning in the Assessment of Liver Damage from Therapeutic External Irradiation

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The normal liver has generally been considered an organ resistant to x-ray irradiation when given in the usual therapeutic range. Recent observation based on study of liver scans of patients undergoing irradiation for control of testicular tumors suggest, however, that the liver may in fact be quite sensitive to x-irradiation.

Case(1) reviewed the early literature and cited the experimental work of Seldin in 1903-04 who found no histologic differences between irradiated and nonirradiated liver cells. Heinke (1904) confirmed the work of Seldin. Werthin (1905) had demonstrated atrophy, chronic passive congestion and minimal parenchymal degeneration in the liver of humans who were treated by irradiation, but the effects were nonspecific and the causal relationship of the irradiation could not be established definitely. Tribondeau and Hudelet (1907) using fractionated dosage in diabetics were unable to demonstrate definite damage. Ellinger(2) has stated no agreement exists among clinicians and investigators as to the radiosensitivity or radioresistance of the liver. A threshold for liver cell injury exists which approximately equals the LD80 for any species of animal and if fractionated irradiation is administered, liver damage will result only after an absolute lethal dose is given. He also pointed out that liver cell death may be caused indirectly by the action of histamine, and the total effect of liver damage is the sum of the direct irradiation damage and the indirect action of histamine.

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Weinbren, *et al*, (3), however, in 1960 postulated that irradiation damage to liver cells may be latent, becoming evident only when the cell undergoes mitosis. Whether the liver cell is radioresistant or sensitive can not be estimated on the microscopic appearance of the resting postirradiated cell. After mitosis has occurred evidence of damage may be pronounced, particularly if only a portion of the liver has been irradiated.

#### OBSERVATIONS

A patient who had undergone extensive irradiation to mediastinal and abdominal areas was subjected recently to liver scanning. No significant uptake of the isotope in the liver beneath the therapy portal (Fig. 1) was observed although a pretreatment scan done to detect possible metastasis had been entirely normal. Since  $^{198}\text{Au}$  (the isotope used for these two scans) is fixed by the Kupffer cells and not by the functioning liver cell, it was decided to repeat the scan using Rose Bengal  $^{131}\text{I}$  in the knowledge that the polygonal cell selectively secretes this agent while the Kupffer cell is unaffected. A very similar scan was obtained suggesting that liver cell damage had occurred. Because it was originally speculated that this could be due to local metastatic disease or be a finding peculiar to this patient, it was decided to examine other patients who had been subjected to a similar course of irradiation for therapy. Very similar scans were obtained from many of these patients. The scans and case histories are presented.

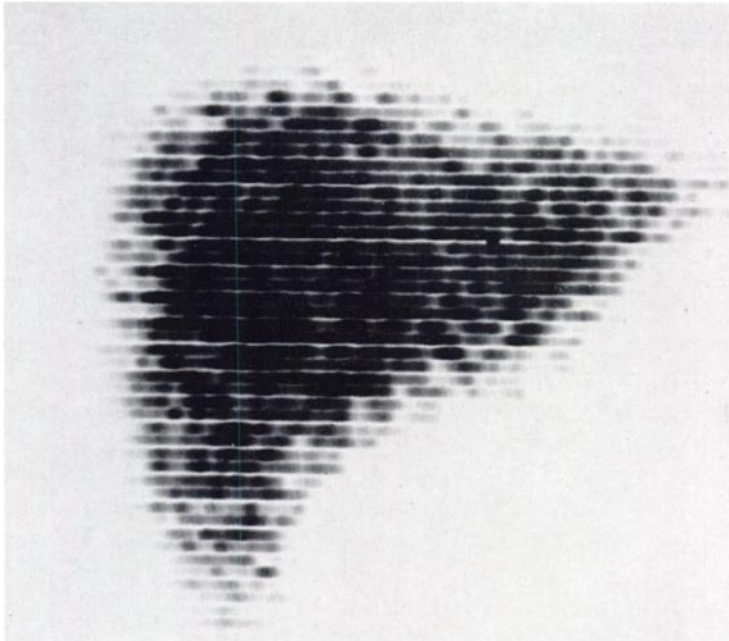


Fig. 1

*Case 1:* HVK, developed a right testicular mass two weeks prior to admission. A right orchidectomy was performed October 24, 1963. Pathologic diagnosis was embryonal cell carcinoma with vascular invasion. Bilateral retroperitoneal node dissection on December 2 revealed gross and microscopic involvement to one cm below the renal veins. Radiation therapy was begun and 4500 rads were delivered to each of four portals as outlined in Diagram 1. Figure 1 shows the normal liver scan obtained before therapy was started. Figures 2 and 3 are the scans described above demonstrating sharp cut-off of uptake in the regions of the liver over which irradiation had been administered, while the remainder of the two scans compares quite closely in appearance to the original scan.

*Case 2:* LLL, experienced pain in the right testis region from October until December when a right orchidectomy was performed. A pathological diagnosis of embryonal cell carcinoma with teratomatous elements was returned. Bilateral retroperitoneal node dissection was done and one of thirty-five nodes was found to contain malignant elements. A midplane dose of 4200 rads was delivered to each portal area outlined in Diagram 1. When the liver scans from Case 1 were reviewed it was decided to obtain a scan on LLL on the occasion of his first posttherapy evaluation. This was performed and is shown in Figure 4. Again noted is the sharp medial border of the uptake of isotope. This border exactly outlined the right lateral margin of the therapy port.

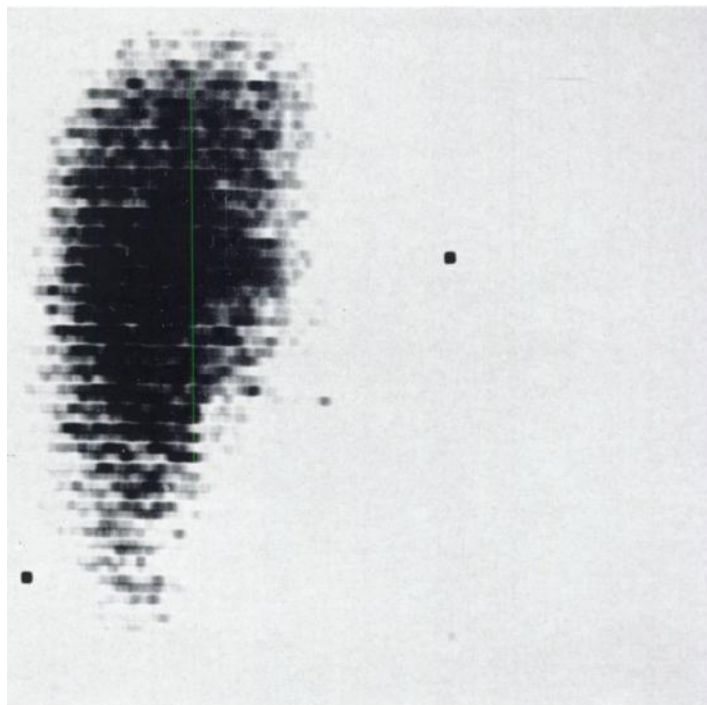


Fig. 2

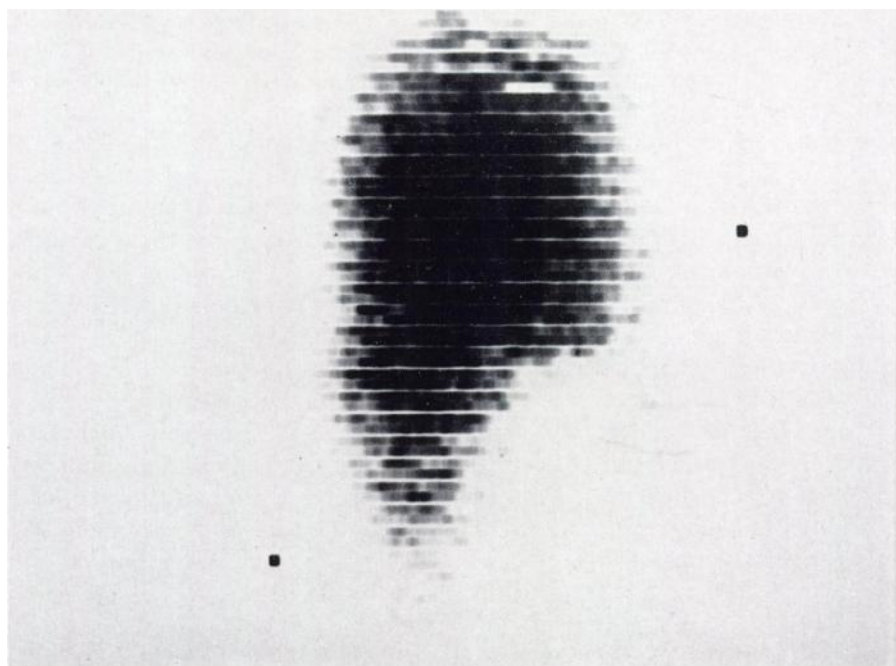


Fig. 3

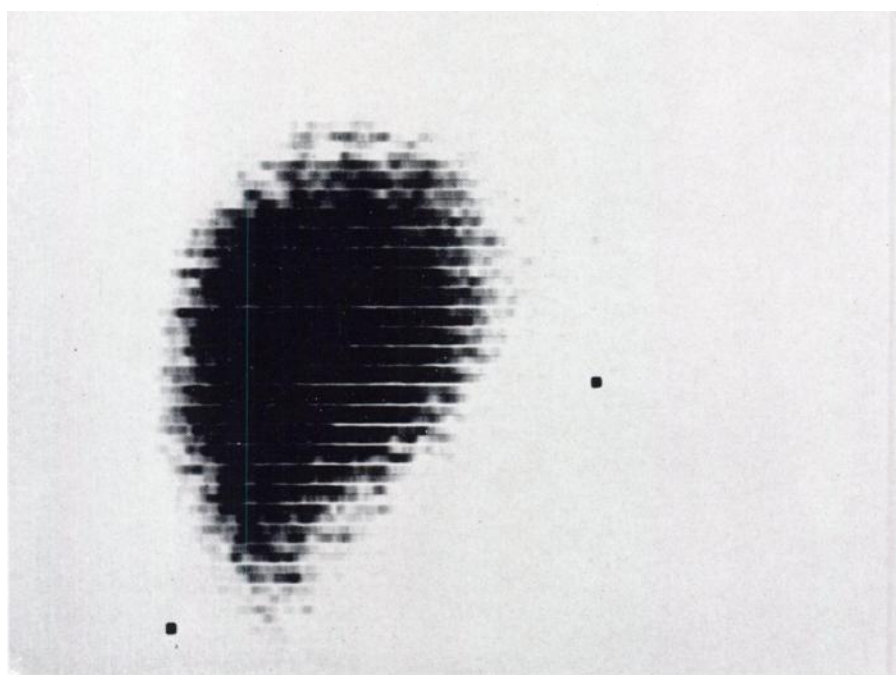
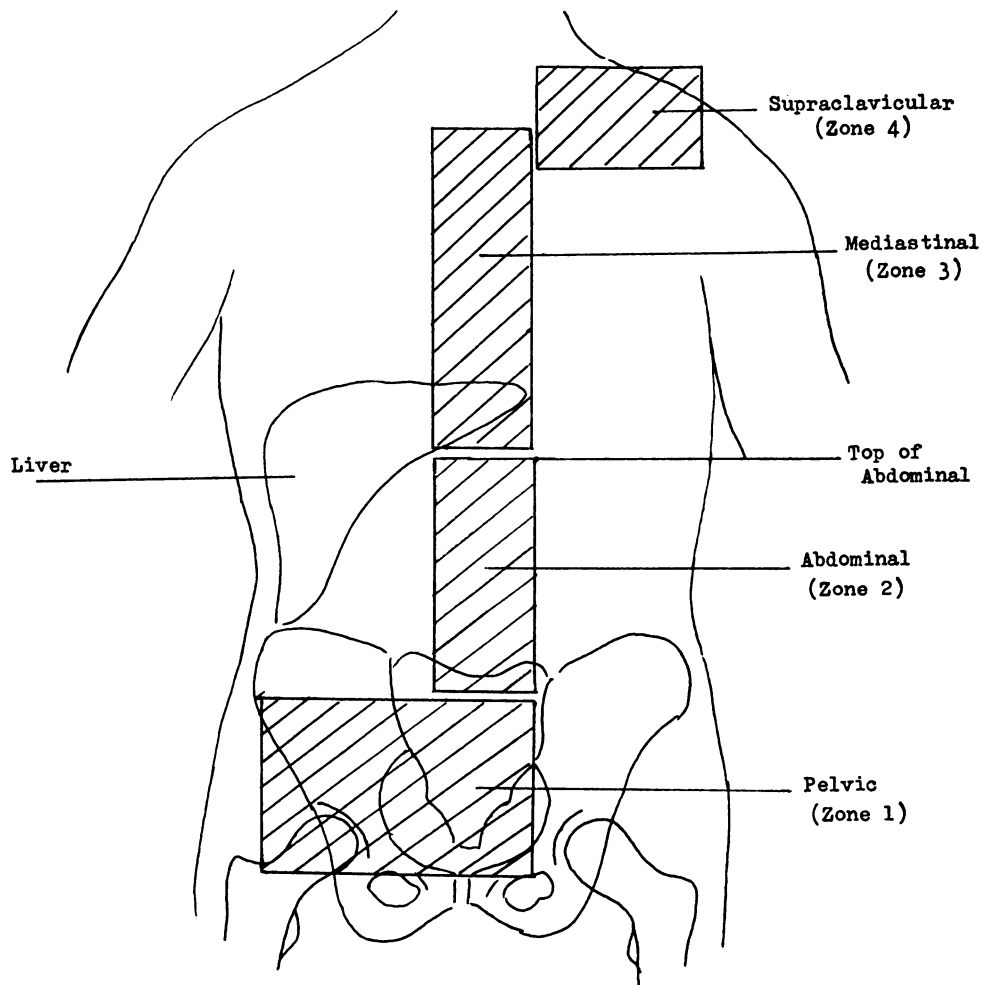


Fig. 4

*Case 3:* RPJ, underwent simple excision of an undescended right testicle which on pathological examination was found to contain pure seminoma. No metastasis was detected. Radiation therapy was begun only to the two regions outlined in Diagram 2, because no evidence of metastasis was found within the abdomen. Following review of the first two cases, and after delivery of 2800 rads to the two portal areas described, it was decided that liver scanning of this patient was in order. Rose Bengal  $^{131}\text{I}$  scan was performed and found entirely normal (Fig 5) It was observed during the scanning that the superior margin of the abdominal portal was well below the inferior margin of the left lobe of the liver which normally lies at or just below the nipple line in the supine treatment and scanning positions.



**Diagram 1: Portal arrangement for Cases 1, 2 and 5. Note position of liver in relation to top of Abdominal portal.**

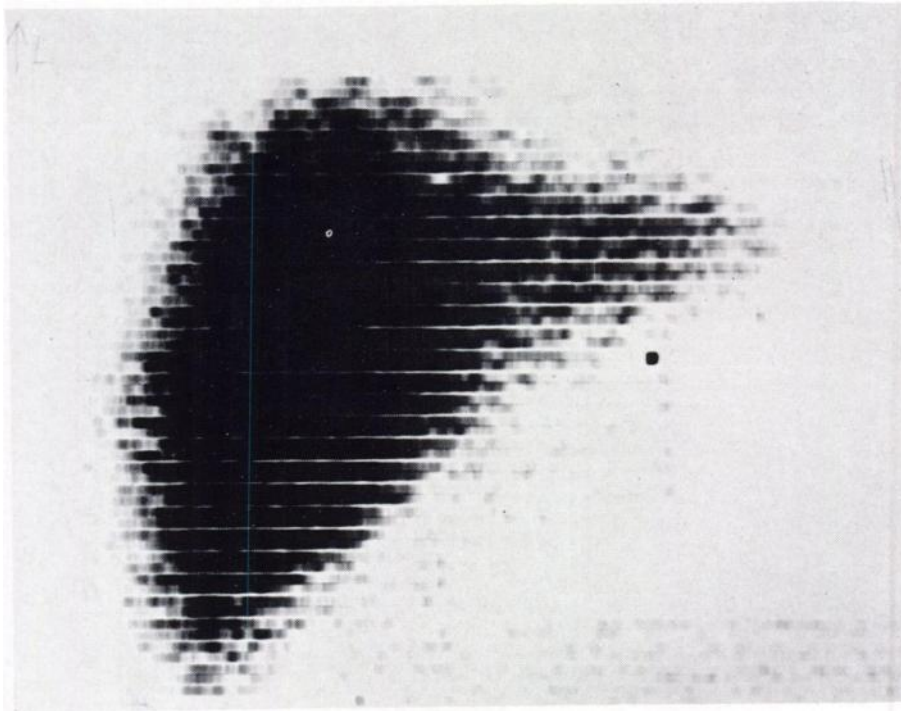


Fig. 5

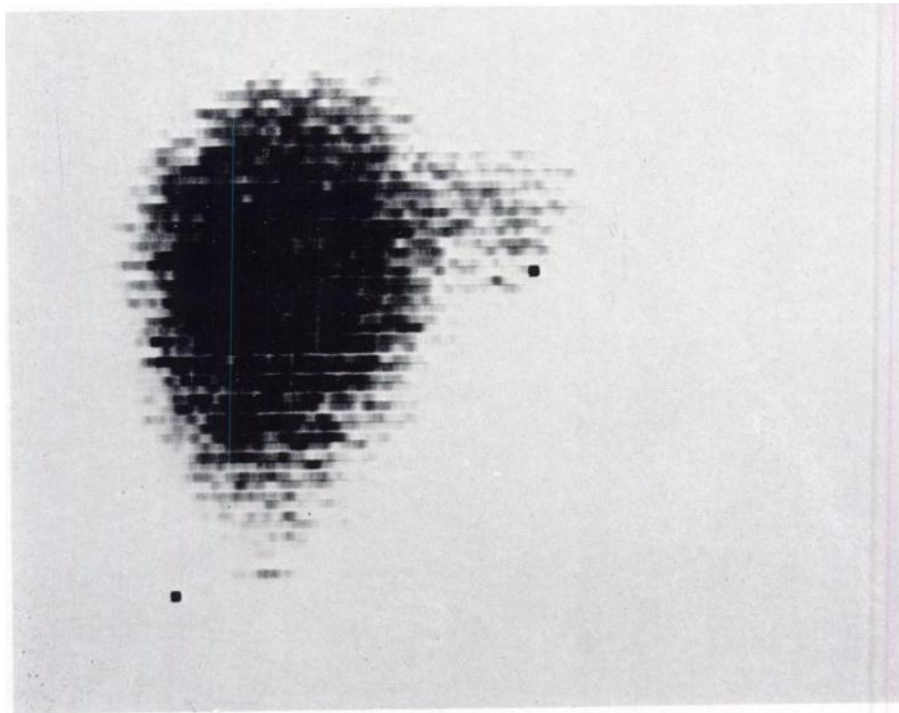
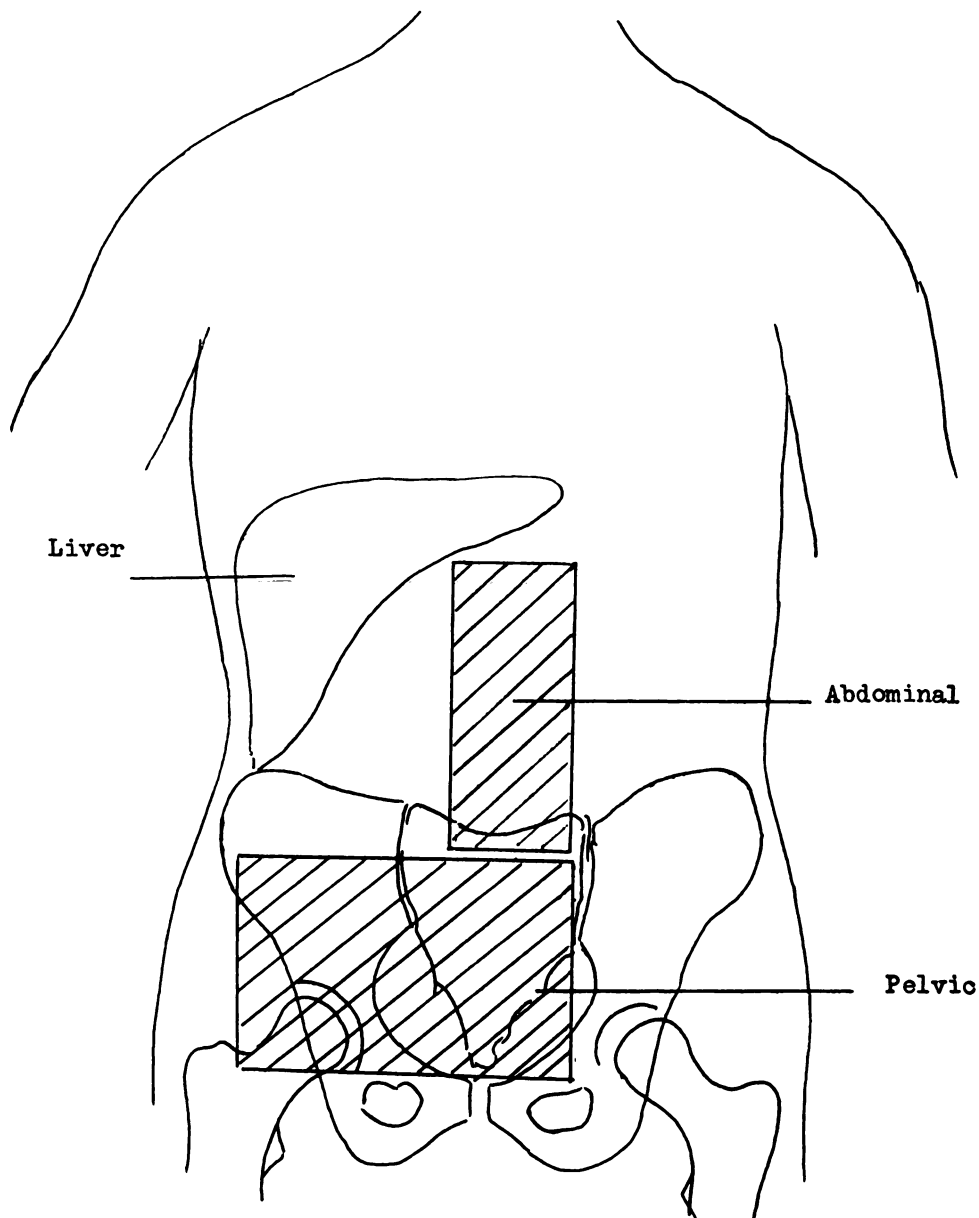


Fig. 6

*Case 4:* RSS underwent right radical orchidectomy February 3, 1964 which revealed embryonal cell carcinoma. A single involved lymph node was found during a bilateral retroperitoneal node dissection. The node was near the right renal hilum. X-ray therapy was begun and the two portals outlined in Diagram 2 were each treated to 4500 rads. At the time of the first abnormal liver scan performed on Case 1, this patient had already been given half the anticipated total dose to the two remaining portals outlined in Diagram 1. A liver scan using Rose



**Diagram 2:** Portal arrangement for Case 4 and initial arrangement for Case 3.



Bengal  $^{131}\text{I}$  was then thought in order to evaluate the possibility of very early liver cell damage from irradiation. This scan, carried out after only 2400 rads had been delivered over the left lobe of the liver is shown in Figure 6. Some isotope uptake persists in the treated area and yet there is a definite change from a normal pre-therapy scan (Fig 7). Following the observation of the abnormal scan treatment was continued as planned to a total mediastinal dose of 4000 rads. A third scan prior to discharge revealed evidence of progressive damage to the left liver lobe (Fig. 8).

*Case 5:* REN, had a left orchidectomy for seminoma in 1950 followed by pelvic and abdominal irradiation (Diagram 2) to 1050R in air to anterior and posterior areas. Metastatic deposits were found in 1957, 1963 and 1964 each necessitating moderate doses of radiation in the regions of the chest and left cervical area (Zones 3, 4; Diagram 1). An  $^{198}\text{Au}$  scan performed in May, 1962 was normal (Fig 9). Rose Bengal  $^{131}\text{I}$  and  $^{198}\text{Au}$  scans were done during a post-treatment evaluation visit after noting the abnormalities of the previously described scans. These latter two scans demonstrate decreased but not absent left lobe function. (Figs 10 and 11)

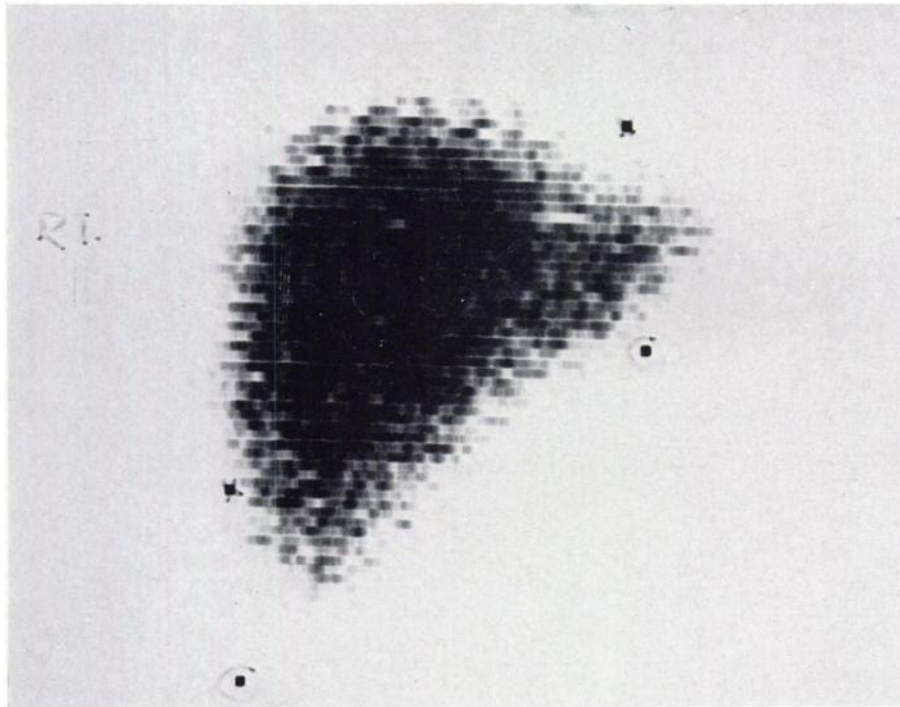


Fig. 7



## DISCUSSION

Although the exact mechanism producing liver cell dysfunction following Roentgen therapy is not known, it would appear that the  $^{198}\text{Au}$  and Rose Bengal  $^{131}\text{I}$  scans presented provide reliable evidence to indicate that such damage does occur. Since it is known that  $^{198}\text{Au}$  is not taken up by the functioning liver cell (polygonal cell) but is fixed by the Kupffer cell (a tissue macrophage), and because the polygonal cell selectively secretes the labelled Rose Bengal, the Kupffer cell not being influenced by Rose Bengal, it would seem both elements are sensitive to external irradiation. Since the scans of both types are practically identical in their demonstration of sharp cut-off of activity in the left lobe of the liver following external irradiation, it would appear quite evident that both cell types are affected.

It is considered doubtful that the changes demonstrated in the left lobe of the liver by scanning can be related to the combined effect of any complication from surgery and the radiotherapy. Rather, it would seem the radiation has a sole role in causing liver cell dysfunction.

It is also evident that damage to the left lobe will not appear in patients who receive treatment only over the areas outlined in Diagram 2. Damage occurs when the mediastinum is irradiated and the high-riding left lobe of liver is necessarily included in the treatment portals.

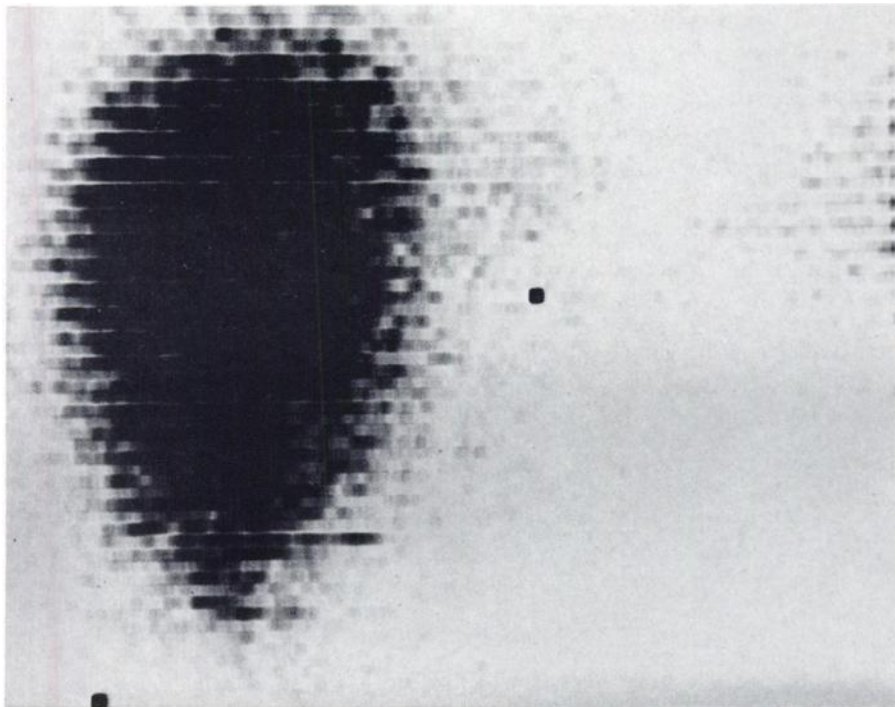


Fig. 8

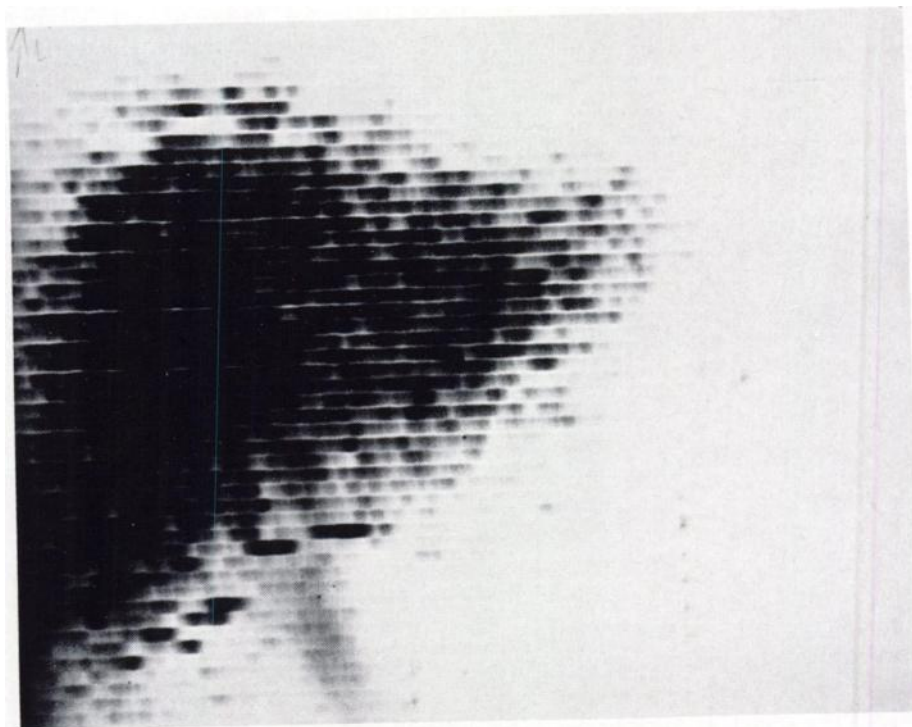


Fig. 9

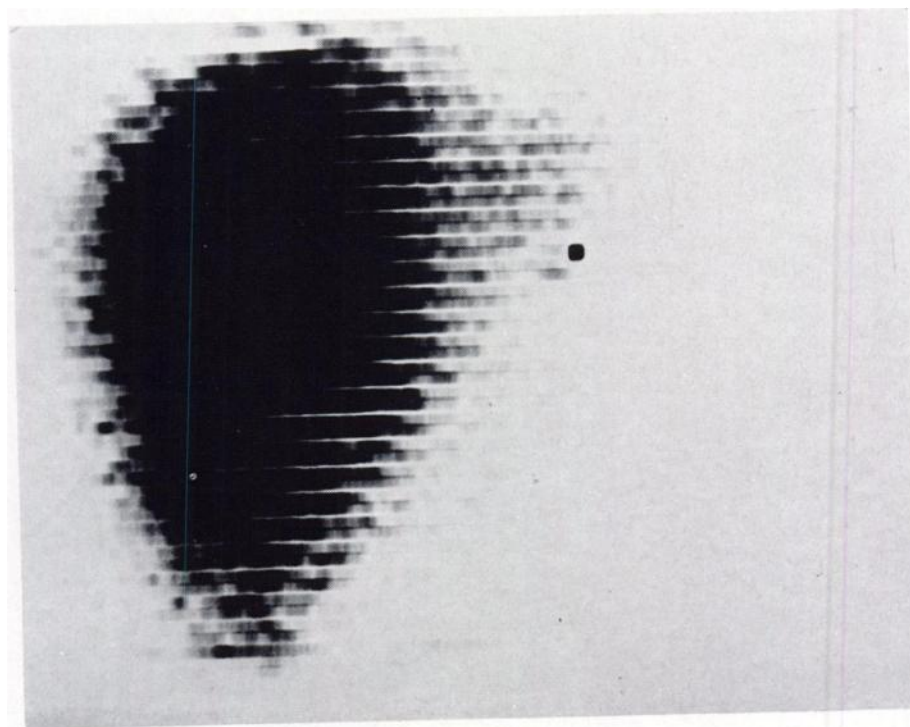


Fig. 10

The scan obtained in Case 4 after 2400 rads had been delivered suggests that the liver may in fact be quite highly sensitive to irradiation. Further investigations are under way including evaluation by periodic scanning of all patients who have had therapy over a portion of the liver in an effort to correlate dose with functional impairment. In addition followup scanning of patients is being done in those who have previously demonstrated liver cell dysfunction by either  $^{198}\text{Au}$  or Rose Bengal  $^{131}\text{I}$  scanning on the occasion of their return for regular checkups. The most recent scan carried out on Case 1, after one year demonstrated no change in the appearance of the uptake from that seen in Figure 2, while the patient remains in perfect health.

#### SUMMARY

Five case histories of patients subjected to external irradiation for treatment of testicular tumors have been presented together with liver scans made as part of their workup and evaluation during and after therapy. The scans would appear to provide a reliable indication that the liver is more susceptible to external irradiation than had been thought and that moderate dosage may be sufficient to produce dysfunction. When the left lobe of the liver has been irradiated through mediastinal portals scans show sharp vertical cut-off of activity in that liver in the treatment beam. Further, considering the complete lack of change in the appearance of two scans taken one year apart on Case 1, without change in his

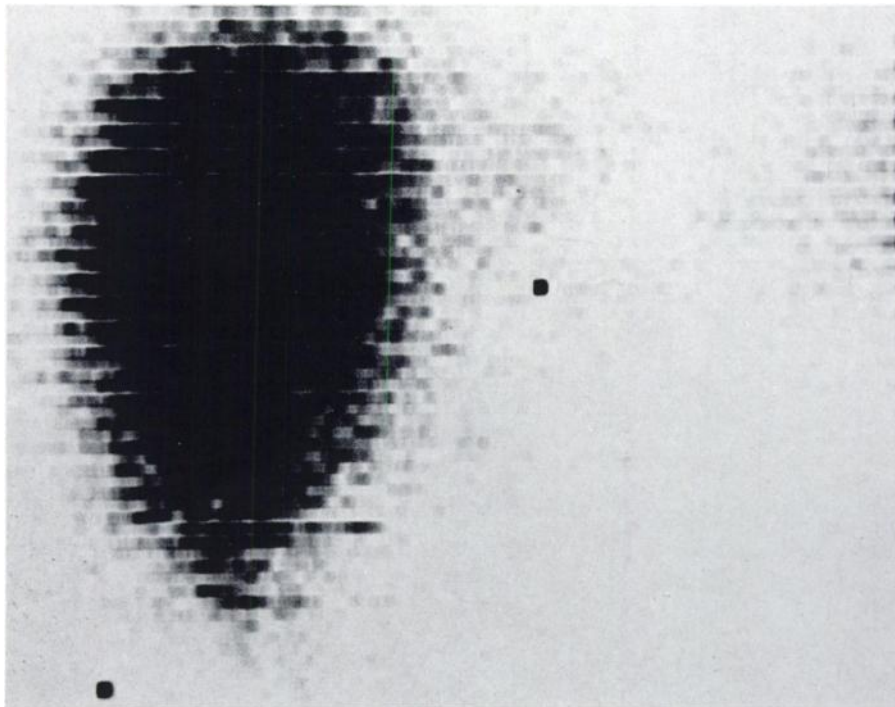


Fig. 11

physical status, the thought that the findings might be due to metastatic disease appears to be improbable. Also, this would tend to suggest that the finding demonstrated by scanning is not temporary. Further studies are in progress to evaluate doses required to produce dysfunction and to assess the degree of permanence of the liver impairment.

#### ACKNOWLEDGMENT

The author wishes to acknowledge the assistance of Haywood Ferguson, HM1, USN and Robert Galloway, HM2, USN, in the making and photographing of the liver scans.

#### REFERENCES

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### EARL JONES TO ADMINISTER NEW LABORATORY ANIMAL LAW

Dr. Earl M. Jones, D.V.M., will head the Agriculture Department unit created to administer the new laboratory animal law (PL89-544).

Since July, 1965, Dr. Jones has served as Chief Staff Veterinarian, Health and Humane Requirements, Animal Health Division, Agricultural Research Service.

The new unit Dr. Jones will head has been designated the Laboratory Animals Staff (LAS). It will be a function of the Animal Health Division under the direction of Dr. F. J. Mulhern.