of platelet adhesiveness caused by the drug. The effective dose of ADP to induce an increase in platelet adhesiveness is thus determined. A change in the required amount of ADP to induce this effect in an individual post irradiation animal as compared to that animal's pre irradiation requirement indicates the increase in platelet adhesiveness.

Histology, Liver Function Tests and Blood Chemistries

Tissue samples were obtained, fixed and stained using standard histological techniques for microscopy studies. Liver function tests and blood chemistries performed include LDH, SGOT, Bilirubin, Total Colloid, Serum Albumin, Total Serum Protein, A/G Ratio, Prothrombin Time, Alkaline Phosphatase, HCT, WBC, RBC, BUN, Na+ and K+. Standard methodology was used in all tests. Blood samples were drawn before and after radiation treatments for testing.

General Experimental Plan

The experiments were performed on female beagle dogs, 1 year old when treatment was started. All determinations were performed prior to radiation, and then again two weeks after radiation treatments ended.

Whole liver radiation was performed through parallel lateral opposing ports after radiological confirmation of field localization. The animals were treated to 4600 rads delivered in 23 treatments, total treatment time being 35 days. A Co^{60} Teletherapy HVL 11 pb unit at a SSD of 50 cm was used. Isodose curves were determined for each animal.

When determining TpO_2 the animals were under barbituate anesthesia with tracheal intubation and cannulation of the femoral artery and vein. Blood samples for *in vitro* studies were obtained from the cannulated femoral vein. All surgical procedures were done under sterile conditions.

RESULTS AND DISCUSSION

At the present time, pre and post irradiation studies have been completed in 9 beagles.

Reoxygenation times: It was found that the normal reoxygenation time in the dog's liver is 2.14 minutes. This figure is larger than the RT in the cat's brain (0.68 min.) as previously reported (7). After ionizing radiation the liver RT is significantly prolonged, to an average of 3.26 minutes (See Table 1, Figs. 1 and 2).

TABLE 1

AVERAGE BEAGLE REOXYGENATION TIMES - LIVER

DOG	PRE-IRRAD.	POST-IRRAD.	P VALUES
A-5	1.56 ± 0.42	3.36 ± 1.11	< .001
A-6	2.53 ± 1.35	4.87 ± 1.21	< .001
A-7	1.30 ± 0.20	5.50 ± 1.89	< .001
A-8	2.00 ± 1.13	1.84 ± 0.45	< .7
A-9	1.60 ± 0.49	2.72 ± 0.65	< .001
A-10	2.72 ± 1.54	2.17 ± 0.71	< .3
A-11	2.80 ± 0.84	3.15 ± 0.90	< .001
A-12	3.26 ± 0.88	3.79 ± 0.92	< .001
A-13	1.58 ± 0.21	2.98 ± 0.93	< .001
Avg.	2.14 ± 1.12	3.26 ± 1.54	< .001

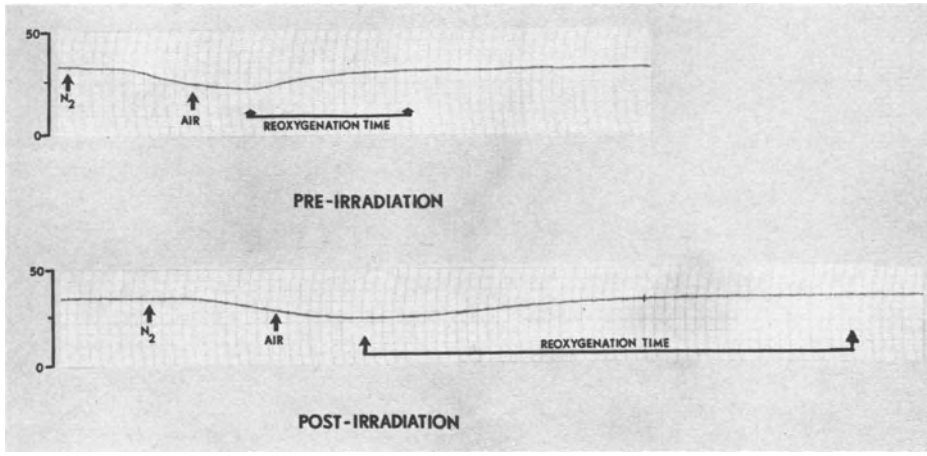

Fig. 1: BEAGLE REOXYGENATION TIMES. Note prolonged RT after irradiation. For explanation see text.

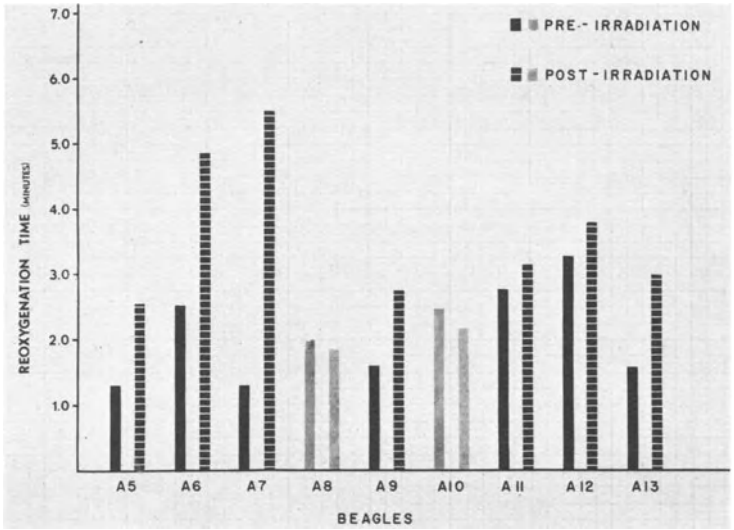

Fig. 2: REOXYGENATION TIMES IN LIVER, PRE & POST IRRADIATION.

Platelet aggregation and adhesiveness: Both platelet aggregation and adhesiveness increased markedly after irradiation. The mean effective dose (MED) of ADP to induce 50% aggregation or adhesiveness decreased from 2.5 µg/ml to 1.3 µg/ml. The adhesiveness induced by the pre-irradiation MED was 46.6% before irradiation and 86.2% after irradiation (See Table 2).

Histology and Blood Chemistry: No significant changes were observed histologically in pre and post irradiation sections. The only significant changes in blood chemistry were: a decrease in albumin from 3.11 mg% to 1.91 mg% in 6 out of 9 dogs; alkaline phosphatase increased from 56 to 300 units in 7 out of 9 dogs. All other parameters were unchanged.

Recently Ingold (9) demonstrated that the liver is not radioresistant to ionizing radiation, but rather one of the more sensitive tissues. Ingold's studies indicated that the sensitivity of the liver is comparable to that of bone marrow, lymphoid tissue, germinal tissue and the kidneys.

Kinzie et al. (10) reported results which indicate that the prevention of intravascular coagulation (by heparinization) greatly reduced the impact of radiation upon the livers of rats. The apparent mechanism is the prevention of ischemic atrophic changes which would follow the post irradiation obliteration of the microcirculation. Although these results would seem to indicate a principle of considerable importance in clinical oncology, additional

TABLE 2

RADIATION INDUCED CHANGES IN PLATELET AGGREGATION
IN VIVO UTILIZATION OF OXYGEN AND GLUCOSE BY NEOPLASTIC TISSUE

DOG	DOSE ADP CAUSING MAXIMUM AGGREGATION		% PLATELETS ADHERING (With Pre-Irrad. Dose for Maximum Aggregation)		% PLATELETS ADHERING (With Post-Irrad. Dose for Maximum Aggregation)
	Pre-Irrad.	Post-Irrad.	Pre-Irrad.	Post-Irrad.	
A-5	2.0 ug	2.0 ug	44.5	93.2	70.6
A-6	2.0 ug	0.25 ug	56.1	91.6	33.7
A-7	1.0 ug	0.5 ug	46.4	85.6	64.9
A-8	1.0 ug	0.5 ug	61.1	86.5	38.9
A-9	5.0 ug	2.5 ug	44.4	95.8	69.1
A-10	3.0 ug	1.5 ug	22.6	84.1	49.9
A-11	2.0 ug	2.0 ug	51.3	66.7	60.1
Avg.	2.3 ug	1.3 ug	46.6	86.2	54.7

information is not available.

The present studies clearly demonstrate that ionizing radiation induces profound deleterious changes in the ability of the microcirculation to oxygenate liver tissue. This is indicated by the marked prolongation in reoxygenation time, a sensitive parameter of this function (3). The microcirculation disturbance could probably be mediated by increased intravascular blood cell aggregation, as indicated by the increase in platelet aggregation and adhesiveness hereby reported.

SUMMARY

Platelet aggregation and adhesiveness, as well as TpO_2 responses to hypoxia were measured as microcirculation parameters in beagle dogs subject to Co^{60} ionizing radiation to a dose of 4600 rads in 5 weeks. Simultaneously, changes in blood chemistry and coagulation were also determined. Marked changes in all studied parameters in the post radiation period lead to the conclusion that radiation liver damage is at least in part mediated through microcirculation disturbances.

REFERENCES

1. Bicher, H.I. Prevention of sludge induced myocardial damage by an anti-adhesive drug. Bibl. anat., 10:202, 1969.

2. Bicher, H.I. Anti-adhesive drugs in thrombosis. Throm. et Diath Haem., Suppl. 42:197, 1970.

3. Bicher, H.I. Brain oxygen autoregulation: A protective reflex to hypoxia. Microvasc. Res., 8:291-313, 1974.

4. Bicher, H.I. and Beemer, A.M. Induction of ischemic myocardial damage by red cell aggregation (sludge) in the rabbit. J. Atherosclerosis Res., 7:409, 1967.

5. Bicher, H.I. and Beemer, A.M. Prevention by an anti-adhesive drug of thrombosis caused by blood cell aggregation. Angiol., 21:413, 1970.

6. Bicher, H.I., Bruely, D.F., Reneau, D.D., and Knisely, M.H. Effect of microcirculation changes on brain tissue oxygenation. J. Physiol., 217:689-707, 1971.

7. Bicher, H.I., Marvin, P., Hunt, D.H., and Bruley, D.F. Autonomic and pharmacologic control of oxygen autoregulation mechanisms in brain tissue. ISOTT Symposium, Mainz, Germany, 1975. (To be published by Plenum Press, N.Y.)

8. Born, G.V. Quantitative investigations into aggregation of blood platelets. J. Physiol., 162:67p, 1962.

9. Ingold, J., Reed, G. and Kaplan, M.D. Am. J. Roentgenology, 93:200, 1965.

10. Kinzie, J., Studer, R.K., Perez, B. and Potcher, E.J. Noncytokinetic radiation injury; anticoagulants as radioprotective agents in experimental radiation hepatitis. Science, 175:1481, 1972.

11. Rubin, P. The radiographic expression of radiotherapeutic injury. An overview. Seminars in Roentgenology, 1:5, 1974.

12. Silver, I. A simple microelectrode for measuring pO_2 in gas or fluid. Med. Electron. Biol. Eng., 1:547, 1963.