much more extensive Great Lakes, and the consequent effect on crustal elevation and concomitant eustatic movement of sea level. The material on isostacy from Evans' journal is on pages 29 and 30 of the 1776 edition (*10*) and on pages 112–116 of that of 1949 (*11*):

Amidst the Detail of these dry Descriptions, it may perhaps relieve and amuse the Reader to insert some Observations and Opinions which I found in and extracted from Mr. Evans' Journal.

"The Stones in all Parts of these Mountains are full of Sea Shells: . . .

"Various Systems and Theories of the present Earth have been devised in order to account for this Phaenominon. One System supposes that the Whole of this Continent, the highest Mountains themselves, as they now appear, were formerly but one large Plain, inclining with a considerable Slant towards the Sea; that this has been worn into its present Appearance of Ridges, with Vales between them, by the Rains of the Heavens and Waters of the Earth washing away the Soil from the upper Parts, and carrying it down to Seawards. That the Soil thus carried down and lodged in various Places hath in a Series of Ages formed the lower Plains of the Jerseys, Pennsylvania, Maryland, Virginia, and the Carolinas. . . .

"But we must have recourse to some other Explanation in order to account for the Situation of the Shells on the Tops of the Mountains.

"It is easy to shew the Earth and Sea may assume one another's Places, but positively to assert how that hath actually happened in Times past, is hazardous; we know what an immease Body of Water is contained in the great Lakes at the Top of the Country, and this is a damm'd and held up by Ridges of Rocks: Let us suppose these Ridges broken down by any natural Accident, or that in a long Course of Ages a Passage may be worn through them, the Space occupied by the Water would be drained: This part of America, disburthened of such a Load of Waters, would of course rise, as the immediate Effect of the shifting of the Center of Gravity in the Globe at once or by Degrees, much or little, accordingly as the Operation of such Event had Effect on that Center. . . .

". . . Some such Changes may have come gradually and advanced by such slow Degrees, as that in a Period of a few Ages would not be perceptible; History therefore could take no Notice of them."

Evans recognized the late Pleistocene beach ridges near Lake Ontario as former shore lines of a once more extensive lake, but he assumed also that the fossils in the Paleozoic rocks of the northern Appalachian mountains and Allegheny plateau were remains of forms which once lived in the very much larger body of water which spread to the eastern margin of the mountains. There is some evidence that Evans realized the consolidated Paleozoic rocks were much older that the lacustrine Pleistocene deposits near Lake Ontario. The belief in a great water body extending to the eastern margin of the mountains was held at least until 1818, when Mitchill set forth the idea in great detail (*12*). A few years earlier Volney (*13*) had proposed the same theory. Their source was Evans, but neither followed him in ascribing land uplift to reduction in crustal load.

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Liver Cirrhosis with Ascites, Induced in Dogs by Chronic Massive Hepatic Irradiation with Radioactive Colloidal Gold[1]

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In a comprehensive review of the effects of radiation on normal tissue Shields Warren (*1*) has stated that "without much conclusive evidence, it has been assumed that the liver as an organ is relatively resistant to radiation injury." Chronic damage was induced in the liver of the dog by Bolliger and Inglis (*2*) using repeated very high doses (1,800–5,250 r) of unfiltered radiation, fibrosis being noted in some dogs as early as 6 weeks after exposure. In one dog a dense portal fibrosis was observed after 6 months. To the best of our knowledge no instance of extensive cirrhosis associated with ascites has been reported.

Fouts (*3*), as well as McKibbin, Thayer, and Stare (*4*), have shown that it is possible to induce cirrhosis in dogs by prolonged dietary restrictions. McKee and associates (*5*) have briefly summarized the experimental approach to the production of ascites by means of mechanical constriction of the hepatic blood vessels.

We wish to describe briefly a means of producing highly interesting lesions in the dog liver made possible by the relatively high degree of selective uptake by that organ of radioactive colloids of gold which, following intravenous administration, undergo rapid phagocytosis.

[1] This work was carried out under Contract At-(40-1)-269 with the Division of Biology and Medicine, Atomic Energy Commission.

Four littermate mongrel coonhound pups 7 weeks old were used in this experiment. With one animal serving as a control the remaining 3 were given radioactive metallic colloidal gold[2] by vein in increasingly greater quantities, as shown in Table 1. Two weeks later, the only changes of note being a moderate amount of leukopenia, approximately twice the former radiation doses were administered, again by vein. One month later each animal was given another injection of the radioactive gold in quantities approximating 1½ times the previous dose. Blood studies, including the hematocrit and white blood cell count and differential counts, were carried out at approximately 3-day intervals. Dog 50-7, which had received the largest amount of the colloid, developed a marked leukopenia and anemia and about 10 days following the last administration of radioactive material had tarry stools. (Representing an acute radiation injury, this will be discussed at length elsewhere.) Dogs 50-6 and 50-8, although mutually receiving different quantities of the radioactive gold, nevertheless are estimated to have received approximately the same amount of total radiation, using the formula of Marinelli, Quimby, and Hine (*6*), since their body weights were somewhat discrepant. Using the above-mentioned formulas, they received, respectively, an estimated 67,000 and 65,000 equivalent β-roentgen to the liver.[3]

Approximately 6 weeks after the last injection of the colloid, 50-6 and 50-8 showed increasing amounts of ascitic fluid accumulating in the abdominal cavity. Their weights as compared with that of the control are also of interest (Table 1). It is to be noted in addition that both these animals demonstrated a marked retardation in their growth and general appearance. In contrast to the normal control dog, 50-9, which had the appearance of a healthy young hound, the 2 injected animals showed many of the characteristics of young puppies, including the texture of the fur, which was long and silky as compared to the short and tougher texture in that of the control. The results of conventional function and damage tests will be reported in detail later.

Elsewhere we, and others, have discussed the disappearance of radioactive colloidal gold from the circulation of animals following its intravenous administration (*8–10*). Normally the colloid initially disappears from the circulation at a logarithmic rate with respect to time, the concentration reaching half its initial level in several minutes. Tracer quantities of the radioactive gold colloid were administered by vein to the 2 injected animals, as well as the control, and the results can be seen in Fig. 1. The marked differences in the rate of disappearance of the colloid in Dogs 50-8 and 50-6 as compared with the normal 50-9 appeared to be significant, and suggestive of an impaired ability for phagocytosis by the reticuloendothelial system.

[2] Radioactive colloidal gold was produced by n, γ reaction in Oak Ridge pile and processed by D. L. Tabern, of Abbott Research Laboratories.

[3] Doses used in these animals are 20–40 times those used in human therapy. A chronic human leukemia will undergo remission following 2,000–3,000 r to the liver.

TABLE 1

DOSAGE AND SURVIVAL IN ACUTE AND CHRONIC HEPATIC RADIATION

Dog	Age initially (wks)	Dose (mc)		Initial wt (kg)	Est. liver wt (g)*	Est. liver dose β-e r	Survival time (days)	Wt at death (kg)
			Acute damage					
50-21	11	54		2.3	55	67,000	9	1.1
50-22	11	74		3.1	75	67,000	9	3.0
50-20	11	39		2.4	57	47,000	15	2.7
			Chronic damage					
50-7	7	20, 38, 44	† 102	3.4	82	85,000	62	3.6
50-6	7	13, 29, 40	† 82	3.5	84	67,000	119‡	6.0
50-8	7	10, 19, 30	† 59	2.6	62	65,000	112‡	4.9
50-9	7	0		3.4	82	0	Alive in good health	9.0 on 2/26§

* Assuming liver represents 2.4% body weight (7).
† Interval between the 1st and the 2nd dose was 2 weeks; between the 2nd and 3rd, one month..
‡ Sacrificed because clinical condition poor.
§ Wt at time of sacrifice of 50–6.

At autopsy about 1,000 ml of clear, slightly yellow fluid was withdrawn from the peritoneal cavity of Dog 50-6 and about 1,800 ml (37% of the body weight) from Dog 50-8. When the abdomen was opened, the liver of the latter (68 g) was barely discernible deep under the rib cage, was markedly atrophic, and of a deep chocolate color. The liver of Dog 50-6 (91 g) had a nodular appearance. In Dog 50-6 there were numerous ecchymotic areas on the skin over the whole body and limbs; the serous surface of the peritoneum showed many hemorrhagic areas; the intestines appeared shrunken and were filled with dark blood. There were no clinical signs of jaundice in any of the animals before death or at autopsy.

The most obvious effects of irradiation in both dogs were disappearance of endothelium and marked increase in connective tissue surrounding the blood vessels. There was proliferation of fibrous tissue in and around the central veins and the portal tracts. Many veins were obliterated (replacement fibrosis), and fibrous bands extended from their thickened walls to anastomose with similar strands from other veins. Branches of connective tissue overgrowth often encircled areas of parenchymatous cells, which latter showed cloudy swelling of varying degrees. Many areas were noted to have what might be considered "ghost vessels." In some obstructed vessels there was evidence of proliferation of endothelial cells. Thus it may be presumed that in other vessels of the same

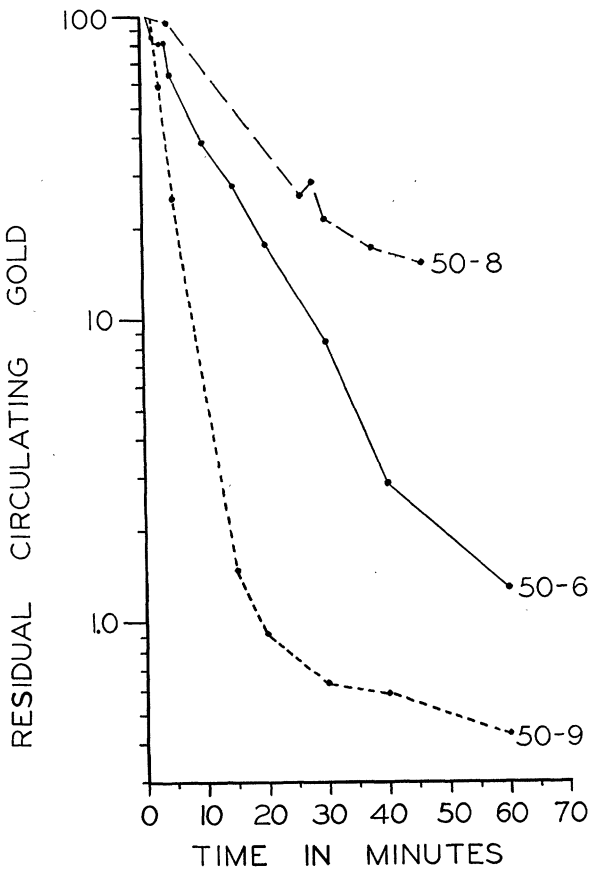

FIG. 1. Disappearance curves of tracer quantities of Au^{198} colloid given intravenously.

liver the initial proliferation of endothelial cells was followed by their disappearance and later by replacement with fibrous tissue. Some areas were almost avascular and showed no regeneration. It seems likely that damage to the liver parenchyma because of irradiation was secondary to impairment of the blood supply.

The outstanding changes in the spleen were the large-scale destruction of lymphocytes and the extensive fibrous tissue proliferation. The Malpighian bodies were hardly identifiable and showed no tendency toward regeneration. The proliferation of fibrous tissue was manifested by thickening and condensation of pre-existing trabeculae and of the capsule.

In Dog 50-22 considerable changes were found in the histological structure of the kidney, many glomeruli having thickened basement membranes. The majority were hyalinized, and the tubular epithelium was swollen.

The pathological changes in the liver induced by massive irradiation (chronic) may be said to resemble a combination of Chiari's syndrome (obliteration of the hepatic veins) and of central fibrosis. Some special features that do not fit into such a definition will be reported at a later date.

In Table 1 are summarized the dosages of gold administered; the estimated liver dose in β-equivalent roentgens, and the time of survival in days. A number of points of interest are apparent on perusal of these data. First of all, Dogs 50-21 and 50-22, although of different weights and having received different total mc dosages, have the same estimated β-equivalent dosage delivered to the liver. Their survival time was the same in both cases, namely, 9 days. Dog 50-20 received an estimated 70% of the liver dose given to 50-21 and 50-22 and survived 15 days. Dog 50-7, although receiving a considerably *higher* dose than any of those previously mentioned, nevertheless survived 62 days, presumably because the radioactive material was given in divided doses on 3 occasions, probably allowing sufficient time for some regeneration of hepatic parenchyma to take place before the second and third radiation insults were delivered. Dogs 50-6 and 50-8 again differed considerably in their weights and, although given different total amounts of radioactivity, received an estimated similar dose of β-equivalent roentgens to the liver as the first two animals mentioned. Again the survival time was greatly increased, presumably also because the radiation was administered in divided doses. Both animals died from the severe damage induced by the radiation in the liver and not from the primary radiation effect on the hematopoietic system.

Continuation of this work has shown that age of the animal may play a decisive role in survival. It appears from the above-reported work that the method of radioactive colloidal gold may prove of considerable value where other techniques of experimental liver damage have failed.

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