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**WESTERN RESERVE UNIVERSITY
ATOMIC ENERGY PROJECT
Cleveland 6, Ohio**

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**QUARTERLY PROGRESS REPORT - July, August, September
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RADIATION TOXICOLOGY SECTION

Potentiation of the protective action of cysteine by nembutal.

40 mg/kg of sodium pentobarbital significantly increased the protection afforded by cysteine against 917 r (x-rays) in the rat.

<u>Treatment</u>	<u>Mortality</u>
Cysteine + 917 r	$\frac{15}{16}$
Nembutal + cysteine + 917 r	$\frac{7}{16}$
917 r	$\frac{16}{16}$

It is believed that the respiratory depression effected by nembutal decreased intravascular oxygen tension which in turn decreased tissue oxygenation to augment the cysteine effect in tissues.

Relationship between toxicity of colloidal Au¹⁹⁸ and its distribution in the rat.

Rats were injected intraperitoneally with tracer doses of colloidal Au¹⁹⁸ and distribution studies were conducted.

Per cent of injected dose per:

	(24 hr.) <u>gram</u>	<u>Organ</u>	(72 hr.) <u>gram</u>	<u>Organ</u>	(10 days) <u>gram</u>	<u>Organ</u>
Bone + bone marrow	0.21	3.9	0.26	5.0	0.27	5.2
Liver	6.5	52.0	6.8	60.3	6.4	60.8
Spleen	2.7	1.15	3.42	1.04	5.06	1.03
Omentum	-	-		14%		11%

The results were surprising in that the colloid was readily absorbed from the peritoneal cavity of rats. The distribution to bone marrow is at least as great as that observed following intravenous administration. The toxicity of colloidal Au¹⁹⁸ by the intraperitoneal route was also found to be at least as great as that produced by intravenous administration. The deposition in the liver was significantly but apparently not critically reduced.

Toxicity of P³² and Au¹⁹⁸ in Mice.

The 30-day LD50 values for P³² as Na₂HPO₄ and colloidal Au¹⁹⁸ in mice were found to be approximately 6 and 24 μ c/gram respectively. Comparing these values with those for rat (3.8 and 34 μ c/gram) reveals that the mouse is much less sensitive to P³² but more sensitive to colloidal Au¹⁹⁸. P³² is much more uniformly distributed in the mouse since the bone retains but one per cent of the

injected dose per gram of tissue. The role of the spleen in survival of the mouse is also an important factor which renders this species less sensitive to more uniformly distributed ionizing radiation but more sensitive to colloidal Au¹⁹⁸ which is deposited in high concentration in the spleen.

Protection studies in mice.

A) Nembutal was found to significantly potentiate the protective action of cysteine in mice.

Treatment	Mortality
750 r	16/16
Cysteine + 750 r	14/16
Nembutal + cysteine + 750 r	3/16

B) CaCl₂, MgCl₂, formate, tetraethyl ammonium injected before exposure did not significantly alter the mortality in mice following 600 r of whole body irradiation.

C) The protective action of thiosorbitol which we have previously demonstrated was found to be reproducible. Sorbitol was also found to confer some protection.

Splenectomy experiments in mice.

Large numbers of mice were used to determine what effect splenectomy has on survival following total body exposure in mice.

	Normal		Splenectomized	
450 r	1/16		3/16	
450 r	5/16		6/16	
% Mortality	19%		28%	
480 r	2/16	13%	8/16	50%
510 r	12/16		15/16	
510 r	10/16		8/16	
% Mortality		69%	72%	
540 r	8/16	50%	12/16	75%

Thus it appears that in the mouse as in the rat, the spleen plays an important role in survival only if it is shielded. The radiation sensitivity of the spleen is such that when it sustains the same dose (in lethal range) of radiation as does the bone marrow, it is then no longer able to exert a special beneficial action.

Combination studies in mice.

In progress and will be summarized in the next report.

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RADIOLOGY SECTION
CLINICAL INVESTIGATION

The effects of cysteine on the sensitivity of the rat sarcoma to irradiation.

Preliminary investigation has shown that cysteine in doses of 800 mg/kg body weight will definitely protect the Murphy sarcoma from the lethal effect of irradiation in the rat. Using lethal effects due to tumor growth as an end point, results indicate that approximately 95% of a control group of animals will die of tumor in 30 days. If a group of animals is treated with 800 r 200 KV x-ray, the lethal percentage will be reduced to approximately 25. However, if cysteine is given prior to irradiation, approximately 70% of the animals will die with a similar amount of irradiation.

The effect of early fractionation of x-ray on survival curves in rats.

It can be shown that the lethal effects of total body x-ray can be decreased by early fractionation of the radiation dosage. 780 r total body irradiation with 200 KV apparatus is lethal to approximately 100% of the animals. However, if 130 r per minute of total body irradiation is given in six increments, with time intervals of 0, 10, 20, 30, 45 and 60 minutes, these survival rates are definitely increased as the time intervals are increased from 20 to 60 minutes.

The preliminary study has been completed and will be published in the near future.

The effect of food and water on the thyroid uptake of radioiodine in rats.

Data have been accumulated which show that intake of food and water, and water alone, influence the uptake of radioactive iodine in the thyroid gland of rats. At 6 and 24 hours, the thyroid uptake is reduced significantly if water is given. An even more profound reduction in uptake and correspondingly increased excretion has been observed if both food and water are allowed. This material is being prepared for publication.

The study of the early accumulation rate of I^{131} in the thyroid gland.

This work is being done in conjunction with the Radiation Physics Section in an attempt to ascertain the most reliable method for studying thyroid disorders. There is little doubt that early accumulation rate studies give more informative data than does a simple 24-hour thyroid uptake. The advantages of the method, however, are somewhat offset by the limited number of patients that can be studied at any one time. 150 patients have been studied and the data are being accumulated in an attempt to find the most reliable portion of the curve to work with and which affords the least amount of time in measuring.

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The effect of thyrotropin on the thyroid I¹³¹ uptake in various thyroid states.

This work is being done in conjunction with the Department of Medicine.

A "TSH test" was devised for comparing the 3 hour I¹³¹ uptake over the thyroid gland before and after a single injection of thyrotropin. A series of 59 tests have been made to date. Normal patients were clearly separated from those with hypothyroidism whether or not the individual was taking thyroid extract.

This work has been completed and will be published in the near future.

The use of P³² as a Diagnostic aid in ocular tumors.

This work is being continued in conjunction with the Radiation Physics Section and the Department of Ophthalmology. A second report on this work is to be presented at the Radiological Society meeting in December.

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RADIATION PHYSICS SECTION

Isotope disappearance rate.

Continuous flow measurements of the disappearance of tagged (I^{131}) plasma and tagged (P^{32}) red cells from dogs before and immediately after radiation has been continued. No change in disappearance rates have been perceived with whole body radiation up to 2000 r. A report of the general techniques and method is being prepared.

Clinical investigation.

In conjunction with the Section on Clinical Investigation, studies utilizing specially designed equipment involving scintillation counters and continuous recorders were continued. A sealed sodium iodide scintillation counter has been placed in operation for thyroid uptake measurements replacing the older anthracene counter. Tracer doses are now routinely at $10 \mu\text{c}$ and can be reduced lower if desired. At a distance of 15 cm. from the counter these $10 \mu\text{c}$ standards give a rate of 13,000 c/m, thus a dose of $1 \mu\text{c}$ could be used. A lead filter has been added for reduction of scattering from tissue.

A report of thyroid uptake rates, method of measurements, and clinical studies is being prepared in conjunction with the Section on Clinical Investigation.

The disappearance of iodinated (I^{131}) human serum albumin has been followed in ten patients by continuous flow up to two hours and up to six hours in two patients in conjunction with the artificial kidney.

Construction of scintillation counters and counting apparatus.

The experimental scintillation counter eye probe has been compared with the Geiger counter on exposed ocular tumors. The efficiency compares well with the Geiger counter with the expected advantage of greater ease in placement because of the small size of the effective counting volume.

A decade scaler with high voltage power supply has been constructed. This unit incorporates glow transfer tubes and is to be utilized for long term experiments wherein the long tube life and lack of moving parts (relays or register) should insure greater long term stability.

Assays.

Continuing.

Health Physics.

Laboratory and badge surveys conducted as usual.

BIOCHEMISTRY SECTION

Effect of irradiation on nucleic acid synthesis.

The effect of x-irradiation synthesis (400 r) on the synthesis of desoxy-ribonucleic acid (DNA) in 14-day old chick embryos was studied by measuring the incorporation of formate- C^{14} into the purines and pyrimidines. Formate- C^{14} was administered immediately after x-irradiation and the embryo sacrificed 5 days later. The purines and pyrimidines from the DNA fraction were separated and purified on Dowex-50 and Dowex-1 columns, and the specific activity of each dish was determined. In the case of the irradiated embryos, the C^{14} contents of the DNA adenine, guanine, and thymine was only about 1/2 as radioactive as in the controls; neither group of embryos showed any appreciable incorporation of isotope into the DNA cytosine.

Protection of irradiated dogs by cross-transfusion.

An additional 5 dogs were subjected to 550 r of x-irradiation and immediately thereafter cross-transfused with a normal donor dog. The total blood volume exchanged amounted to 1/3 of the body weight in 5 of the dogs; in previous experiments, the blood exchange was about 5 times the body weight of the recipient animals.

A total of 11 dogs receiving 550 r x-irradiation were cross-transfused with normal donor dogs during the post irradiation period (3-9 days after irradiation). Three of these experimental animals received 3 separate cross-transfusions during the post irradiation period and 1 received 4. The average survival of the irradiated dogs treated by a cross-transfusion were not significantly different than the irradiated control animals, regardless of the amount of blood exchanged or the time selected for the procedure. A complete report of these studies will be made in the near future.

Protection of the irradiated dog by perfusion of its blood through a donor spleen.

Previous results indicated that the survival of dogs given 700 r was somewhat prolonged if its blood was perfused for 3 hours following irradiation through an isolated spleen from a donor animal. However, we have recently repeated the study in 5 dogs given 550 r x-irradiation, and the survival of these animals were found to be approximately the same as the irradiated control dogs.

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PATHOLOGY SECTION

Effect of internally administered radioactive isotopes in rats.

Investigation is proceeding on the biologic effects of intravenously administered radioactive colloidal gold¹⁹⁸. It is known that this isotope can produce massive liver cell necrosis with loss of function. The effect of graded single doses and repeated doses are being studied. There will be emphasis on the late effects especially with regard to the development of neoplasms. The capacity of liver cells injured by radioactive colloidal gold¹⁹⁸ to regenerate after partial hepatectomy is also under investigation. Another aspect of this problem is concerned with the effect of antibiotics on the severity of the hepatic lesion in comparison with untreated control animals.

Effect of whole body x-irradiation in rats.

A large colony of rats subjected to a single dose of whole body x-irradiation in the LD₅₀ range is under observation. Particular emphasis is placed on the development of late lesions especially with regard to neoplasia. So far a number of neoplastic lesions have developed, particularly in the skin. Some of these being large tumors of connective tissue origin. In addition, lesions in bone have resulted in the nature of sarcoma.

Role of bacterial toxemia in radiation death.

Further experiments are under study relative to the effect of the antibiotics in alleviating the radiation syndrome and also improving mortality. In several experiments the importance of the time interval following radiation for institution of the antibiotic treatment is receiving especial attention.

Effect of I¹³¹ on the thyroid gland.

A colony of rats have been given a single dose of radioactive I¹³¹ in dosage comparable to a relatively low therapeutic dosage in man. The object of this study is to determine any possible late effects especially with regard to development of adenoma or possibly carcinoma.