RESTRICTED

MEDICAL DEPARTMENT

RESEARCH PROGRAM

1 JANUARY - 30 JUNE 1950

MEDICAL RESEARCH AND DEVELOPMENT BOARD
OFFICE OF THE SURGEON GENERAL
U. S. ARMY

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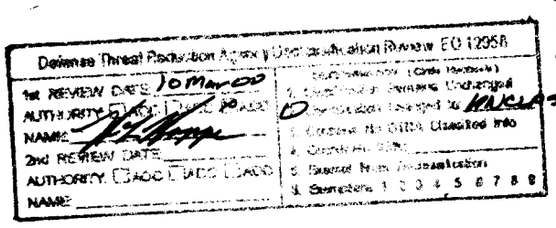

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1. PROJECT TITLE Prevention of Growth of Hair in Skin Grafts; Irradiation		4. 5. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP AW-6	
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e. Progress.

Animals and Equipment. The population of the animal colony has been maintained at about 250 rats for the past six months. No additional groups of Holtzmann rats have been maintained for study.

Depilation. The experiments in depilation using the long wave length, high-intensity radiation produced by the Bracke-Seib apparatus are continuing. The back of the neck of human volunteers is being irradiated with a small field in single doses. The effect with added filter is now being studied.

Follow-up Study. No additional replies have been received from the persons whose thighs were radiated in 1942-43. So far, the irradiated area has been excised in 24 individuals. A second letter is being sent out in an effort to contact those who have not yet responded.

It has been demonstrated that the following agents or procedures have a protective effect against local irradiation: pitressin, epinephrine, other vasoconstrictors, tourniquet ischemia, cyanide, and cysteine. The effect of the first four could be due either to reduced blood flow or tissue anoxia. It has been presumed that the effect is due to tissue anoxia because cyanide and cysteine protect. Reviewing the data reveals that the effect of cysteine is not unequivocal by any means. The effect of cyanide in this study is almost certainly real. It is generally believed that the principal effect of cyanide in the intact animal is inactivation of the cytochrome system by the formation of a cyanide-ion complex. This produces tissue anoxia in the presence of an adequate oxygen tension. This is the critical observation upon which future investigation is planned. It is important to point out that the reasoning on this point is based upon assumption only. A vasoconstrictor action of cyanide has not been ruled out, and it is known that vasoconstriction will produce protection. It

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seems to be of critical importance to collect evidence bearing upon this point.

If the effect of CN is due to inactivation of the cytochrome system, it is of primary interest to explore the mechanism whereby protection occurs. At the suggestion of biochemical consultants, the summer will be devoted to a study of the effect of other enzyme inhibitors on the reaction to local irradiation. A number of other enzyme inhibitors may be studied later, but those to be investigated this summer are:

1. Sodium azide. (NaN_3). This compound inhibits a variety of intracellular enzymes, but it is thought that its effect is primarily on the cytochrome-cytochrome oxidase system. Its effect should parallel that of cyanide.
2. Malonate. This compound has the specific ability to block the enzyme succinoxidase by virtue of its structural similarity to succinate, the normal substrate. This should interrupt the Krebs cycle and leave the tissue oxygen tension high, and the hydrogen transport system in the oxidized state largely.
3. Iodoacetate. This compound is a specific binding agent for sulfhydril groups. It may be expected to affect a great many different enzyme systems in the intact animal. Triosephosphate dehydrogenase is considered to be the most sensitive of these enzymes.
4. Fluoride. This ion probably exerts its effect primarily by virtue of its ability to bind and inactivate magnesium. The enzyme thought to be most sensitive to fluoride is Enolase. The action of the former is fairly diffuse in that it may inactivate various phosphatases and other Mg-dependent enzymes.
5. Dinitrophenol. This compound has the ability to bypass the hydrogen transport system, allowing intracellular oxidation to proceed without the participation of these enzymes. It increases the rate of tissue oxidation, producing a picture in the intact animal that is remarkably similar to hyperthyroidism. Its effect, therefore, should be of considerable interest. If dinitrophenol protects, it would point quite specifically to the hydrogen transport system as the one most vulnerable to the effects of irradiation.
6. The effects of a high tissue oxygen tension should be explored. It has been repeatedly shown that low oxygen tension protects lower forms from the effects of irradiation, and there is a controversy over whether this is due to absence of molecular oxygen or to the fact that oxidation-reduction systems within the cell are present in the reduced state. If the effect is due to O_2 concentration, high oxygen tensions should enhance the effect of irradiation.

Because of the interest of this project in intracellular biochemical mechanism a study of irradiation of another tissue seems advisable. Within the near future there will be considerable interest in conducting some in-vitro studies of metabolism of tissues which have been irradiated. An organ which is readily accessible, for which there is an adequate control, and for which a suitable technique for irradiation could be developed without too much difficulty is the testicle. Since only male rats are being used in these studies, techniques could be developed for irradiating one of two testicles on an experimental animal, and a suitable control-series with adequate pathologic studies accumulated. The testicle has the advantages of being readily accessible for local irradiation, of being relatively unimportant to the life of the animal, and of being readily accessible with a paired control for removal for in-vitro studies. It lends itself well to the Warburg technique, it contains large quantities of the nucleic acids, and it is possible to estimate the testicular tissue.

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Table I. A vasoconstrictor, pitressin, was used to determine whether radiation-sensitivity could be reduced; a very dramatic decrease in sensitivity to local x-radiation resulted. This effect of pitressin has been the basis for further work attempting to explain its protective action in local irradiation effects.

Methods. Animals. Male albino rats, Wistar strain, obtained from the Wistar Institute were kept for at least nine days before being used for experimental work. They were fed Purina Dog Chow, presumably an adequate diet, since all the animals were in excellent condition and followed Zucker's weight-age relation curve. At the time of irradiation the rats' weights ranged from 180-230 gm. They were housed, three animals per cage, in an air-conditioned room at a temperature of 25-27° C. (77-80° F.). Each animal was individually-marked for identification.

Anesthesia. About 15 minutes prior to irradiation the rats were given pentobarbital sodium intraperitoneally: 4.5 mg. per 100 gm. body-weight, prepared as a freshly-made 0.9-per-cent solution in water.

Technique of Irradiation. The leg to be irradiated was immobilized by pinning it to a wooden block (2 cm. thick) with a single thumb tack inserted through the web of the toes. The left hind legs of four animals were attached near the center of the block within an area 4 cm. square. The upper portion of the leg and the rest of the animal's body were shielded by lead-plates 2 mm. thick. During irradiation the animals lay on a rice mattress 10 cm. thick. Air dosages of 1400-3000 r were delivered at about 270 r per minute. Radiation factors were 200 KV, 25 cm. distance, and filters of 0.5 mm. of Cu. and 1.0 mm. of Al.

Pitressin. Pitressin, the pressor fraction of the posterior pituitary as prepared by Parke, Davis and Company, was given in a single dose intraperitoneally at varying intervals before and after irradiation. Two forms were used, pitressin in water, 20 units per ml. and pitressin tannate in oil, 5 units per ml. Except where indicated the water-solution was used./ Dosages of any drug appearing on charts represent the total amount administered per animal.

Gross Reaction and Method of Evaluation. The animals were examined daily in a good light and records were kept for each. The un-irradiated leg served as a control for the irradiated leg. Following irradiation there were no gross changes for seven to eight days except for slight erythema in most cases. Then there followed a series of inflammatory changes characteristic of radiation-reaction. The earliest changes seen at seven to eight days were slight swelling of the foot pad, erythema, and venous congestion on the dorsal surface. These increased during the next 24 to 48 hours. When the swelling became maximal (12 to 13 days) ulceration often developed. Depending on the experimental procedure used, any degree of reaction could be obtained, from none to a severe ulcerating lesion. For evaluation of the reaction the following arbitrary categories were set up:

A. No Reaction. When there was doubt about the presence or absence of a reaction it was recorded in this group.
B. Mild Reaction. Definite, but often slight, reaction.
C. Moderate Reaction. Advanced swelling and erythema without ulceration.
D. Severe Reaction. Severe swelling with ulceration.

This classification of course gives only a rough clinical estimate of the severity of the reaction but does provide a crude yardstick for measuring the degree of reaction produced.

Results. The reaction following local irradiation of the rat's leg can be decreased or suppressed by the administration of pitressin. Such protection is influenced by several factors: (1) the dosage of pitressin, (2) the time pitressin is given in relationship to irradiation, and (3) the amount of irradiation.

Influence of the Pitressin-Dosage. Five units of pitressin given 15 minutes before irradiation leads to a definite reduction in the subsequent local reaction (Table I). When the dosage of pitressin is decreased, other factors remaining constant, the degree of protection is greatly decreased. With 0.2 units little protection is obtained.

Table I

INFLUENCE OF PITRESSIN DOSAGE ON LOCAL RADIATION REACTION

Pitressin (units)	Number of Rats	Maximal Reaction			
		None	Mild	Moderate	Severe
0.0 (Control)	74	2	13	27	32
0.2	8	1	3	4	-
1.0	9	2	5	-	2
2.0	37	16	9	5	7
5.0	31	26	1	1	3

The figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. Pitressin was given 15-30 minutes before irradiation of the hind leg with 2,000 r.

Influence of Other Vasoconstrictors. Other vasoconstrictors were tested for their ability to alter the rat's radiation-sensitivity. Adrenalin and nor-adrenalin gave definite protection. In fact, adrenalin appears to give better protection than pitressin (Table V). Ice (used as a vasoconstrictor and an agent to lower the temperature of the extremity) and Neosynephrin each give definite protection, but not nearly to the degree of adrenalin.

Influence of the Time of Administration of Pitressin. Pitressin gives protection only when given prior to irradiation. While the maximum effect is obtained when pitressin is administered about 10 minutes before irradiation, there is considerable effect up to one hour. By two hours the influence is considerably reduced (Table II).

TABLE V

INFLUENCE OF OTHER VASCONSTRICTORS ON LOCAL RADIATION REACTION

Drug	Dosage	Number of Rats	Maximal Reaction			
			None	Mild	Moderate	Severe
Control	---	16	1	1	3	11
Pitressin	5 u	15	12	-	1	2
Adrenalin	0.2mg	5	5	-	-	-
Adrenalin	0.3mg	7	1	6	-	-
Adrenalin	0.06mg	6	5	1	-	-
Adrenalin 1 min. after irradiation	0.06mg	7	-	1	4	2
Nor-Adrenalin	0.2mg	17	5	8	3	1
Nor-Adrenalin	0.3mg	5	5	-	-	-
Neosynephrin	1.0mg	8	-	7	1	-
Ice	-	8	-	3	4	1

The figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. The various vasoconstrictors were given before irradiation of the hind leg with 2,000 r except where indicated for adrenalin. The ice was applied to the leg five minutes before irradiation and remained in contact during the procedure.

TABLE II

INFLUENCE OF THE TIME OF ADMINISTRATION OF PITRESSIN ON LOCAL RADIATION REACTION

Time before or after irradiation	Number of Rats	Maximal Reaction None	Mild	Moderate	Severe
Controls	7	-	1	3	3
2 hr. before	5	-	2	3	-
1 hr. before	7	2	4	-	1
30 min. before	7	6	-	1	1
10 min. before	8	7	-	-	1
1 min. after	8	-	1	2	5
30 min. after	6	-	-	-	6

The figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. Pitressin (5 units) was given before or after irradiation of the hind leg with 2,000 r.

Influence of Pitressin on the Radiation-Threshold. The rats used in these experiments show but little radiation-reaction until about 1,500 r is given (Table III). When 5 units of pitressin are given this local radiation-threshold is increased to about 2,400 r. Thus the radiation-threshold is raised roughly 900 r by pitressin.

Following the study of the limitations of pitressin in protecting against local radiation-reaction, other substances and procedures were used to evaluate their protective properties.

Influence of Posterior Pituitary Fractions. Pitressin in water is not the only factor of the posterior pituitary that is protective (Table IV). Pitressin tannate in oil and pituitrin in water (the whole extract of the posterior pituitary) are probably just as active as pitressin in water. Pitocin, the oxytocic factor, is probably inactive.

Influence of Miscellaneous Factors. Eschatin (the whole adrenal cortex extract) was found to increase slightly the sensitivity to radiation (Table VI). The same result was obtained for ACTH. Colchicine apparently gives a little protection.

Other factors in the sensitivity to irradiation have been observed. In the preliminary studies it was repeatedly seen that rats weighing more than 250 gms. were more resistant to local irradiation; for this reason animals of standard weights were used. It has also been observed many times that a sick rat will not develop the "normal" radiation-reaction but will show almost no reaction.

TABLE III

INFLUENCE OF PITRESSIN ON THE RADIATION THRESHOLD*

Condition of rat	Roentgens	Number of Rats	Maximal Reaction None	Mild	Moderate	Severe
Control	1400	8	6	2	-	-
Control	1500	7	1	6		
Control	1600	8	-	1	3	4
Control	1800	7	-	1	2	4
Control	2000	8	1	1	2	4
Pitressin 5 u	2000	8	6	-	-	2
Pitressin 5 u	2200	5	4	-	-	1
Pitressin 5 u	2400	6	3	2	-	1
Pitressin 5 u	2600	8	3	2	-	3
Pitressin 5 u	2800	7	-	2	-	5
Pitressin 5 u	3000	6	-	1	3	2

Figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. Pitressin (15 units) was given 15 minutes before irradiation of the hind leg.

*Radiation-threshold is defined as the number of roentgens it takes to produce a definite local reaction in 50 per cent of the test-animals, with no reaction in the remaining animals.

TABLE IV

INFLUENCE OF POSTERIOR PITUITARY FRACTIONS ON LOCAL RADIATION REACTION

Drug and Dosage	Time Before Radiation	Number of Rats	Maximal Reaction None	Mild	Moderate	Severe
Control	-	8	-	-	1	7
Pitressin in water: 5 u	30 min.	8	6	-	-	2
Pitressin Tannate in oil: 5 u	2 hrs.	11	9	-	-	2
Pituitrin: 5 u	30 min.	11	7	-	2	2
Pitocin: 5 u	30 min.	6	-	3	2	1

(See next page for explanation.)

(Explanation, Table IV, preceding page: The figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. The various posterior pituitary fractions were given intraperitoneally before irradiation of the hind leg with 2,000 r.)

TABLE VI

INFLUENCE OF MISCELLANEOUS DRUGS OF LOCAL RADIATION REACTION

Drug	Dosage & Route	Time Before Radiation	No. of Rats	Maximal Reaction None	Mild	Moderate	Severe
Control	-	-	11	-	-	1	10
Eschatin	5ml I.M., S.Q. & I.P.	2 hrs.	9	-	-	-	9
ACTH	5 mg S.Q.	5 hrs.	8	-	-	-	8
Colchicine	0.4 mg I.P.	5.5 hrs.	14	1	6	2	5
Pitressin	5 u I.P.	15 min.	15	12	-	1	2

The figures in the table indicate the numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. The various drugs were administered as indicated in the table, before irradiation of the hind leg with 2,000 r.

For Table VII, see next page.

TABLE VIII

EFFECT OF SODIUM CYANIDE ON LOCAL RADIATION REACTION

Condition of Rat	Number of Rats	Reaction None	Mild	Moderate	Severe
Control	7	-	-	1	6
Sodium Cyanide	13	8	2	1	2

The figures in the table indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. Sodium cyanide, 1.0 mg. per 200-gm. rat, was given intraperitoneally five minutes before irradiation of the hind leg with 2,000 r.

Table VIII. From the experiments with tourniquets it appeared that the protection against local irradiation given by pitressin might be due to an induced anoxia. Consequently, sodium cyanide (1.0 mg./rat) was tried. Table VIII shows that this agent gives definite protection against local irradiation.

TABLE VII

EFFECT OF THE TOURNIQUET ON LOCAL RADIATION REACTION

Condition of rats	Dosage of roentgens	Number of Rats	Number of maximum reactions None	Mild	Moderate	Severe
Control	1400	8	6	2	-	-
Control	1500	7	1	6	-	-
Control	1600	8	-	1	3	4
Control	1800	7	-	1	2	4
Control	2000	7	-	-	1	6
Tourniquet	2000	8	8	-	-	-
Tourniquet	2200	7	7	-	-	-
Tourniquet	2400	7	5	2	-	-
Tourniquet	2600	7	6	1	-	-
Tourniquet	2700	8	8	-	-	-
Tourniquet	2800	8	5	3	-	-
Tourniquet	2900	7	5	2	-	-
Tourniquet	3000	7	-	2	3	2

Figures indicate numbers of animals. Each animal irradiated has been classified according to the maximal reaction attained. The tourniquet was applied five minutes before irradiation to the hind leg, and removed immediately after irradiation.

Table II. Whole-Body Irradiation: Treatment with Pitressin. Results of Experiment 71. Procedure. This experiment was carried out on 108 white male rats of the Holtzman strain ranging in weight from 154 to 220 gms. The average body-weight for the entire group was 167.7 gms. at the time of irradiation. The rats were divided into two groups of 54 rats each. Group A was treated with 5 units of water-base solution of pitressin intraperitoneally 15 minutes before irradiation; Group B was the irradiated control-group.

Irradiation: 800 r in air, whole-body irradiation at 50-cm. distance; filters were 0.5 mm. cu. and 1.0 mm. Al., rate of dose about 70.4 r/min.

Exp. No.	Date	No. of Rats	Procedure	No. Died Pit.	No. Died Con.
71-A	3/4/50	54	Pitressin	30	
71-B	3/4/50	54	Control	--	49
			Total	30	49
			% Dead	55.5	90.7

Pitressin gave 38.7% protection.

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Discussion. These animals were in very good condition. Only two were showing signs of respiratory congestion (pneumonia); they died between the period of 82 to 90 days after irradiation. Both were treated animals. The resistance of these animals probably was impaired by irradiation.

The LD 50-800 r and rate of dose for pitressin were calculated from the results of previous experiments with this particular strain of animals.

Conclusion. Pitressin in the manner used gives a significant amount of protection but the percentage of protection is not satisfactory. It is improbable that the rate of protection can be advanced, when pitressin is used in this manner, since 5 units has been calculated to give maximum protection for animals in this weight-range.

f. Future Plans. Studies will be continued as indicated above.

g. Reports. None listed. Material summarized under heading of Table I is being prepared for publication.

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PROGRESS REPORT

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-59-08-03
1. PROJECT TITLE Medical Aspects of Atomic Bomb		4. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP AW-6	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/W. O. NO.
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e. Progress. It had been hoped that the monograph would be completed by July 1950, but this will not be possible because the editors have been ill and because authors engaged in other activities have not been able to complete their sections of the volume./ It was decided to include in the book a concise account of the physics involved in an atomic bomb. Four drafts of Part I have been prepared during the last six months and reviewed by Dr. Ralph E. Lapp. His criticism has been severe, but good from the standpoint of physics. It was decided that more rapid progress in this highly technical field could be made if Dr. Lapp were responsible for the final draft. He has assumed this responsibility and has promised the manuscript by 15 July./ Dr. Joe Howland of the University of Rochester has been slow in submitting his chapter on the biologic effects of radiation. He expects to complete the material by 15 August./ Part II, "Catastrophic Effects," is in final draft./ Part III, "Incidence of Casualties"—a large part of which is statistical—has been checked by Dr. Cuyler Hammond who is at present in Puerto Rico. This manuscript is expected within a few weeks of his return./ Part IV, "Clinical and Pathologic Observations," has been largely completed, and most of the material has been published in the American Journal of Pathology.

f. Future Plans. Completion of the manuscript is now slated for autumn, 1950.

g. Detailed Reports. None listed.

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1. PROJECT TITLE: Radiation and Thermal Burns | 4. | 5. REPORT DATE 30 Jn 50

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No report was received.

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1. PROJECT TITLE Ionization Effects		4.	5. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP AW-6		
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY		CONTRACT/W. O. NO.
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The following is a summary of a detailed report on work completed during Fiscal Year 1950:

1. The in-vitro clotting determination of whole blood was investigated and evaluated. Data were presented to show the manner in which the whole-blood clotting-time is affected by variations in the experimental conditions and by changes in the clotting-time technique. Of particular importance in achieving maximal usefulness of the test is careful venipuncture technique and meticulous handling of the unclotted blood.

2. Summary of the Irradiation Effect on Coagulation Mechanism. The individual and collective roles and possible significance of the various changes seen in the irradiation syndrome that have been studied in this laboratory are discussed. New data are also presented on recently-completed work in which an attempt was made to isolate an inhibitory substance from the blood of irradiated animals. The possible origin and fate of clotting inhibitors are discussed in the light of current knowledge. The effects of irradiation thrombocytopenia and direct damage to the capillary bed are considered as changes capable of altering the hemostatic mechanism following irradiation.

3. Whole-Blood Transfusions in Total-Body X-Irradiation Injury. Transfusions of whole blood in sufficient amounts, about 8-10 ml./kg. body weight daily, overcome the anemia of 450r total-body irradiation but do not affect the leukopenia or thrombocytopenia in dogs. While the total plasma protein level is maintained better in the transfused animals than in a control group, the plasma albumin levels show less elevation. Whole-blood transfusions to the irradiated animal fail to prolong the survival time.

4. Treatment of the Irradiation Syndrome with Aureomycin. Aureomycin is more effective in increasing the survival time of dogs following total-body

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x-irradiation than any other agent known to the investigators. While aureomycin apprently is capable of decreasing the bacteremia of a dog given 300r total-body irradiation, it seems unable to influence the bacteremia of dogs given 450r. Aureomycin does not produce any significant alteration in the chemical or hematologic determinations made on these animals or in their appearance at postmortem examination.

5. The possible relationship of the method of preservation of plasma to the incidence of homologous serum jaundice. While 16 cases of probable homologous serum jaundice due to whole-blood transfusions are reported, no recognized cases of homologous serum jaundice or hepatitis have occurred in patients given pooled human plasma from the Blood Bank of the University of Chicago Clinics. This plasma has been stored in liquid state without preservative at 26-35° C. for at least two to three months prior to its administration. A survey of the previous reports of transmissible hepatitis from human blood products discloses that the method of preservation for these products was also highly suitable for the preservation of any virus that may have been present.

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PROGRESS REPORT (NC)

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1. PROJECT TITLE Nutritional Requirements in Radiation Injury | 4. | 5. REPORT DATE 30 Jn '50

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10. REQUESTING AGENCY | 13. RELATED PROJECTS | 17. EST. COMPL. DATES RES. DEV. TEST OR EVAL

11. PARTICIPATION AND/OR COORDINATION | 14. DATE APPROVED | FY 18. FISCAL EST'S.

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21. BRIEF OF PROJECT AND OBJECTIVE

e. Progress. Metabolism after Thermal Burns and Radiation Injury. Four young adult male mongrel dogs have been followed through a lengthy control period prior to radiation and thermal injury. Hematologic observations (RBC, WBC, hemoglobin, hematocrit, plasma volume, platelets, and eosinophils) have been normal, as have liver functions (BSP retention, thymol turbidity, thymol flocculation, cephalin flocculation, prothrombin time, and serum bilirubin), direct and indirect. Oral food intakes were fixed, and urinary nitrogen excretion and body weight were relatively constant during the control period. One dog (R) was irradiated (100 r) whole body; one (B) burned (20 per cent deep second-degree); and one (RB) irradiated and burned. The fourth dog (C) served as a pair-fed control for the irradiated and burned animal. Liver functions remained normal. Anemia developed about two weeks after injury in B and RB, while red cells and hemoglobin remained normal in C and R. A mild leukopenia was present in R (10th day) post-radiation. Although leukopenia did not develop in the dog irradiated and burned (RB), the white blood cell count was considerably lower in this dog than in the one (B) only burned. The latter dog showed a leucocytosis for about three weeks. Platelets were normal in C and B, but low (1-2 weeks post-injury) in R and RB. Eosinopenia was present for the first few days after injury in the burned (B) and irradiated and burned (RB) dogs, but not in the control (C) or irradiated-only (R) dogs. The burned dog (B) and the one irradiated only (R) remained in apparently good condition. Their appetites were good, they were alert, and in general were not seriously ill. Nitrogen balance was unchanged in the dog irradiated only, but became moderately negative for two weeks in the burned dog. The dog irradiated and burned (RB) appeared well for the first two weeks after injury, but then became progressively sicker, lost his appetite, stopped eating and died three weeks after radiation. He had lost about six pounds. He consistently excreted somewhat more nitrogen than his pair-fed control. At autopsy

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the only positive gross findings were more severe infection and less healing of the wounds than in the dog only burned, and evidence of recent weight loss. Histologic sections are being prepared. These observations will be extended to additional dogs. In some, constant dietary intake will be insured by continuous intravenous feedings. The influence of antibiotics will be investigated.

Dog Blood Bank. In preparation for metabolic and hematologic studies of radiation and thermal injury in dogs a blood-bank system was set up. There are four established blood groups (A,B,C,D) in dogs. To date, anti-A and anti-B sera have been produced.

Eosinophils in Dog Blood. A method for the direct counting of dog eosinophils has been developed. The following procedure is used for staining:

Staining fluids: (a) 0.2% phloxin in propylene glycol
(b) 0.05 methylene blue in propylene

Equal parts of each are mixed just prior to staining.

Staining procedure: Blood is taken in a white cell pipette up to the 1 mark and then diluted with the staining mixture to the 11 mark. The staining is allowed to continue for two hours before counting is done.

f. Future Plans. Studies will be continued as indicated.

g. Reports. None.

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PROGRESS REPORT (NC)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-59-08-08
1. PROJECT TITLE X-Ray Therapy, 1000-KV		4. REPORT DATE 30 Jn '5
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP PO-16	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/V. O. NO.
9. DIRECTING AGENCY		
10. REQUESTING AGENCY	13. RELATED PROJECTS	17. EST. COMPL. DATES RES. DEV. TEST OP. EVAL
11. PARTICIPATION AND/OR COORDINATION	14. DATE APPROVED	FY 18. FISCAL EST'S.
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21. BRIEF OF PROJECT AND OBJECTIVE

No report was received.

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.NO. 6-59-08-08
REPORT DATE 30 Jn '50
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PROGRESS REPORT (NC)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~ | 2. SEC. U | 3. PROJ. NO. 6-59-08-09

1. PROJECT TITLE Thermal Effects of an Atomic Explosion, Manuscript | 4. | 5. REPORT DATE 30 Jn '50

6. BASIC FIELD OR SUBJECT | 7. SUB FIELD OR SUBJECT SUB GROUP AVI-6

8. COGNIZANT AGENCY | 12. CONTRACTOR AND/OR LABORATORY | CONTRACT/W. O. NO.

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10. REQUESTING AGENCY | 13. RELATED PROJECTS | 17. EST. COMPL. DATES RES. DEV. TEST OP. EVAL

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21. BRIEF OF PROJECT AND OBJECTIVE

e. Progress. Dr. Longer has submitted the manuscript and it is being prepared for duplication, in the SGO.

f. Future Plans. As soon as the report is typed and corrected the required number of copies will be produced by the multilith process.

g. Reports. None; the end-product of this work is the manuscript.

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PROGRESS REPORT (RC)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-59-08-10
1. PROJECT TITLE Irradiation on Enzyme Systems, Effects of		4. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP AN-6	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/W. O. NO.
9. DIRECTING AGENCY		
10. REQUESTING AGENCY	13. RELATED PROJECTS	17. EST. COMPL. DATES RES.
11. PARTICIPATION AND/OR COORDINATION		DEV.
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21. BRIEF OF PROJECT AND OBJECTIVE

e. Progress. A study of the protective effect of pitressin and epinephrine against local (leg) reaction produced by x-radiation (2000 r) in rats is being carried out in collaboration with the Department of Radiobiology, University of Pennsylvania Hospital.

Mice were subjected to whole-body x-radiation totaling 800 r/air delivered in 15 minutes. Preliminary work indicates that irradiation produced a definite depression of the succinic acid dehydrogenase activity of the liver near the time of death. In the kidney the enzyme activity did not vary significantly from that of the control group.

There was no significant alteration of the hexokinase activity in muscle or kidney after irradiation when compared with the control group.

Phosphate Distribution. Liver. There was no definite change in the inorganic phosphate after irradiation. There was a slight but definite decrease in the readily hydrolyzable phosphate content up to the fifth day following irradiation. Kidney. There was no definite change in the inorganic and slight decrease in the labile phosphate. Muscle. There was a definite increase in the inorganic phosphate. A slight but definite decline in the labile phosphate occurred up to the third day following irradiation, then there was a gradual continuous rise above normal until time of death.

f. Future Plans. X-radiation studies will be continued along the lines mentioned above.

g. Reports. None.

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6-64-12-12

Behavior of Peripheral Blood Vessels — 11 Apr 50

PO-11

Basic Medical Science — Physiology

The Surgeon General, DA
Med Res & Dev Bd

Tulane University
New Orleans, La.
(Dr. Burch)

W-49-007-MD-389

10-50

17 March 1947
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To study the behavior of the peripheral blood vessels under tropical and cold environmental conditions, with particular reference to acclimatization and injury.

The objectives of this project are to study:

1. The influence of tropical and cold environments on the cardiovascular and peripheral vascular phenomena of man.

2. The turnover of water and sodium and potassium in urine, sweat, blood, and inter-cellular fluids of patients in normal and diseased states and under surgical stress.

3. The influence of tropical and cold environments upon certain phases of the processes of depolarization and repolarization in normal and diseased hearts.

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PROGRESS REPORT (NC)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-64-12-12
1. PROJECT TITLE Peripheral Blood Vessels		4. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP PO-11	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/W. O. NO.
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e. Progress. For a better understanding of disturbance in electrolyte physiology in normal man and in subjects with congestive heart failure as an abnormal state, the behavior of several elements has been observed, with the use of radioisotopes, in control subjects, subjects with congestive heart failure, and subjects with other edematous states.

Radiomercury ($Hg^{203,205}$; $t_{\frac{1}{2}} \approx 45$ days) labeling a mercurial diuretic (Mercuhydrin) was studied with reference to the duration of its retention in the body, decline in serum concentration rates of turnover, and distribution. Intravenous catheterization was employed to determine the time-course of renal, hepatic, and extremital arteriovenous differences. Urinary excretion and serum levels obtained after oral administration of the diuretic in capsular form were also determined.

Radiochloride (Cl^{36}; $t_{\frac{1}{2}} \approx 2 \times 10^6$ yrs.) was studied in dogs in order to determine the biologic decay periods (urinary excretion rates, decline in serum concentration, and recovery rates) and chloride space. Similar studies are now in progress in humans, both in controls and in patients with congestive heart failure and other edematous states. The effects of intake and drugs on these measurements are being studied.

Earlier studies with radiosodium (Na^{22}; $t_{\frac{1}{2}} \approx 3$ yrs.) have been reported, and further observations are contemplated. Technical problems dealing with methods of assaying radioisotopes and some of the physical problems encountered have been reported.

As time permits, studies are being carried out concerning the uptake of various elements by erythrocytes, in an effort to establish a model with which may be tested various antidiuretic substances believed to be concerned with the pathogenesis of congestive heart failure, retention of electrolytes, and edematous states. This model may then be used to assay other substances

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ympathetic Nerve
87 (June) 1950.
Vascular Dis-

age 3 of 7

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derived in the future.

Studies with the vectorcardiogram are progressing satisfactorily. The normal spatial vectorcardiogram is and will continue to be under observation because of its extreme variability. The patterns for left ventricular hypertrophy and right and left ventricular bundle branch block have been studied sufficiently to define them generally. These data indicate that the more or less empiric criteria for their electrocardiographic identification is in need of modification. It is hoped that additional studies will yield a more precise definition.

Mr. J. A. Cronvich has practically completed a movable unit which will allow recordings to be made in the wards of Charity Hospital as well as in the laboratory. Various types of electrical interference, which have offered the greatest difficulty, have delayed completion of the apparatus, but it is hoped that the unit will be in operation by autumn. Certain standardization factors have been defined for use in spatial vectorcardiography. Reports of these and other aspects of the problem are in press or in preparation for publication.

In addition to these main programs, several young persons have been in training in various aspects of cardiology to which the research program has contributed significantly. For example, Dr. F. J. Kelly, who is on an American Heart Association Fellowship, has completed a study of the rates of diffusion of radiosodium, radiomercury, and radiochloride across the blister surface of the normal human skin and across that of patients with congestive heart failure. This study, now in preparation for publication, has contributed to a better understanding of the exchange rates and related phenomena of electrolytes across the walls of blood vessels.

Other studies have been concerned with determinations of venous pressure in the superficial veins and the larger veins of the thorax and abdomen of normal resting man which are accessible by means of the cardiac catheter.

f. Future Plans. Studies as indicated above will be continued.

g. Detailed Reports. "Regression of a Radioactive Mercurial Diuretic from the Plasma of Man," Nature, 163:640, April 23, 1949.

"A Stereoscopic Method for Obtaining Spatial Vectorcardiogram," Cronvich, Abildskov, Jackson, and Burch (in press).

"An Approximate Derivation for Stereoscopic Vectorcardiograms with the Equilateral Tetrahedron," Cronvich, Abildskov, Jackson, and Burch (in press).

"A Derivation for Stereoscopic Vectorcardiograms and Analysis of Vectorcardiograms by High-Speed Motion Pictures," Burch, Cronvich, Abildskov, and Jackson (in press).

"The Transfer of Radioactive Mercury across a Membrane Produced by the Application of Cantharides to the Skin of Man," Kelly, Svedberg, and Harp, J. Clin. Investigation (in press).

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PROGRESS REPORT (NC)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-64-12-14
1. PROJECT TITLE Protein Metabolism in Disease and Injury		4. REPORT DATE 30 Jn '50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP AW-6	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/W. O. NO.
9. DIRECTING AGENCY		
10. REQUESTING AGENCY	13. RELATED PROJECTS	17. EST. COMPL. DATES
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	14. DATE APPROVED	OP EVAL
	15. PRIORITY 16.	FY 18. FISCAL EST'S.
19. Completed.		

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21. BRIEF OF PROJECT AND OBJECTIVE

Final Report. General Statement. Work began in July 1946, using the facilities of the Departments of Physiology and Surgery, Tulane University, and the Charity Hospital. In early 1947 a metabolic unit was established in the Foundation Hospital and the work was transferred to that location during the summer. On 31 May 1949 the metabolic unit was discontinued and the work transferred to the Laboratory of Physiology.

The following is a brief summary of accomplishments:

1. Development of methods for the clinical estimation of blood volume. The dye (T 1824) method was standardized for clinical use and its limitations described for the determination of plasma volume./ Radioactive phosphorus (P-32) was introduced for the measurement of red-cell volume and the method adapted for clinical use./ Radioactive iodine (I 131) was used for plasma volume and shown to be a very excellent method for plasma-volume determination which is probably superior to the dye method. Clinical studies with this method are projected.

2. Clinical studies. The term "chronic shock" was introduced to describe the condition seen in chronically-ill and debilitated patients who show a significant anemia due to a decreased red-cell volume. While this term is not an ideal one, it does serve to distinguish this particular condition./ The investigators have shown that quantitative replacement of blood designed to restore the red-cell volume serves to make these patients good surgical risks and hastens recovery. This work, amply confirmed by other investigators, has emphasized the importance of blood-volume determinations in these patients./ Studies on protein metabolism indicate that the negative N balance frequently seen after surgery is not necessarily due to an inability to handle protein but rather to increased excretion or some other mechanism./ The work during the last year of the contract (1949-50) was concerned with an experimental study on the exchange of albumin between plasma and lymph. This work has yielded quanti-

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tative data on the disappearance of albumin from plasma as well as information regarding lymph flow and albumin metabolism. Clinical application of this work is projected. Incomplete studies on the fate of infused albumin (and plasma) are being completed and definitive data on this problem are hoped for in the near future.

Reports. "Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient," Ann. Surg., 125:618-646, 1947.

"Studies of Blood Volume in the Tetralogy of Fallot and in Other Types of Congential Heart Disease," J. Clin. Inv., 26:860-868, 1947.

"Essential Therapeutic Adjuvants in the Surgical Arrest of Wolff-Israel Actinomycosis," Ann. Surg., 126:568-578, 1947.

"The Surgical Significance of Hemoglobin Deficiency in Protein Depletion," J.A.M.A., 135:9-10, 1947.

"Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient," Postgr. Med., 5:227-232, 1949.

"Determination of Circulating Red Blood Cell Volume with Radioactive Phosphorus," Amer. J. Physiol., 155:226-231, 1948.

"Comparison of Results of Measurements of Red Blood Cell Volume by Direct and Indirect Technics," Amer. J. Physiol., 155:232-238, 1948.

"Effect of Administration of Adrenalin on the Circulating Red Cell Volume," Amer. J. Physiol., 155:239-241, 1948.

"Metabolic Changes Associated with the Administration of Salt-poor Human Serum Albumin in Two Cases of Infectious Hepatitis," J. Clin. Invest., 29:381-388, 1950.

"The Utilization of Amino Acids by Patients following Surgery," J. Lab. & Clin. Med., 35:385-390, 1950.

"The Exchange of Albumin between Plasma and Lymph" (being prepared).

In addition, various aspects of the work have been presented to clinical and experimental groups at their respective meetings. Exhibits have also been presented at such meetings, and the one on chronic shock at the Centennial Meeting, AMA, in June 1947 was awarded honorable mention.

Besides work that has been published, considerable data have been accumulated on various aspects of the general problem of protein metabolism in disease. Much of this work, such as the utilization of glycine, distribution of fluids, etc., will eventually be continued by various members of the group as opportunity arises.