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MEDICAL SERVICE

RESEARCH PROGRAM

1 JULY - 31 DECEMBER 1950

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

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6-59-03-02

Dr. Pendergrass
U. Pennsylvania

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PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-59-08-01
1. PROJECT TITLE Radiation Injury		4.
		5. REPORT DATE 30 Dec 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		
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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.

b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. During the past several years the investigators have developed a gross index of protection against local radiation which consists, briefly, of radiating the hind leg of a rat in a control group and in a treated group to measure the protective effect of materials such as pitressin, rutin, aureomycin, sodium cyanide, dinitrophenol, epinephrine, and miscellaneous intracelluiar enzyme system inhibitors. The experiments have indicated that the protective action demonstrated by certain compounds so far seems to evolve around vasoconstriction and oxygen tension of the local tissues. It is manifest that the tissues of the leg are not those particularly susceptible to variations in oxygen tension and accordingly are not considered as sensitive as other types, especially glandular tissue. In general, they have developed a testing technique by which materials which promise protection against local ionizing radiation can be reasonably well screened.

It was proposed to extend this work to involve a more sensitive tissue such as the testicular tissues of the rat and also to include certain tissue chemical determinations, principally the known and measurable enzyme systems.

Progress. No report was received.

f. Future. It is planned to have this study evaluated and reviewed by the National Research Council.

g. Reports. None listed, this period.

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Dr. Oughterson
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PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECT)~~	2. SEC. U	3. PROJ. NO. 6-59-08-03
1. PROJECT TITLE Medical Aspects of Atomic Bomb - Report		4. 5. REPORT DATE 31 Dec 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 RES. DEV. TEST OP EVAL
11. PARTICIPATION AND/OR COORDINATION	14. DATE APPROVED	FY 18. FISCAL EST'S.
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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.

b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. Tentative chapter-headings of this book are: Introduction, Catastrophic Effects, Nature & Incidence of Casualties, Clinical and Pathologic Observations, Effects on Plant & Animal Life, The Problem of Reconstruction, and Summary & Recommendations./ Because of the importance of the subject-matter and the need for accuracy and security, much checking of material has been done, with consequent slowing of the work; delay has also resulted from the illness of the editors and the slowness of the authors to complete their sections./ A concise account of the physics involved in an atomic bomb will be included. Four drafts of that section were prepared for review by Dr. Ralph E. Lapp. It was decided that more rapid progress in this highly technical field could be made if he were to prepare the final draft; he agreed to do this./ A chapter on the biologic effects of radiation was being prepared./ Part II, "Catastrophic Effects," was in final draft in June 1950./ Part III, "Incidence of Casualties"—much of which is statistical—was to be checked by Dr. Cuyler Hammond, who was out of the country./ Part IV, "Clinical & Pathologic Observations," was largely completed, and most of the material has been published in the American Journal of Pathology./ Completion of the manuscript was last slated for autumn, 1950; no report has been made since.

Progress. No report was received.

f. Future. Specific plans have not been stated, but efforts are being made to complete this manuscript.

g. Reports. None.

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PROGRESS REPORT (C)

Dr. E. I. Evans
Med. College Va.

RESEARCH AND DEVELOPMENT [redacted] 2. SEC. 3. PROJ. NO. 6-59-08-04

1. PROJECT TITLE
Radiation and Thermal Burns

4. 5. REPORT DATE 31 Dec 50

6. BASIC FIELD OR SUBJECT

7. SUB FIELD OR SUBJECT SUB GROUP
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8. COGNIZANT AGENCY

12. CONTRACTOR AND/OR LABORATORY

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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.

b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. through d. No change.

e. Background. The report of December 1949 described in detail the plans and set-up of the various departments collaborating in this study. The report given below covers the period January through December 1950.

Progress. An atomic bomb explosion releases an enormous quantity of energy (blast, radiation, gamma and neutron) and ordinary heat. Observations by competent observers on the results of the explosion at Hiroshima indicate that immediately in the region of the hypocentre of an air burst the energy release is so great that, in general, animal or vegetable life cannot survive, but that the attenuation of the radiation flux from the centre outward is great enough so that at around 2100 yards only a small amount of radiation damage is inflicted. However, in this region the heat of the flash is still so great that moderately severe burns result.

It has been felt that in the search for methods of improved medical and surgical care for atomic bomb victims, the greatest effort should be pushed for those victims who happen to be in the 1500 to 2500 yard zone. Accordingly, most of the experimental studies being conducted here have had as their purpose the elucidation of the mechanism of injury caused by combining heat with minimal amounts of ionizing radiation in the experimental animal; in the clinic, every effort has been made to use human burn material in order to work out simpler and more efficient methods for the care of mass burn casualties.

I. Biophysics Group: Following the initial survey of the problem of thermal and radiation injury concerned with atomic bomb explosions, it appeared highly desirable to have available a powerful source of ionizing radiation which would allow a high dosage rate in a very short period of time. After many conferences here and abroad it was decided to secure a

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one-million-volt beryllium-window x-ray tube. Early efforts to calibrate this equipment by ordinary radiologic methods failed; strenuous efforts to develop better methods for calibration of this type of equipment were successful. Later this equipment was calibrated by calorimetric means using the constant flow calorimetric technique. These two studies were reported under the following titles: (a) "Million-Volt-Beryllium-Window X-Ray Equipment for Biophysical and Biochemical Research," by Ham and Trout; (b) "High Intensity X-Ray Dosimetry by Calorimetric Means," by Ham, Williams, Schmidt and Smith.

The biophysics group has made much of the equipment employed for experimental burns; supervised all experimental work involving the use of radioactive isotopes; and made a double slit, Nier-type mass spectrometer for metabolic studies in the human with stable isotopes.

II. Experimental Surgery: It was early recognised that a method for producing standard and uniform thermal injury in the dog was necessary to understand some of the important phases of disturbances following thermal injury. Accordingly, a serious effort was made for the past 18 months to develop a standard burn technique in the dog. This is reported as: "A Standard Burn——Method of Production and Observations on the Blood Picture Following Its Production in Dogs" by Brooks, Robinett, and Evans.

It is believed that this standard experimental method has allowed accurate estimates of the relations of the extent of body surface burned to plasma and red cell loss, the influence of depth of burn on healing time, etc.

A study of the details of the response to the standard burn in 38 normal dogs followed from the time of burning to healing provided a valuable tool for the evaluation of combined effects of radiation and thermal injury. Accordingly, preliminary experiments were done on the effect of 100r and 25r external radiation as a complicating factor in the standard 20 per cent burn in the dog. Preliminary data indicate that the addition of 100r external body radiation (approximately 1800 yards, Hiroshima-type bomb) alters considerably the response of the dog to the standard burn. Whereas the mortality to the 20 per cent burn alone is very low (around 10 per cent) when 100r external body radiation is given immediately before or immediately after the thermal injury, the combined effects become quite lethal (78 per cent). Cursory observations on the possible cause of death in these animals indicate that blood-stream infection with beta hemolytic streptococcus may play a role, but not enough data have been collected to allow a firm statement.

The combined 100r external body radiation and the 20 per cent standard burn in the dog result in a rather sharp drop in white blood cell count. There is almost complete disappearance of the lymphocytes from the circulating blood. Autopsies of all dogs dying as a result of this combined injury have indicated no distinct cause of death; it should be pointed out that in no way do these animals resemble those in which 400r - 600r alone has been used except for the pronounced effect on the myeloblastic elements of the bone marrow.

Following these studies on the combined effects of the standard 20 per cent burn and 100r external body radiation, preliminary observations were made on the combined effect of burn and of only 25r external body radiation.

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he data collected so far indicate that the addition of even this small
mount of external body radiation may have a pronounced effect on the myelo-

B. Dextran in Burn Shock: During the past 18 months the use of Swedish dextran in place of ordinary plasma has been studied in 46 severely-burned patients. Dextran was given in the same amounts required by the formula described above for plasma; the same amount of salt solutions was given also. These observations indicate that dextran is a safe and effective plasma substitute for burn shock. In most patients an early and steady urine output was attained when proper amounts of dextran were infused. No evidences were seen of adverse effects (liver or kidney) of dextran, nor were any accompanying allergic phenomena noted. These preliminary observations indicated to the investigators that it is likely that dextran may safely be stockpiled for emergency use in the treatment of mass burn casualties. These studies were an important part of those that allowed the National Research Council to advise the Department of Defense to stockpile dextran. A detailed report on dextran in burn shock is in preparation.

C. The Universal Protective Dressing: The closed dressing principle for the treatment of extensive burns has been widely accepted for hospital use since its introduction by Allen and Koch in 1942. Its chief drawbacks in the treatment of mass burn casualties would be that presently-available dressings make the method time-consuming and require relatively well trained medical personnel. For this reason (with the cooperation of Dr. John Henderson, Johnson & Johnson Company), a single one-piece large burn dressing for extensive burns was developed. This dressing was used on approximately 80 burns in the past 8 months, and in the experience to date it has proved to be a highly valuable method for the immediate emergency care of the severely-burned patient.

The dressing consists of an inner layer of dry, fine surgical gauze (36 x44 gauge); an intermediate filler of 1 inch of cotton and 30 layers of cellulose, the outer 6 layers of which are treated to make them water-repellent; and an outer layer of water-repellent material. There were problems of sticking of the dry inner surface to the burn wound even when the dressing was left in place for as long as 14 days. The requirements set forth for this type of dressing for military and civilian defense use seem to be adequately met. This dressing will soon be produced commercially.

D. The Anemia of Thermal Injury: 1. Moderate to severe secondary anemia accompanies extensive thermal injury in man. This anemia has proved refractive to all measures except whole-blood transfusions. Because anemia in the burn patient results in non-healing of the burn wound and other important disturbances, it is considered to be one of the more serious problems to be dealt with in a research program on burns leading to more adequate care of mass casualties in atomic warfare. Accordingly, serious attention has been given to this problem in the clinical studies here.

Seventeen severely-burned patients were selected for study of the hemolysis of the red blood cell. Urine and fecal urobilinogen studies were made with coproporphyrin estimations. This study indicates strongly that hemolysis is a significant factor in the anemia which accompanies burns. 2. Liver Function in Severe Burns: Since no study of hemoglobin metabolism in the severely burned patient would be satisfactory or complete without a study of the liver function of the same patient, an attempt was made to study liver function in 15 of the 17 burned patients on whom hemoglobin studies were made. In all deep burns studied there appeared to be a significant alteration of liver

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function as determined by ordinary laboratory investigations. The liver dysfunction appeared very early after the burn had been received and was not affected by any of the therapeutic means employed. It was concluded that because of the liver dysfunction seen early after burning, attention should be directed at its prevention as well as its treatment. 3. Tagged Glycine Studies in Dogs: Following the studies of Rittenberg, Shemin, and London it has become apparent that N^{15} tagged hemin is a powerful tool for the study of hemoglobin metabolism in man. Realizing the superiority of this tool over all others for the study of red blood cell production and destruction in the burned patient, the investigators secured the equipment, personnel, and methods to allow the use of N^{15} in the study of the anemia of thermal injury.

The first portion of the past 18 months was spent in the development and building of a Nier-type mass spectrometer, the development of chemical methods in the laboratory for the estimation of N^{15} in hemin samples, etc.

Progress was necessarily slow in the beginning, but this study is now well under way. In the past 4 months preliminary observations have been made with this tool in the study of anemia of thermal injury in the standard burn dog. Tagged N^{15} glycine has been fed to 2 animals in the normal and burned state, each animal acting as his own control. Preliminary observations indicate already that the production of hemoglobin in the normal dog runs a similar course to that in man but that after burning there is a tremendous reduction in the rate of hemoglobin synthesis (with the 2 dogs studied, the rate of new red cell formation was approximately only 15 per cent of that found in the normal state). That this was not due to interference with absorption of the tagged glycine from the gut or abnormal excretion by urinary and fecal routes is indicated by the fact that the figures for these estimations are the same for both the normal and burned state. This all points to seriously disturbed hemoglobin synthesis following burning. Insufficient data in this experiment have been collected to warrant further discussion here. The investigators believe that they have in the N^{15} tagged red cell a powerful tool for the study of the mechanism of the anemia which accompanies burns.

E. The Stress Response and Related Adrenocortical Functions in Burns. Following announcements of the apparent advantage of treating severely-burned patients with ACTH, studies on the stress response in such patients were begun here.

Since it was recognized that for any rational approach to treating burn patients with ACTH or Cortisone baseline control studies would have to be done on the adrenocortical response in the burn patient without such therapy, every effort has been made in the past 5 months to study burned patinets under carefully controlled conditions in order to obtain these data. These studies have included the eosinophil count response to burns in various age groups and of various extents of body surface involved. An attempt has been made to correlate the eosinophil response to other measures of adrenal function such as potassium excretion, sodium retention, diuresis, oedema of the burn region, nitrogen excretion and, more recently, corticosteroid and ketosteroid excretion. Finally, serious attempts have been made to study the effect of ACTH therapy on the fate of massive homografts in 3 severely burned patients. These studies were reported as: "Stress Response and Related Adrenocortical Function in Burns," by Butterfield and Evans.

f. Future. I. Biophysics. A. High Temperature Studies: A 24-inch Army searchlight was obtained for use as a source of heat for experiments in man. The accurate calibration of the heat output from this lamp at various distances will occupy the attention of the biophysics group for some time.
B. Human and Dog Burns: Attempts will be made to cross-calibrate the experimental burn in the dog and man (volunteers) with certain heat-sensitive paper and cloths already under study by the Quartermaster Corps. The biophysics group will be very useful in efforts to learn more about contact burning.

II. Experimental Surgery: A. The standard burn mentioned earlier was produced by a relatively low temperature burning iron placed against the dog's skin for a relatively long period of time (60°C. for one minute). This is a "low temperature burn" such as is seen in civilian practice in burns caused by hot water or steam; the atomic bomb thermal injury is produced by a relatively high temperature acting for only a short period of time. The production and study of experimental high temperature burns in dogs will be studied, therefore, for an estimate of the relative plasma and red cell loss in high temperature burns, healing time, etc. These studies will be undertaken when the searchlight has been calibrated accurately and there is a constant output for each burn. Preliminary observations already made indicate that it will be feasible to produce a high temperature, deep second degree burn with the arc lamp in approximately 2 to 3 seconds.

B. As indicated above, considerable progress has been made in the comparison of a standard burn with a standard burn complicated by minimal external body radiation. Several phases of this work greatly need clarification if a better understanding of the problem and proper therapeutic methods for bomb victims in case of attack are to result. One of the most important of these is a complete bacteriologic survey of the burn wound, the air of the kennels, the dogs' saliva, blood cultures, etc. At present such studies are hindered by lack of bacteriologic aid, a problem which may soon be solved.

When the baseline studies on the effect of combining minimal radiation and standard burns are completed various therapeutic aids such as penicillin, aureomycin, and terramycin will be tested; in the experiments with 100r the effects of the several plasma substitutes and whole blood and plasma of the dog will also be studied.

C. Clinical Burn Surgery: The study of the influence of dextran in the prevention and treatment of burn shock can be completed soon; the relation of molecular size of the dextran employed to the extent of plasma volume expansion remains to be determined. Clinical trials of dextran of 3 different molecular ranges have already been begun..

As soon as polyvinyl pyrrolidone becomes available for clinical trials its use as an anti-shock agent in the severely-burned patient will be studied. An attempt will be made to correlate the molecular range of the PVP used with the extent of plasma volume expansion in normal human subjects.

At the recent meeting on the universal protective dressing it was obvious that a cheap and efficient bandage to go with this dressing must be developed rapidly. Clinical trials have been made of a few different types of bandage, and there is indication that a satisfactory one can be produced for 25¢ to 30¢ for a 6-yard, 6-inch bandage.

In the program on anemia, tagged N^{15} studies on the human are in progress. It is hoped that red cell formation and destruction can be studied in at least 6 burn patients in the next year. Doctor Ham's laboratory will make serious efforts to carry this study forward by N^{15} analyses of fecal stercobilin. There are at least 3 metabolic sources of stercobilin; the largest, about 70 per cent, appears to come from the destruction of hemoglobin. Because of the possibility that myoglobin may be a source of some stercobilin in the burn patient, attention will be devoted to this problem; such studies may amplify knowledge of the cause of the rather marked "hemolytic phase" in the first few weeks after burning.

One series of observations indicates that with the open exposure method of treatment in the severely burned patient the red cell destruction may be somewhat less than with the closed. It is hoped to observe at least 5 more severely-burned patients treated by the exposure method to learn of its possible beneficial role in lessening the anemia of severe burns.

Control observations on the stress response in severely-burned patients will continue. When enough data have been collected, burn patients in the early phase will be treated with cortisone and ACTH. In the later burn phases the effect of ACTH and cortisone on joint mobility, scar tissue, burn contractures, etc., will be studied.

Dr. Mote of Armour Laboratories has indicated the importance of continuing observations on the effect of ACTH on homografts in burned patients here. He was impressed that one patient now being studied has the best homograft result so far achieved. At least 3 more burn patients will be studied similarly if possible.

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Dr. J.G.Allen
University of Chicago

PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT~~ (NEW PROJECT)	2. SEC. U	3. PROJ. NO. 6-59-03-05
1. PROJECT TITLE: Ionization Effects		4. REPORT DATE 31 Dec 50
5. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP: AM-5	
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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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change

b. No change

21. BRIEF OF PROJECT AND OBJECTIVE

a. through d. No change.

e. Background. Exercise Tolerance Following Irradiation. A series of 200 rats was separated into groups of 20 each and allowed to swim daily until exhausted. The time of swimming was considered to be a measure of exercise-tolerance. For the average rat during the control period, this was approximately three hours. In groups of 20 these animals were exposed to a single dose of x-radiation at: 50r, 100r, 200r, 300r, 400r, 500r, 600r, 700r, and (two groups) 800r. All animals receiving more than 300r showed a marked reduction in exercise-tolerance within the first 24 hours after exposure. Thereafter the animals swam with increasing efficiency until they reached their control levels. Three to 10 days after irradiation-exposure the animals exposed to 500-800r showed a second sharp decline which was persistent./ Nutrition. In a series of metabolic studies on irradiated dogs (450r) increases in nitrogen-excretion were pronounced during the first 24 to 48 hours following irradiation. This figure then returned to normal but increased during the last three to four days of life. The plasma-protein concentration fell steadily from day 1, and the total quantity was frequently below 4 gm. per cent. The greatest decline was in serum albumin. There was a pre-mortal rise in the protein nitrogen which appeared to be the result of an increase in polypeptides rather than in actual proteins. Also anemia became pronounced and the cellular hemoglobin as determined by blood-volume measures frequently fell to 20 per cent or less of the control value. The animals did not eat after the 5th or 6th day. Their condition was further complicated by diarrhea and vomiting./ Anoxia. Anoxia, in some cases severe, developed between the 4th and 12th days following irradiation. The many factors

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apparently contributing to this state included anemia, fever, a decreased oxygen-combining power, venous stasis, and altered permeability of membranes. This anoxemic state could be rectified in part by the administration of toluidine blue (an oxidant) or the administration of oxygen. Infection. Infection was more real than apparent. Organisms were cultured from heart-blood of mice and dogs. Presumably the organisms gained entrance to the blood stream through the intestinal tract (which was frequently ulcerated) or through the respiratory system. In addition, it was found that antibody titer was reduced after irradiation and contributed to infection. There was evidence that some degree of protection was afforded through the administration of streptomycin during the post-irradiation period. A study of pathologic sections from ulcerated areas showed that the tissue was unable to produce an inflammatory type of reaction; i.e., the leucocytic response was not evident although bacterial organisms could be seen frequently in the tissue./ Fluid Balance. Studies were completed on changes in blood-volume, extracellular fluid, and total body water in dogs following irradiation. In general the data indicated a decrease in plasma-volume and increase in extracellular fluid and total body water. During this work, however, the selective diffusion of these various agents in different tissues was clearly demonstrated. For example, the content of sulfanilamide in the red cells exceeded that of a comparable volume of plasma. While the data obtained were reproducible, conclusions must be guarded because of inherent difficulties with the methods employed. This problem will be studied later by different techniques./ Protection. In protective experiments, shielding of the bone marrow, even of as little as 5 to 15 per cent of the total bone marrow of the body, enabled animals to survive doses which were otherwise uniformly fatal. This was not due to the cellular elements contributed to the peripheral blood; it strongly suggests that there are humoral factors, the nature of which is unknown, which are extremely important and which if protected will increase survival rate to a remarkable degree.

The in-vitro clotting determination of whole blood was investigated and evaluated. Data were accumulated 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./ Summary of the Irradiation Effect on Coagulation Mechanism. The individual and collective roles and possible significance of the various changes seen in the irradiation that were studied in this laboratory were discussed. An attempt was made to isolate an inhibitory substance from the blood of irradiated animals. The possible origin and fate of clotting inhibitors were considered in the light of current knowledge. The effects of irradiation thrombocytopenia and direct damage to the capillary bed are considered as changes capable to altering the hemostatic mechanism following irradiation./ Whole-Blood Transfusions in Total-Body X-Irradiation Injury. Transfusions of whole blood in sufficient amounts, about 5-10 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./

Treatment of the Irradiation Syndrome with Aureomycin. Aureomycin is more effective in increasing the survival time of dogs following total-body x-irradiation than any other agent investigated. While aureomycin apparently 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 nor in their appearance at postmortem examination./

Relationship of Method of Preservation of Plasma to Incidence of Homologous Serum Jaundice. No recognized cases of homologous serum jaundice or hepatitis occurred in patients given pooled human plasma which had been stored in liquid state without preservative at 78-96°F. for three months or more prior to administration. A survey of the previous reports of transmissible hepatitis from human blood products disclosed that the method of preservation for these products was also highly suitable for the preservation of any virus that may have been present.

Progress. Reference has been made to the observation in this laboratory that shielding the head or the liver had a protective effect in a dog exposed to 450r irradiation. This report deals with 20 animals in which the head was shielded at the time of total-body exposure to 450r. Ten dogs irradiated during this same period with 450r total-body x-ray had no shielding, and all died between the 5th and 12th days. These served only to control survival periods and were not paired controls for this study. Unselected animals from the pound were exposed within less than a week after receipt. They were not subjected to the usual quarantine, vaccination, and de-worming procedures. A series of 157 irradiated 450r dogs which received no treatment was used for controls./

Comment. Two features about this series of animals appear unusual and somewhat unexpected. First is the extent to which shielding of the skull alone seemed to protect the animal from the ravages of irradiation of the rest of the body. The results obtained might have been improved had a better group of animals been available for irradiation. In the survivors the general condition of the animal was excellent in most instances throughout the three months' period of observation. Second, bleeding, even about the teeth, was strictly absent. The clotting-times in these surviving head-shielded animals were prolonged, but to a lesser extent than in the 5 shielded animals which died, or in comparison with the total-body exposures of the 157 controls. In this connection the platelet counts in the head-shielded survivors, as well as in the 5 which died, closely paralleled those of the untreated total-body irradiated dogs. The fact that the 15 shielded animals had a thrombocytopenia comparable to that in the animals which died, but nevertheless did not bleed, raises again the question as to the contributing role of platelets in the hemorrhagic syndrome of irradiation. It must be pointed out, however, that internal bleeding in these 15 shielded animals may have occurred but was overlooked, since none of these animals was sacrificed.

These observations seem to implicate the hemopoietic system as a primary disturbance responsible for death in these 450r unshielded animals; and to indicate that many of the other disturbances such as diarrhea, infection, and loss of appetite either fail to occur or are much less evident when the head is shielded. It is probable that by head-shielding the L.D. 100 x-ray dose in

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the dog can be nearly doubled. It has thus far been the most effective means encountered for protecting the dog exposed to 450r. Compared with post-irradiation therapeutic procedures, head-shielding is unique. Perhaps more significant than the survival rate are some of the physiologic and pathologic implications that such observations pose. It is planned to study the 15 surviving animals as follows: shield the pelvis in 7 and deliver 450r to the remaining part of the body; and expose the other 8 to 450r without any protection.

f. Future. As indicated above.

g. Reports. Volume IV-A, Head Shielding. "Effect of Head Shielding in 20 Dogs Exposed to 450r Total Body Irradiation."

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PROGRESS REPORT (C)

Medical Nutrition Lab
Chicago; and Dr. Evans,
Med. Coll. of Virginia

RESEARCH AND DEVELOPMENT ~~PROJECT CARD-(MEN-PROJECTS)~~ | 2. SEC. U | 3. PROJ. NO. 6-59-08-06

1. PROJECT TITLE Nutritional Requirements in Radiation Injury | 4. | 5. REPORT DATE 1 Dec 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: RES. / DEV. / TEST / OP EVAL

11. PARTICIPATION AND/OR COORDINATION

14. DATE APPROVED | 15. PRIORITY | 16. | FY 18. FISCAL EST'S.

19.

20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.
b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. Normal mongrel dogs received in a single exposure 450 r (total body) x-irradiation. No adjuvant therapy was given. White blood cell counts, totals and differentials, hematocrits, platelets, clotting times, prothrombin times, and fibrinolysis were followed. Complete autopsies were performed. There was a marked drop in white blood cells and platelets in a few days with a lesser and slower drop in hematocrits. Prothrombin and clotting times were only moderately prolonged. Hemorrhagic manifestations were minimal except in the lungs. Spontaneous fibrinolysis of recalcified plasma clots or clotted whole blood was not observed after irradiation. Eleven of the 12 dogs studied died, most of the deaths occurring in the second week. The histologic sections are being examined by the Pathology Division in Chicago. Eosinophils in Dog Blood. A method for the direct counting of dog eosinophils was developed. Details were given in the preceding report.

Progress. Ashby Counts in Dogs. A method for the serologic quantitative identification of infused red cells in dogs was developed. Both saline and serum systems for the suspension of red cells were tried. The former was discarded because of high free counts found. Wet serum for both suspension of cells and antisera was also discarded because of the necessary dilution introduced. Attempts made to perform Ashby counts with saline washed red cells resuspended in homologous serum and dog (Coombs) serum were not successful. So far, the best method has been the use of lyophilized antisera with wet autologous serum for the suspension of the red cells. Anti-A serum has a nonspecific hemolysin which hemolyzes A cells rapidly but cells lacking A, more slowly. It was decided, therefore, to absorb the dog anti-A sera against CD red cells in an attempt to remove the hemolysin. (CD cells were used because BCD cells were not available. The B agglutinogen occurs in only 3½ per cent of dogs.) Complement

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was inactivated in the dried anti-A sera but not when fresh autologous serum was used for the suspension of the red cells. By this method satisfactory Ashby counts can be made. Metabolism after Thermal Burns and Radiation Injury. Observations on various hematologic and metabolic functions following radiation (100 r) and thermal injury (20 per cent deep 2°) in dogs were made. The hematologic observations include: red blood cell counts, white blood cell counts, differentials, hemoglobins, hematocrits, plasma volumes, platelets, and eosinophils. Metabolic observations include body weights, nitrogen intake and output (BSP retention, thymol turbidity, thymol flocculation, cephalin flocculation, serum bilirubin direct and indirect, and prothrombin times). Observations on four dogs were given in the last report; since then three additional dogs have been studied. N^{15} glycine was given orally at appropriate times as a tracer to two of the dogs. These samples are now being analyzed in the mass spectrometer. The data from these studies will be reported in detail later. Survey and Review. An extensive survey of the literature on the metabolic and nutritional sequelae of thermal burns and radiation injury was made and a critical review written for the Subcommittee on Radiation and Thermal Burns of the NRC Committee on Therapeutic Nutrition.

f. Future. Additional animals (dogs and other species) will be studied, with N^{15} glycine as a tracer. The possible role of proteolytic enzymes (and anti-proteolytic enzymes) as well as antibiotics will be investigated.

g. Reports. "The Treatment of Burns," Lund and Levenson, Nelson's System of

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PROGRESS REPORT (C)

Army Medical Cent

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. | 5. REPORT DATE: 31 Dec 50

6. BASIC FIELD OR SUBJECT | 7. SUB FIELD OR SUBJECT SUB GROUP: PO-16

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

11. PARTICIPATION AND/OR COORDINATION

14. DATE APPROVED | FY 18. FISCAL EST'S.

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19. Completed; study terminated by MSTC 15 January 1951.

20. REQUIREMENT AND/OR JUSTIFICATION

21. BRIEF OF PROJECT AND OBJECTIVE

Final Report. This study was approved 31 August 1948. Pertinent information wa tabulated on the following numbers of cases: testicular tumors, 178; Hodgkin's disease, 244; brain tumors, 37; lymphosarcoma, 80; pituitary tumors, 16; carcinoma of the nasopharynx, 24; and carcinoma of the cervix uteri, 51.

Three clinical scientific papers were prepared and presented to radiologic societies:

"Irradiation Damage of the Intestines following 1000 KV Roentgen Therapy. Evaluation of Tolerance Dose," Amory and Brick; presented at the meeting of the Eastern Radiological Society, March 1949, and published in Radiology, 56:49-57, January 1951. Twenty cases receiving unusually large amounts of radiation to th abdomen are presented. Roentgenographic changes not previously described are di cussed and illustrated. It was concluded that the normal intestine of the adult male can tolerate 4,500 to 5,000 r, 1000-KV irradiation therapy without permanen disability.

"Million Volt X-ray Therapy of Brain Tumors," by Major Keene M. Wallace, MC presented at the same meeting.

"Irradiation Effect on the Stomach following 1,000 KV Radiation Therapy," by Wallace and Wallace; presented at a national meeting of pathologists.

Study was made of about 50 cases develcping radiation pneumonitis and pulmonary fibrosis following 1000-KV irradiation for treatment of diseases such as Hodgkin's, lymphosarcoma, carcinoma of the breast, testes, lung, and esophagus. A striking difference was shown in distribution of the fibrosis and a more striking sharp demarcation between pathologic and normal pulmonary fibrosis after 200-KV therapy. This difference had not been described previously.

A 4-month check of the effectiveness of radiation-protection methods in the hospital showed them to be highly efficient except in one section, where corrective changes were made immediately.

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Dr. Langer

PROGRESS REPORT (C)

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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 31 Dec 50

6. BASIC FIELD OR SUBJECT 7. SUB FIELD OR SUBJECT SUB GROUP AV.-6

8. COGNIZANT AGENCY 12. CONTRACTOR AND/OR LABORATORY Dr. Langer (Purchase Order) CONTRACT/W. 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

15. PRIORITY 16. FY 18. FISCAL EST'S.

19. Completed (project terminated, MSTC, 29 May 1950).

20. REQUIREMENT AND/OR JUSTIFICATION

21. BRIEF OF PROJECT AND OBJECTIVE

FINAL REPORT. The manuscript entitled "A Study of the Physical Basis of Burn Production with Applications to the Defensive Reactions to An Atomic Bomb Air Burst," which was produced under this project, has been multilithed and is now available in booklet-form for distribution.

The author states that in this report the mechanism of burns has been developed in much more complete form than ever before, with the protein denaturation hypothesis of skin destruction proposed by Moritz and Henriques used as a base. The results so far give strong support for this hypothesis and provide a powerful method for anticipating the details of burn production in atomic air attack. These details will serve, along lines illustrated in the text, in the formulation of a doctrine for evasive action in case of an air burst and in the design of protective clothing and equipment as well.

It is stated that the arguments have often been too brief for good exposition, but to go into full detail would have lengthened the report unduly. It is important to have the present form perused by those seriously occupied in the field and to learn what reactions follow, in order to judge the form the next study should take. If a particular element is especially interesting, the analysis should be repeated in greater detail and with greater accuracy. In this, slide-rule methods were used throughout; machine calculations might well be included in a future report.

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PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECT)~~	2. SEC. U	3. PROJ. NO. 6-59-08-10
1. PROJECT TITLE Irradiation on Enzyme Systems, Effects of		4. REPORT DATE 31 Dec 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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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.
b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. This study was approved in October 1949 in order to determine the effects of irradiation on oxidase and proteolytic enzyme systems and adrenal and thyroid activity. A detailed outline of study was reported in December 1949; it was planned to study the following systems and activities in irradiated mice: cytochrome-cytochrome oxidase system; hexokinase and adenosine triphosphate systems; adrenal activity; and thyroid activity./ A collaborative study with Dr. Pendergrass was undertaken on the protective effect of pitressin and epinephrine against local (leg) reaction produced by x-radiation (2000 r) in rats./ Mice were subjected to whole-body x-radiation totaling 800 r/air delivered in 15 minutes. Preliminary results indicated that this amount of radiation 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./ The liver showed 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 5th day following irradiation. An abrupt increase occurred near the time of death. The kidney showed no definite change in the inorganic, and only slight decrease in the labile, phosphate. The muscle showed a definite increase in inorganic phosphate content; a slight but definite decline in the labile phosphate up to the 3rd day following irradiation; and then a gradual continuous rise above normal until the time of death.

Progress. The protective effect of pitressin and epinephrine apparently is due to local tissue anoxia produced by these substances. It has been reported that injection of pitressin will produce anaerobic conditions in the muscles. Administration of epinephrine causes an immediate increase in the oxygen-

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consumption of muscle tissue, thus producing a temporary anoxia. These assumptions are supported by the results of the effect of pitressin- or epinephrine-administration on the cytochrome oxidase activity of muscle. Administration of pitressin produced an inhibition, and of epinephrine an acceleration, of cytochrome oxidase activity. Results on the phosphate-distribution of muscle after administration of either pitressin or epinephrine also indicate a temporary local anoxia in the muscle tissue.

f. Future. The possible relationship between radiation-sensitivity and degree of the anoxic state of the organism will be studied./ The effect of total-body x-irradiation on the cytochrome oxidase activity and on the phosphate-distribution of the liver is being studied in rats. These results will be compared with those obtained in mice./ The possible protective effect of various agents administered either prior to or after irradiation (total-body) is also being investigated.

g. Reports. None.

SECURITY RESTRICTED CLASSIFICATION

Dr. Cope
Mass. GH

PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-59-08-11
1. PROJECT TITLE Thermal Burns		4.
		5. REPORT DATE 31 Dec 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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11. PARTICIPATION AND/OR COORDINATION	14. DATE APPROVED	FY 18. FISCAL EST'S.
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20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.
b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

The reporting agency for this project is the Office of Naval Research. It is reported under the following title and numbers:
"Intracellular Changes in Trauma Depletion and Repair,"
N5 Ori-76, Project XIII; NR-114-198.

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SECURITY RESTRICTED INFORMATION

Dr. Ravdin
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PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT PROJECT CARD (NEW PROJECTS)	2. SEC. U	3. PROJ. NO. 6-59-10-04
4. PROJECT TITLE: Vein Ligation -- Acute Arterial Occlusion		5. REPORT DATE 31 Dec 50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP: PO-16	
8. COGNIZANT AGENCY	12. CONTRACTOR AND/OR LABORATORY	CONTRACT/W. O. NO.
9. DIRECTING AGENCY		
10. SPONSORING 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.
	15. PRIORITY / 16.	
19. Completed; this is the final report.		

20. REQUIREMENT AND/OR JUSTIFICATION

21. BRIEF OF PROJECT AND OBJECTIVE

The following is the final report on this study.

Method. Kety's radiosodium clearance method was used to evaluate calf-muscle circulation in various circumstances. A value called "k", representing the rate of disappearance of Na 24 from the site of injection, was obtained. The tests were done at room temperature under standard conditions of rest and posture./ The normal range of "k" in 46 determinations was 0.018 to 0.076, with a mean of 0.040. The mean of 11 determinations in arteriosclerosis was 0.027 with a range of 0.013 to 0.044. In 9 normal subjects, after exercise of the gastrocnemius by plantar flexion, the "k" increased from 0.033 to 0.046. Then the anterior leg muscles were exercised by dorsiflexion, the "k" of the antagonistic gastrocnemius decreased from 0.049 to 0.038 in 7 experiments./ These results indicated that the method was capable of reflecting changes in the calf-muscle circulation of man. The exercise experiments indicate that in an exercised extremity the circulation is reduced in antagonistic muscles and that blood by some mechanism is shunted toward the tissue of higher metabolic activity.

Study of Calf-Muscle Circulation in Postoperative Patients. Studies of calf-muscle circulation in postoperative patients were made to observe whether there is any circulatory change in this region which predisposes to phlebothrombosis. There was no significant difference in the mean pre- and postoperative "k's" of 45 patients undergoing major surgical procedures, indicating that operation does not adversely affect calf-muscle circulation. Individually there was such variation between the pre- and postoperative "k" that only a postoperative change greater than 0.037 would appear to be significant. This individual variation represents one of the difficulties in using the test to

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predict postoperative phlebitis. The mean "k" in 9 patients with definite postoperative phlebothrombosis was 0.045. Three patients had low "k's", and 6 had normal or high "k's". Of 4 patients studied after superficial femoral vein ligation for phlebothrombosis, 1 had a low "k" and 3 were normal. The mean "k" of 6 patients with questionable phlebothrombosis was 0.039; 1 patient in this group had a low "k" of 0.023, but his preoperative "k" of 0.015 was also low. "K's" were done on 3 patients before the onset of clinical phlebothrombosis; none was low enough to indicate the onset of phlebothrombosis. It appears, therefore, that the clearance of sodium in the presence of phlebitis is not markedly reduced and in some cases may actually be increased./ In summary, operation does not adversely affect calf-muscle circulation. The clearance of sodium from the calf muscles cannot be used for the diagnosis of postoperative phlebothrombosis.

Effects of Direct Heat and Priscoline on Calf-Muscle Circulation. In 12 normal subjects the mean "k" of the control left leg was 0.047 and of the right leg after direct heating by electric pads, 0.041. In 8 normal subjects the mean "k" of the control left leg was 0.045, and of the right leg after intravenous priscoline, 0.032. These results indicate that increasing skin blood flow with direct heat or intravenous priscoline reduces effective calf-muscle circulation.

Effects of Reflex Heat. Following application of heating pads to the trunk of 14 normal individuals, the mean "k" in the calf muscles was unchanged over previous determinations made under control conditions. At the same time there was a uniform increase of skin temperatures of the thumbs.

Effect of Common-Duct Distention on the Myocardial Circulation of Dogs. Kety's method was applied to the study of myocardial circulation in dogs. Coronary artery ligation reduced markedly the clearance of sodium from the myocardium. When intravenous sodium cyanide was used to produce anoxia, the clearance of sodium was markedly increased. These results indicated that the method was capable of reflecting changes in the coronary circulation. After the cystic duct and the distal end of the common duct were ligated, a cannula was placed within the lumen of the common duct. Na 24 Cl, .5 cc., was injected into the myocardium and a controlled clearance obtained for 45 seconds. The common duct was then rapidly distended with physiologic saline. In 8 experiments the "k" decreased in each case after common-duct distention. The mean "k" before distention was 0.683, and after distention, 0.519. The blood pressure also dropped in each case after distention. In two dogs after bilateral vagotomy in the neck no change was observed in the "k" or blood pressure after common-duct distention.

Report. "Calf Muscle Blood Flow, Pre and Postoperatively and During Various Normal and Pathologic States," Reese, Darrow, and Cullen; accepted for publication in Surgery, Gynecology, and Obstetrics," June 1951 issue.

Two other reports being prepared will be submitted.

RESEARCH AND DEVELOPMENT PROJECT CARD (NEW PROJECTS) | 2. SEC. | 3. PROJ. NO. 6-60-13-12

1. PROJECT TITLE Bacterial and Fungous Infections of the Skin | 4. | 5. REPORT DATE 31 Dec '50

6. BASIC FIELD OR SUBJECT | 7. SUB FIELD OR SUBJECT SUB GROUP: PO-16

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. / DEV. / TEST / OP EVAL

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

15. PRIORITY | 16.

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20. REQUIRMENT AND/OR JUSTIFICATION

a. No change
b. No change

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. Factors possibly related to "infections of the moist skin surfaces" and progress made toward determining these factors follow:

1. Bacterial infections. What changes in the bacterial flora occur under such conditions? How rapidly does this change occur? Answers to both these questions which should be of real value have been and are being obtained. It is becoming apparent that the fundamental changes in the bacterial flora and sensitization to such bacteria represent an important part of the mechanism of chronic and prolonged dermatoid changes which may occur.

2. Interference with sweating mechanism. What effect does prolonged moisture on the skin have in producing interference with the sweating mechanism and in producing subsequent inflammatory changes? Studies, supported jointly by this contract and a grant from the Public Health Service have shown unquestionably that moistening of the skin for 24 to 48 hours produces local blocking of the sweat ducts, with sweat retention and inflammation in many individuals. When even mildly irritant local applications are made, including that of adhesive tape, this effect is increased. Under conditions of a warm environment, or in the case of sweating of the hands and feet and emotional tension, a fairly high percentage of individuals will develop mild to severe inflammatory changes. The methods of prevention are fairly clear, although not always practical; studies are therefore being directed toward preventing this sweat-duct blockage, and finding an internal medication to reduce sweat flow without undesirable physiologic side-effects.

3. The effect of fungous infections, and how often fungous infections are concerned in processes of this sort. In this connection, a new highly-specific stain for fungi, something never available previously, has been developed. It can be used even in small laboratories, and is applicable to

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superficial and deep fungous infections. It appears that inflammatory tions on moist skin surfaces are not caused by fungous infections nearly frequently as had been supposed. Nevertheless, there has been constant loring or developing of better fungicides because there is no good one a- lable. Studies thus far indicate that the effectiveness of the fatty acid parations now in use in the armed forces is greatly overrated.

4. A considerable number of new antifungal, antibacterial, antipruritic, antiperspirant preparations have received study under controlled conditions. stant lookout is kept for new preparations which may be of value to the ed forces. Manufacturers' statements cannot always be accepted at face- lue because their studies are not ordinarily controlled, and insufficient tention is paid to potential sensitizing effects. Recently the effect of rtisone applied locally has been studied. (This work has also been support- by other sources.)

5. Studies of x-ray and Grenz-ray therapy in various inflammatory erupt- s of the skin have been continued. X-ray therapy has a highly uncertain questionable effect on such eruptions. It is felt that the installation such units in general hospitals overseas cannot be justified, except poss- ly in one hospital in a large stable Theater (if there be such). The effects Grenz-ray appear to be superior but temporary. (This study is now being pported elsewhere.)

6. The mechanisms of induced sensitization of the skin are of the great- t practical importance, and little is known about them. It is in this field hat most of the "basic" studies are being carried out. It is now apparent hat Cortisone and ACTH have only temporary palliative effects, but these may nable us to obtain more exact knowledge of the mechanisms involved. This gen- ral field is of great potential practical importance in military medicine.

7. Preliminary studies leading to the development of a truly specific imple serologic test for syphilis have been carried out, and these studies ave necessarily involved basic work in the life cycles of spirochetes. These tudies have now reached the point where they should either be expanded or dropped entirely.

Progress. Bacterial Sensitization. More bacterial antigens of various kinds have been and are being prepared, such as bacterial polysaccharides, nucleoprotein, ground whole cells, and filtrate concentrates from a variety of staphylococci, streptococci, and other bacteria from dermatologic lesions. Autogenous vaccines are also being prepared by various methods. These will be used to determine the state of sensitivity of a series of patients and normal controls and for experimental disensitization of patients. Of part- icular interest are the following groups of subjects: Children with pyogenic lesions; adults without pyogenic lesions; adults with a series of specific lesions of pyogenic or suspected pyogenic cause, including impetigo and ecthyma, folliculitis and sycosis, furunculosis and hydroadenitis, secondarily infected eczematous eruptions of all kinds, and acne. Two aspects of the problem de- serve special mention. First, tissue-culture technics are being used to deter- mine the sensitivity of buffy coat cells to bacterial antigens, as a gauge of tissue sensitivity; second, the so-called bacteriostatic antibodies in whole blood are being used to determine strain-specificity of infections. Parallel work on laboratory animals is planned. The importance of this work is clear- ly evident when it is realized upon how flimsy a base the diagnosis of bacter- ial sensitivity and desensitization therapy now rests.

Bacterial and Fungous Infections of the Skin 6-60-13-12

It is proposed to continue the survey of the normal skin flora, which is now near completion, and to continue work with the specific objective of determining the specific ecologic factors which are responsible for the type and stability of the flora on the skin and specific skin sites. This project relates to the whole question of the effect of sweating, sebum output, etc., on the bacteria of the skin. The immediate objective, now being pursued, is to determine the range of tolerance of normal skin bacteria to temperature, pH, and desiccation; and to determine their response to fatty acids, etc., as nutriment on the one hand and bacteriostatic agents on the other. Various related questions, such as the role of skin charge in the effectiveness of detergents and the relationship of keratin to bacteriostatic effect of other skin components, are being investigated simultaneously.

Knowledge of methods of prevention and treatment of fungous infections is still very incomplete. It is unquestionably related to the maintenance of a dry surface on the skin, and with prevention of disturbances of sweat physiology. Powders containing various fatty acids as antifungal agents, on which much experimental work was done during World War II, have the advantage of being non-irritating and relatively non-sensitizing. However, their in-vitro effects on fungi cannot be confirmed clinically in studies here, and furthermore these compounds are inactivated in regard to antifungal activity by 3 to 5 per cent of blood serum, and hence are probably entirely useless in vesicular or oozing phases of fungous infections. Whether the answer to fungous infections of the human skin will be through a chemical applied externally is questionable, but further efforts to find a more satisfactory antifungal agent seem indicated. In addition, it is becoming apparent that the administration of various antibodies produces marked changes in the fungous flora of the skin of man, and of the internal organs of animals (and possibly man). Studies of these effects are considered of great practical importance, and are outlined:

1. The clinical and experimental study of a wide variety of industrial antifungal agents with potential application to man is being continued (wholly supported by other sources). This program should be of considerable potential value to the armed services in their search for practical therapeutic aids for treating common skin disorders such as ringworm.

2. Fungous infections as a complication of antibiotic therapy. The widespread use of aureomycin, chloromycetin, penicillin, and terramycin as chemotherapeutic agents has been attended by an unexpected complication. The incidence of oral thrush in patients receiving these antibiotics has greatly increased. Monilial bronchitis and pneumonitis of a threatening and even fatal character have occurred. Serious mycotic infections have developed during antibiotic therapy, even with such non-virulent species as Aspergillus fumigatus, an ordinary saprophyte. The study being continued relates to the mechanism by which antibiotic therapy predisposes to fungus infection. Two possibilities are to be considered: (1) The stimulating metabolic effect of the antibiotic on the fungus, thereby enhancing its growth; (2) The elimination of bacterial competitors which would normally hold the fungi in check. It has been shown that the stimulatory effect of aureomycin (published by others) on the growth of Candida albicans is factitial. It depends on the presence of the phosphate ion which is an incidental component of the vehicle of the aureomycin capsule. As a result of work here, the manufacturers of aureomycin have already eliminated phosphates from their preparation.

Experiments are in progress to measure the possible stimulating effect

rified aureomycin, penicillin, chloromycetin, and terramycin on fungi under trolled conditions in vitro. It is likely that the elimination of bacterial petition is more important. A routine survey of the fungal and bacterial ora of the mouth and rectum of individuals in the University Hospital receiving any one or a combination of these antibiotics is being undertaken. Already it is clear that large numbers of fungi may be isolated from a great jority of such persons. This contrasts strikingly with the findings in the ntrol group.

The effect of the antibiotic therapy on the fungous flora of experimental animals and their susceptibility to mycotic infection will be studied.

3. The most recent experiments dealing with the effect of aureomycin on moniliasis in mice have produced results which make it necessary to reconsider the manner in which the phenomenon under discussion is brought about. It has been found, for instance, that when a suspension of Candida albicans is made up in a solution containing aureomycin, the intraperitoneal injection of this suspension results in widespread peritoneal lesions. Practically no lesions occur when the suspension is made up in saline solution. Furthermore, if mice infected intraperitoneally with C. albicans are given parenteral injections of aureomycin this, too, produces disseminated lesions. It is quite obvious that this phenomenon cannot be explained on the basis of the elimination of bacterial competitors since the peritoneal cavity may ordinarily be considered sterile.

The phenomenon under discussion is undoubtly not peculiar to aureomycin,

the skin-reactions and eliminates the interfering inflammatory process resulting from other methods of hair-removal (plucking, barium sulfide, etc.)
f. Future. Studies will be continued as indicated under Progress.
g. Reports. "Anhidrosis, An Etiologic Interpretation," Shelley, Horvath, and Pillsbury, Med., 29:195-224, 1950.

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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.
		5. 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.
9. DIRECTING AGENCY		
10. REQUESTING AGENCY	13. RELATED PROJECTS	17. EST. COMPL. DATES
11. PARTICIPATION AND/OR COORDINATION		RES.
		DEV.
		TEST
	14. DATE APPROVED	OP EVAL
	15. PRIORITY 16.	FY 18. FISCAL EST'S.
19.		

20. REQUIREMENT AND/OR JUSTIFICATION

21. BRIEF OF PROJECT AND OBJECTIVE

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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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, 165:640, 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).

Dr. Roy H. Turner
Tulane University

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PROGRESS REPORT (C)

RESEARCH AND DEVELOPMENT ~~PROJECT CARD (NEW PROJECTS)~~	2. SEC. U	3. PROJ. NO. 6-64-01-04
1. PROJECT TITLE Serum Proteins in Liver Disease		4.
		5. REPORT DATE 31 Dec 50
6. BASIC FIELD OR SUBJECT	7. SUB FIELD OR SUBJECT SUB GROUP P0-16	
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. DEV. TEST. OP. EVAL.
11. PARTICIPATION AND/OR COORDINATION	14. DATE APPROVED	FY 18. FISCAL EST'S.
	15. PRIORITY 16.	
19.		

20. REQUIREMENT AND/OR JUSTIFICATION

a. No change.
b. No change.

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change.

e. Background. In a study of the mechanism of the thymol turbidity test an unsuspected globulinemia existing in certain clinical disorders was observed./ Analyses were completed of experiments in which samples of normal and pathologic sera were centrifuged at 800 rps for four hours. Plastic tubes were used; after being quick-frozen each tube was cut at 10 levels to permit physical and chemical analyses, with particular reference to the distribution of protein./ Two briefer experiments were done with a lower rate of centrifugation especially to catch the rapidly-sedimenting beta-globulin which has sedimentation constant of 20 S. The experiments suggest that this beta-globulin may influence the thymol turbidity test./ Ultracentrifugal studies confirmed previous reports that the serum bilirubin and injected bromsulfalein are largely bound to the albumin fraction. Entirely satisfactory electrophoretic patterns were obtained./ Serum Proteins and Lipids in Patients with Liver Disease. After four hours' exposure in a centrifugal field of 200,000 G., certain proteins sediment differentially. Separation is accomplished as described above; a new technique requiring only one slicing and analysis of two specimens increased the number of determinations for study./ In liver disease, lipoprotein complexes which float higher in the tube at lower specific gravities than those of normal serum appeared to be present; and a phosphorus containing lipid, which in normal serum sinks to the bottom, is decreased in hepatitis./ The x-protein of McFarlane was studied. Preliminary experiments showed that electrophoretically it consists of albumin and beta-globulin; chemically it contains a large part of the serum cholesterol and phospholipid of normals; and ultramicroscopically it consists of or at least is associated with large numbers of ultramicroscopic spheres. It was planned to correlate the changes found in "floatable" lipoproteins in liver disease with x-protein concentrations. Preliminary observations suggested that in liver

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disease the amount of lipid occurring as x-protein is increased in comparison with the normal.///It was established that, in the main, fat and lipid compounds are distributed in the column of centrifugate according to their density. The heavier proteins sedimenting create a density gradient and the lipid compounds tend to find their own density-level./ Although there is a high degree of parallelism in the distribution of cholesterol and lipid phosphorus in the upper half of the tube, there is little similarity in distribution in the lower half. This shows clearly that there are phospholipid compounds which are not associated with cholesterol./ When the distribution in the column of centrifugate of albumin, globulins, neutral fat, cholesterol esters, free cholesterol, and phospholipids was determined in serum of normal persons, the results fell into consistent patterns./ The sera of patients with acute hepatitis frequently show an excessive quantity of low-density fat lipid compound in the density zone 1.005-1.015. This material may be related to a diminished rate of removal from the blood by the liver.

Progress. Work has been principally along two lines: detailed analyses of data preparatory to publication, and initiation of study by the investigators' procedure of the physiology of lipid phosphorus with P^{32}./ The distribution in the column of centrifugate of normal serum of total protein nitrogen, specific gravity, albumin, globulins (as a group), free cholesterol, cholesterol esters, lipid phosphorus, neutral fat, and total lipids has been intensely studied statistically, and mean curves of distribution established with standard deviations at each of the 10 levels. These analyses show clearly that the distribution of lipids in hepatitis serum deviates from the normal pattern in a highly significant fashion./ Additional procedures have been used in providing a more complete description of the low-density lipids found in increased concentration in hepatitis serum./ A better understanding has been reached of the mechanisms of sedimentation and flotation underlying the distribution of proteins and lipids. It is hoped that this will lead to a more satisfactory mathematical expression of the factors determining the distribution of both substances./ Study of the interrelationships between the various lipid constituents at certain levels of the column of centrifugate shows that the lipid composition of the centrifugate at these levels may be described with small error by mathematical formulae derived in this project./ Experiments with radioactive phosphorus have been carried out on three normal subjects and one case of polycythemia which show that the rate of labeling of lipid phosphorus is especially rapid at some levels in the column of centrifugate and occurs at a low rate in other levels. These studies encourage the belief that this method separates lipids into components, some of which have highly specific functions. Theories have been formulated as subjects of future experiments which relate these components to the function of the liver.

f. Future. Studies will be continued as indicated.

g. Reports. The following manuscripts are being prepared under title, "Study of Serum Proteins and Lipids with the Aid of the Quantity Ultracentrifuge:" I. Procedure and Principal Features of Distribution of Protein and Lipids in the Centrifugate of Undiluted Normal Serum; II. The Mechanisms of Redistribution of Proteins and Lipids of Undiluted Serum; III. The Protein and Lipid Composition of the Ultracentrifugate of Normal Individuals; IV. The Serum Lipids in Acute Hepatitis; V. The Organization of the Cream Layer of Serum of Normal Individuals in a Post Absorptive State, and after a Lipid-Rich Meal, and from Patients with Hepatitis and Miscellaneous Disease States; VI. Organization of Lipids other than Cream Layer of Serum of Normal Individuals in a Post Absorptive State; VII. Differential Tagging of Lipid Phosphorus with P^{32}.

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Dr. Burch
Tulane University

Progress Report (C)

RESEARCH AND DEVELOPMENT PROJECT CARD (NEW PROJECTS) | 2. SEC. U | 3. PROJ. NO. 6-64-12-12

1. PROJECT TITLE: Peripheral Blood Vessels | 5. REPORT DATE 31 Dec 50

6. BASIC FIELD OR SUBJECT | 7. SUB FIELD OF SUBJECT SUB GROUP: PO-11

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. / DEV. / TEST / OP SVAI

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

15. PRIORITY | 16.

19.

20. REQUIREMENT AND/OR JUSTIFICATION

a. No change

b. No change

21. BRIEF OF PROJECT AND OBJECTIVE

a. thru d. No change

e. Background. Detailed comments on results of observations have not been made until they have reached the stage of publication. This avoids misinterpretation or erroneous reports of date, most of which are not clear until experiments have been completed. In the report of December 1949 summaries were given of articles with the following titles: "The Biologic Decay Periods of Sodium in Normal Men, in Patients with Congestive Heart Failure, and In Patients with the Nephrotic Syndrome as Determined by Na^{22} as the Tracer;" "Theoretic Considerations of Biologic Decay Rates of Isotopes;" "The Behavior of the Venous Pressure During Various Stages of Chronic Congestive Heart Failure;" Environmental Conditions which Initiate Sweating in Resting Man;" and "Concentration-Time Course in the Plasma of Man of Radiomercury Introduced as a Mercurial Diuretic."

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 was observed by the use of radio-isotopes 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

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determine the biologic decay periods (urinary excretion rates, decline in serum concentration, and recovery rates) and chloride space. Similar studies were 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 were being studied.

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

As time permitted, studies were being done 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 derived in the future.

Studies with the vectorcardiogram were progressing satisfactorily. The normal spatial vectorcardiogram was being observed because of its extreme variability. The patterns for left ventricular hypertrophy and right and left ventricular bundle branch block were studied sufficiently to define them generally. These data indicated that the more or less empiric criteria for their electrocardiographic identification needed modification. It was hoped that additional studies would yield a more precise definition.

Mr. Cronvich had nearly completed a movable unit which would allow recordings to be made in the wards of a hospital as well as in the laboratory. Various types of electric interference, which had offered the greatest difficulty, delayed completion of the apparatus. Certain standardization factors had been defined for use in spatial vectorcardiography. Reports of these and other aspects of the problem were in press or in preparation for publication.

In addition to these main programs, several young persons were trained in various aspects of cardiology to which the research program had contributed significantly. For example, Dr. F. J. Kelly, 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, which was being prepared for publication, contributed to a better understanding of the exchange rates and related phenomena of electrolytes across the walls of blood vessels.

Other studies concerned 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.

Progress. The following is a summary of an article entitled "The Spatial Vectorcardiogram in Right Bundle Branch Block," by Abildskov et al.

The QRS $\vec{sE}$-loops of twenty-four subjects with electrocardiographic evidence of right bundle branch block were described. The records were divided into 3 groups, on the basis of clinical and roentgenographic evidence of ventricular hypertrophy.

The QRS $\vec{sE}$-loops of the subjects with left ventricular hypertrophy and right bundle branch block exhibited considerable similarity, suggesting that it may be possible to recognize this combination of lesions by spatial vectorcardiograms.

Records obtained from small groups of subjects with isolated right ventricular hypertrophy and right bundle branch block and with right bundle branch block not associated with cardiac enlargement seemed to have some distinctive

features and indicate the desirability of further study of the spatial vectorcardiogram in these states.

"The Response of Patients with Congestive Heart Failure to Acute Elevation of Temperature and Humidity," by Dr. G. S. Berenson. Observations were made to investigate the intolerance of patients with cardiac disease and congestive heart failure to stress of a hot and humid environment.

By clinical methods, including measurements of blood pressure, cardiac and respiratory rates, and rectal and skin temperatures, 13 patients in various stages of congestive failure were studied. Comparisons were made with 13 control subjects. In 3 experiments, 1 control subject and 1 patient with congestive failure were studied simultaneously. Following observations in comfortable atmospheric conditions, response to a hot and humid atmosphere (40 ± 2° C, 85% RH) for periods of 40 to 114 minutes was noted.

The heated surroundings precipitated acute attacks of "left ventricular failure" (cardiac asthma) characterized by severe dyspnea, orthopnea, and pulmonary rales, associated with apprehension in 5 subjects with cardiac disease. Gallop rhythm developed or was accentuated in 9 patients. Ability to withstand stress of a hot, humid environment was definitely less in subjects with congestive heart failure. This group exhibited primarily cardiovascular and pulmonary intolerance, whereas many central nervous system disturbances developed in the controls, who were able to endure sufficiently prolonged exposures to the environment. The cardiovascular reactions in control subjects tended to be more uniform and were characterized especially by elevation of pulse pressure.

These experiments indicate that patients with certain types of cardiac disease do not tolerate well a hot and humid atmosphere and also suggest the need for control environmental atmosphere during therapy.

f. Future. Since the present contract was negotiated under the War Powers Act it will be necessary to draw up another contract for future work. That new proposal will be referred in the usual manner to the National Research Council for evaluation.

g. Reports. As shown under Progress.

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Army Field Forces Bd 2, Fort Knox
Army Field Forces Bd 3, Fort Benning
Army Field Forces Bd 4, Fort Bliss
Office, Chief, Army Field Forces, Ft. Monroe, Va.
AGO, Personnel Research & Procedures Br, Personnel Research Section
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