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May 19, 1953

The Chairman Medical Research and Development Board
Office of the Surgeon General
Department of the Army
Room 2151, Main Navy Building
Washington 25, D. C.

Dear Colonel Wood:

Enclosed please find the quarterly progress report which was due May 10, 1953. The delay was incurred because it was thought expedient to complete the present series of experiments, so that a digest of the results to date might be available to you. Details of our experiments will be furnished in our final report.

Very truly yours,

Peter F. Salisbury
Peter F. Salisbury, M.D., Ph.D.
Principal Investigator

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TO: Chairman, Medical Research and Development Board
Office of the Surgeon General
Department of the Army
Room 2151, Main Navy Building
Washington 25, D. C.

SUBJECT: PROGRESS REPORT

Reporting Period: 1 February 1953 to 30 April 1953

Principal Investigator: Peter F. Salisbury, M.D., Ph.D.

Institute for Medical Research
Cedars of Lebanon Hospital
4751 Fountain Avenue
Los Angeles 29, California

Title of Study: Analysis of the Indirect Effect
of Radiation

Contract No.: DA-49-007-MD-263

1. ABSTRACT: During the period covered by this report, one control series and one experimental series were processed. The control series comprised twenty six dogs which were given one dose of 450 r total body irradiation but were otherwise untreated. Six animals survived in this series (22% survival). The experimental series comprised twenty three dogs which received the same treatment as the controls, but which also were treated by means of cross transfusion with a normal donor dog. Of the twenty three irradiated and cross transfused dogs thirteen survived (57% survival). The difference between the control group and the cross transfused group would seem to be statistically significant.

It is worthy of note that cross transfusion was performed with a method which differed from the methods used in earlier experiments inasmuch as the blood transferred between the two animals was deliberately traumatized. As a result of our experience it is postulated that the factor which causes protection against ionizing radiation is confined within certain blood cells, which must be injured in order to permit its liberation into the liquid phase.

2. PROGRESS: (1) Control studies: The technique of selection of animals, preparation for the experiments and irradiation has been described before (Progress Report 29 July 1952). All dogs used in this study were treated as before. During our experiments late in 1952 we gained the impression that

a change in the mortality ratio had taken place. Earlier control series from this laboratory had exhibited a lethality of 95% with our irradiation technique. In the present series twenty six dogs were irradiated and followed in the usual manner; twenty of the control dogs died (78% mortality). Twenty two of the control series were irradiated consecutively, and not as partners in a simultaneous irradiation with an experimental dog. The physical constants of the irradiation were checked carefully and found unvaried. The cages were turned every ten minutes during the irradiation (as before) and all other precautions were taken to prevent exposure of the animals to stress after the irradiation procedure. The observed mortality of 78% agrees with similar studies elsewhere, even though it is less than the 95% mortality due to 450 r observed in our earlier control series. It is felt that changes in LD may occur as a result of a change of the intestinal flora of the irradiated dogs. Most of the deaths occurring in dogs irradiated with 450 r are due to infections which start as the result of invasion of the blood stream by intestinal bacteria. The pathogenicity of the intestinal flora may change for unexplained reasons, especially when heterogeneous populations of dogs are used, and when such dogs are obtained from city pounds. It is felt that the significance of the control series is not impaired by the fact that controls and experimental animals were irradiated and treated successively and not simultaneously.

Unless statistically significant groups are used, the simultaneous performance of the experiments and controls is not in itself an additional safeguard, which enhances the validity of these observations. The nature of this work is such that it is physically impossible to perform more than a few experiments at one time. Therefore, when one irradiates two controls and two experimentals simultaneously, the series of two animals each do not constitute a valid experiment for a particular day, and even with simultaneous irradiation of control and test animals one is then forced to rely on successive, and not simultaneous series, in order to obtain reliable results. In spite of our efforts to standardize our dogs as to size, immunity, sex, age and period of observation, the resulting product is still heterogeneous as to general characteristics, intestinal flora and possibly other factors. Control dogs were followed with serial blood studies, clinical observation and necropsy.

(2) Experimental studies: Dogs were selected, prepared, irradiated and treated as described before (Progress Report 29 July 1952) and in a manner identical with the control dogs. Within a period of three hours after the end of irradiation they were then cross transfused with healthy male donors conforming with the technique described earlier, but with one significant difference. The dogs received amounts of blood from the donor corresponding to 1/8th of the body weight of

the experimental animal. During the transfer of one half of this predetermined volume, the intake opening of the cross transfusion machine #12 was occluded with a clamp whenever 16 cc had flown through it, so that the continued sucking action of the pump created a partial vacuum, while the continuing squeezing of the rubber pumping chamber by the cam-driven directional valves provided a degree of injury to some of the formed elements of the blood. It was found that ten of the twenty three irradiated and cross transfused animals died (mortality rate 43%). Furthermore, it was very clear that the picture of the dead cross transfused animals at necropsy was different from the picture presented by the controls. As compared with the controls, there was a conspicuous reduction of hemorrhagic phenomena in those of the treated animals which came to necropsy. Histological studies are in progress at this time.

Our cross dialysis equipment has been perfected and functions well as a cross dialysis machine and also as an artificial kidney. However, attempts to make an all-plastic cross dialysis machine have not been successful. The die from which the plastic pads were to be made was slightly bent and the resulting pads therefore are not suitable.

(3) Interpretation: It is recalled that in an earlier report it was felt that conclusive evidence was at hand which proved the existence of a protective effect of early cross

transfusion after total body irradiation. The cross transfusion procedures which formed the basis of this earlier report were performed with cross transfusion devices "#11" and "#12". It was recognized that cross transfusion pumps "#11" and "#12" had certain drawbacks, notably their slight destructive effect of leucocytes and platelets, which was demonstrated by blood counts. For this reason, it was attempted to improve the cross transfusion technique in such a way as to render it less traumatic to the blood cells. This was done by manipulating the catheters so as to avoid the occasional formation of a partial vacuum in the blood circuit, and also by designing and building blood pump "#13", which virtually eliminates damage to the blood. As reported in earlier communications, these "atraumatic" cross transfusions did not result in reduced morbidity or mortality of cross transfused animals. It was therefore decided to imitate the destructive effect of the earlier equipment and deliberately traumatize the transferred blood, with the results reported above. The experience reported here confirms other authors (Lawrence, Valentine & Dowdy, Leonards and Heisler) who found that "atraumatic" reciprocal blood transfer does not affect the morbidity or mortality of total body irradiation disease. It is felt that the sum total of the experience in this laboratory goes far to demonstrate the existence of the "Cross Transfusion Effect" after total body irradiation. The above results suggest the

following hypothesis:

There is a substance which is necessary for the survival of bone marrow stem cells; this substance is destroyed by irradiation; it is contained within certain formed elements of the blood (and possibly elsewhere), is released into the milieu interieur ~~ff~~ by injury to or destruction of its carrier cell; it should be possible to concentrate and define this material by differential centrifugation of blood and injections of treated cellular blood fractions into irradiated animals.

3. FUTURE: In conformity with the above working hypothesis, experiments are in progress to find the cell type which is the carrier of the protective substance. Immediately after irradiation, dogs will be injected with various fractions of dog blood; such fractions will be prepared by exsanguinating donor dogs, centrifugation of their heparinized blood, separation of the various cell fractions, applying controlled degrees of injury to the cells by various methods (osmotic, temperature variation). If a protective substance is obtained an attempt will be made to characterize it by dialysis, differential centrifugation and other appropriate methods.

Pathological material of the preceding series will be examined in detail and a final report will be prepared.

4. REFERENCES and MANUSCRIPTS: None.

Respectfully submitted,

PKS

Peter F. Salisbury, M.D., Ph.D.

Principal Investigator