THE UNIVERSITY OF ROCHESTER
ATOMIC ENERGY PROJECT

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TENTATIVE PROGRAM FOR STUDIES OF CLINICAL TREATMENT OF RADIATION AT THE UNIVERSITY OF ROCHESTER ATOMIC ENERGY PROJECT

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FOREWORD

A research program for the evaluation of various therapeutic techniques in the clinical treatment of acute whole body radiation is being formulated. As a preliminary step, an analysis of pertinent information of related nature has been made as a prerequisite to the study of this problem. This indicates that except for certain specific information concerning the relation of infection to the radiation syndrome, very little is known concerning the respective values of most of the supposedly beneficial agents, including blood. Most of these have been given unwarranted promise in statements concerning the treatment of the radiation syndrome following lethal amounts of ionizing irradiation.

The first experiments will attempt to incorporate the maximum effect which would be obtained if all of the most discussed agents were used in a statistically significant number of animals. The projected specific treatment to be used in the first experiment will include antibiotics, blood, plus attention to nutritional aspects of the animal. As far as is possible good nursing care will be given which will include feeding and watering of sick animals, attention to skin lacerations, bruises and the like. In order to permit adequate nursing care a schedule of the experiment has been devised so that no more than 12 very sick animals will be expected at any one time.

In preparation for future experiments a limited number of observations will be carried out on each specific experiment. For example, in this original protocol, objective measurements of water and electrolyte balances will be determined. In this manner much valuable information can be obtained which will not condition the experiment in progress but will aid immeasurably in planning future studies.

A group of pilot experiments is included. Many of these have been partially completed, others are in progress. As data of value are obtained

they will be appended in supplements to this report.

In brief, the planning of these experiments has been carried out with the following pertinent factors in mind: all forms of treatment are those routinely used in clinical medicine; time consuming techniques will be avoided as much as possible; oral medication will be administered as far as is practical; medication to be used in general will not be those in short supply; medications will be those which can be stock piled in a satisfactory fashion. In general, the methods will be those readily adaptable to the treatment of large numbers of casualties on an emergency basis.

ANALYSIS OF CURRENT INFORMATION ON RADIATION THERAPY

Agent	Effect	Presumed Action	Source
Antibiotics	Delayed onset Morbidity (sickness) Reduction Mortality	Antibacterial Antitoxic	Local, Miller Local, Gyorgy
Blood	Anemia Correction Nutritional	Replacement of Loss	General
Coagulants Protamine Tol. Blue	Correction of ? Hyperheparinemia (if exists) Shortening of clotting ? Prothrombin relationship	Neutralization of Heparin Correction of Defect	Allen
Rutin	Capillary Permeability	Improve capillary integrity	Rekers
Fluid Therapy	Replacement	Non-specific	General

OTHER LESS WELL ESTABLISHED INFORMATION

Nutrition

Diet

Mechanical Factors
Absorption Factors
Specific Metabolic Factors

Parenteral Feeding

Specific metabolic and fluid balance

Metabolism

Endocrine - (general) - thyroid, androgens, estrogens

Adrenal - whole extract
cortisone
desoxycorticosterone

Pituitary - ACTH

Sulfhydryl compounds - cysteine, methionine, glutathione

Anti folic acid antagonists - citrovorum factors

Abnormal or reduced detoxification of metabolites

"Splenic Factors" - activities following splenic shielding

Exogenous Factors

Physical agents - heat and cold, chilling, etc.
Bacterial Infection
Bacterial Toxins

Adjuncts - possibly of value in convalescence

Vitamin B_{12}
Liver Extract
Iron
Folic acid
Vitamins including "Vitamin P" substances
Intravenous alimentation, i.e. alcohol 7%, etc.

POSITIVE OBSERVATIONS IN THERAPY OF RADIATION DISEASE

1. Antibiotics - delayed morbidity
   delayed mortality
   improvement in total mortality

2. Blood - Replacement of blood lost through hemorrhage.
   No permanent gain - no definite effect on bleeding areas.
   May be detrimental if hemorrhage is marked (lose blood as rapidly as given).

3. Protective Effects (pre-radiation)

   Bone marrow stimulation
   Anoxia
   Local shielding (splenic factors, etc.)
   head shielding
   Physical factors (chilling, etc.)
   Sulfhydryl compounds

TREATMENT SCHEDULE

1. Diet - (Control and Experimental Periods)
   Smooth plus added carbohydrate (glucose, fructose, lactose)
   Special fluid diet enriched with skim milk powder available for animals unable to take solid food
   Force feeding to be used in animals unable to eat.

   No parenteral feeding in first experiment.

2. Blood - Bank blood at least 10 days old prepared from typed animals and stored in Baxter vacuum containers. To be cross-matched before use.
   Maintain hemoglobin at 80% of control values.
   Given by drip. Sedation (to be selected) to be used if necessary.

Time of use will be after the 14 day period in which hemorrhage usually appears.

3. Antibiotics - Aureomycin or Terramycin to be used.
Dosage to be regulated by blood level.
Start 48 hours post irradiation.
Same drug to be used throughout experiment.
Development of resistant bacteria to be checked.

PROPOSED LABORATORY OBSERVATIONS

Control Period (2 weeks)

Blood - Hematology complete, three times a week
- Chemistry - Total Protein, Albumin, Globulin, Na, K, Cl, CO_2
- NPN, glucose once a week
- Blood Cultures - two to three times a week.

Urine - Routine uninalysis two times a week.
- Na, K, Cl, Protein on 24 hour urine (metabolism cages)

Intake - (all)

Output (partial groups)

Food consumption

Temperature

Pulse - if indicated

Weight

Note: During first experiment observations on fluid balance will be made by study of excretion of electrolytes in 24 hour urine specimens. No attempt at extensive evaluation of blood changes will be made because of excessive amount of blood required for such study. In each experiment certain observations of this type can be made, but should only include those which will not influence the experiment.

Experimental Period

Hematology - complete two to three times a week.

Chemistry - spaced observations of certain test indications for which are reflected in urinary changes or in clinical observations.

Urine - routine urinalysis three times weekly.
Na, K, Cl and ? protein on 24 hour urine (metabolism cages).
Could do occasional Ca, P. for balance if indicated.

Bacteriology - blood cultures three times weekly and on dying or sick animals
- stool for resistant organisms

Intake

Output

Food Consumption

Temperature

Pulse

Weight

Special - blood levels for antibiotic - three times weekly.

- protamine titration for heparin - blood
- urine

SCHEDULE OF EXPERIMENT

Number of Animals Required: It is shown by tables calculated by Dr. Lee Crump that if an actual reduction in mortality of 20% from LD/90 to LD/70 is attained 100 dogs, 50 experimental and 50 controls, will have 82% probability of establishing this fact within the arbitrary limits of 5% significance. The probability of detecting a reduction from LD/80 to LD/60 is 71%. It appears that 100 dogs may be necessary for a single trial.

Plan of Experiment: Twelve experimental and twelve control animals is the largest group that can be followed in the acute stage at one time. New groups can be irradiated at 2 week intervals. Therefore, the experiment can be run as in the following table, each group of animals being irradiated at the beginning of its first experimental period of 2 weeks.

Animals	0-2	2-4	4-6	6-8	8-10	10-12	12-14
24 dogs	Control	Experimental	Experimental	Observation			
24 dogs		Control	Experimental	Experimental			
24 dogs			Control	Experimental	Experimental		
24 dogs				Control	Experimental	Experimental	

The experiment will be continued to 4 groups (96 animals) if it appears that 20% or less reduction in mortality is to be achieved. It will be stopped at 3 groups or less if reduction in mortality promises to be sufficiently great to make the more limited experiment significant. If 96 animals do not demonstrate that the treatment reduces mortality by 20% or more the number will not be increased because trial of new treatments is probably more profitable than getting accurate statistics on a procedure which has been shown to be rather ineffective. The choice of this 20% limit is of course arbitrary. It is based on the suggestion from other work that at least 20% decrease in mortality is feasible and the expectation that at least this decrease should be achievable.

Dosage Level: Dosage approximating LD/80 or LD/90 will be used. The reason for studying the dosage region of high mortality rather than low (the LD/50 region for example) is that almost certainly a treatment effective at high dosage will be even more effective at low dosage whereas a treatment effective at low dosage may be of very little value at high dosage.

PILOT EXPERIMENTS

1. Change of antibiotics after resistance develops.

2. Delay of administration to a) specified period
   b) development of symptoms

3. Reduced dosage pilot experiment.

4. Blood transfusion with cross-matched, typed blood.

5. Controlled protamine or toluidine blue experiment.

6. Adrenal Factors - (ACTH in delay or recovery period
   Cortisone urinary steroid measurement.

7. Controlled Rutin experiment.

Technical Information Desirable

Comparative depth dose measurement 250 KV and 1 MEV machine -
LD/50 and LD/80-90 on comparable group of animals - 1 MEV exposure.
Exposure monitoring - film badge or integron - Mr. Mermagen.

Facilities Necessary

Metabolism cages for sick animals
Air conditioning of exposure rooms. 1 MEV room
250 KV room