



HEADQUARTERS
DEPARTMENT OF THE ARMY
OFFICE OF THE ADJUTANT GENERAL
WASHINGTON 25, D. C.

ARM1.940805.149

20 August 1959

IN REPLY REFER TO
AGAM-P (M) 337 (5 Aug 59) CRD/P

SUBJECT: Proceedings of Army Science Conference, 1959

TO: See Distribution

1. Inclosed for your information and use is Volume One of the "Proceedings of Army Science Conference, 1959," which is comprised of the unclassified papers which were read at the conference.

2. Volumes Two and Three of the proceedings will be distributed in the near future.

By Order of Wilber M. Brucker, Secretary of the Army:

1 Incl
Volume One, Proceedings of
Army Science Conference, 1959

R. V. LEE
Major General, USA
The Adjutant General

DISTRIBUTION:

Director of Research and Development
Chief of Staff, US Army
Deputy Chief of Staff for Logistics
Deputy Chief of Staff for Military Operations
Assistant Chief of Staff for Intelligence
Chief of Research and Development
The Adjutant General
ATTN: Chief, Personnel, Research and
Procedures Division
Heads of Technical Staff
Commanding Generals
US Continental Army Command
Army Ordnance Missile Command
US Army Chemical Corps Research and
Development Command
Ordnance Tank Automotive Command
Quartermaster Research and Engineering Command
US Army Engineers Research and Development
Laboratories
Aberdeen Proving Ground
White Sands Proving Ground
US Army Electronic Proving Ground
Frankford Arsenal

(Continued on page 2)

18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62A1582
Box #: 44
File: 337 (West Point) N

ARMY RESEARCH OFFICE

P R O C E E D I N G S
OF THE
1959 ARMY SCIENCE CONFERENCE
UNITED STATES MILITARY ACADEMY, WEST POINT, N. Y.
24-26 JUNE 1959

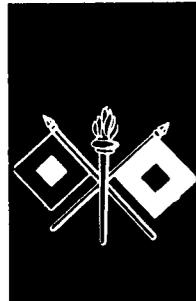
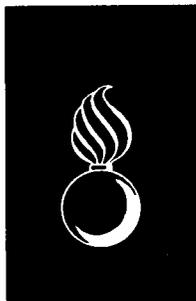
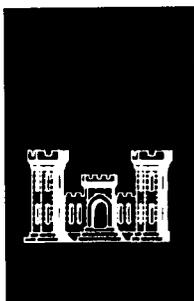
V O L U M E I
(Principal Authors "A" thru "J")



OFFICE OF THE CHIEF OF RESEARCH AND DEVELOPMENT



DEPARTMENT OF THE ARMY
Washington 25, D.C.



18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62 A 1582
Box #: 44
File: 337 (West Point) U

PROPHYLAXIS AGAINST ACUTE RADIATION INJURY

M. P. DACQUISTO, D. P. JACOBUS, and J. B. HARTGERING
DIVISION OF NUCLEAR MEDICINE & CHEMISTRY, WRAIR, WRAMC
WASHINGTON 12, D. C.

In any estimation of the medical requirements necessary to support military forces in future operations the new casualty category of radiation sickness occupies an important position. The increasing use of all types of nuclear energy by the Armed Forces and even the recently publicized radiation hazards of space contribute to the acute radiation problem. Current methods of therapy for acute radiation sickness are of limited value and are in no sense prophylactic. That is, they are useful only after the individual has been exposed and will contribute little to lessening the burden of radiation casualties on the medical services.

The ideal solution to the problem is to prevent the occurrence of the syndrome or at least mitigate the symptomatology and shorten the period of hospitalization. Such a program; if practical, would lead to many benefits, not only to the medical services charged with maintenance of health but also to the individual soldier whose morale certainly will be enhanced.

What are the essential parts of such a program?

1. A method to prevent or lessen the acute effects of whole body radiation by administration before the exposure must be available.

2. This method must be safe when administered, whether in a single dose or repeatedly. The route of administration must be simple, such as tablets to be taken by mouth when the risk of exposure dictates.

18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62 A 1582
Box #: 44
File: 337 (West Point) N

3. The protective agent utilized must not interfere with the ability of the individual to carry on his duties as the risk of exposure may be chronic; yet the individual must pursue his normal duties all through this period.

4. The period of protection afforded should be long lasting so that it need not be repeated at too frequent intervals. The best treatment schedule would be once daily or less.

5. The method utilized should be synergistic or additive, at least not antagonistic, to other forms of management which might be useful after the exposure.

The principles just mentioned are similar to those of the anti-malarial program developed and used by the Armed Forces so successfully in the recent past. The major difference is that now the hazard is exposure to whole body radiation rather than malaria.

Successful accomplishment of such a program will reap obvious advantages. Its impact not only in nuclear war but in clinical medicine will be far-reaching. Even the problem of space travel with the radiation hazards present may be benefited. If space travellers can be protected by a few pounds of a drug rather than hundreds of pounds of metal shielding with the consequent cost in design and fuel, this research effort will have paid for itself many times over.

The ideal solution outlined can be pursued today in its major aspects with certain experimental animals. In an appropriate laboratory animal, such as the mouse, all of the five parts of the program listed may be achieved in whole or in part. Certain drugs may be given by mouth to the mouse which will protect it against a 100% lethal dose of radiation for periods as long as six hours. These drugs are relatively safe and may be repeated several times without permanent damage. Finally, the combination of protection before exposure with other methods of treatment utilized after exposure is at least additive. In this regard we are much ahead of the anti-malarial program as it was in the early days of World War II, at which time the need for an anti-malarial drug was most urgent.

The most important part of the program, a method to prevent or lessen the acute effects of whole body radiation, is available. A number of chemical agents have been found to be of value since this approach was first proposed and used by Barron in 1949 (1) and others in the next few years (2) (3) (4) (5). The most effective of these agents contain free or potentially free sulfhydryl groups, along with an amino group. They are relatively simple compounds. (See Table I) In general, it may be said that the most effective of these compounds will reduce the acute biological effects of any dose of radiation by about 50% (6) (7) (8). They

18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army

Accession #: 62 A 1582
Box #: 44
File: 337 (West Point) U

probably also accelerate recovery from injury when given before exposure.

There are a number of theories as to the mechanism of action of such compounds (1) (9) (10) (11) (12). Until very recently the cornerstone of all theories was that the compound had to be present in the body during the exposure. For practical purposes the compound has to be given before the exposure. But even this now has been questioned, at least as far as one species of hibernating animals is concerned (13). However, these conflicting opinions need not concern us at this time. Undoubtedly, knowledge of the mechanism of action will lead to better agents, and this will make the program outlined even more valuable, without detracting from its present merit.

In reviewing the experimental data of the past years in this area there appeared to be only one major problem that prevented the successful application of this procedure to man. The only laboratory animal to which a large enough dose of any single protective compound can be given without death is the rodent. Attempts to give equivalent doses to other animals were unsuccessful (14) (15) (16). The experiments were done with humans and the amount tolerated was discouragingly small (17) (18), something less than 20% of the dose required to protect rodents against a 100% lethal dose of radiation.

At the Walter Reed Institute of Research it was felt that the toxicity problem could be solved in one of several ways. The immediate solution was by means of a combination of known effective drugs, none at a toxic level but the total amount being additive in protective effect but not toxic effect. Such an approach had been reported by others to be effective in rodents (19) (20). In an experiment reported recently by Jacobus from Walter Reed it was shown for the first time that dogs could tolerate one-half of the known protective level (in rodents) of each of two agents, cysteine and methylethylamine. Such treated dogs also survived a dose of radiation, 700 or 775 roentgens, that was uniformly fatal for non-treated dogs by the 15th post-exposure day (21). This experiment proved that protection before exposure was feasible even in large animals provided a satisfactory drug level could be administered. Such a result in the dog has never before been demonstrated. Laboratory study of these dogs as well as daily observation showed conclusively that they were never as ill as the dose of radiation delivered would suggest. The control dogs did exhibit the typical findings one would expect from such radiation doses. Further refinement of this approach is being pursued at the Walter Reed Institute of Research and indications are that the toxicity can be even further reduced. A long-term solution to the problem of toxicity does not appear to be the combination of now known agents with additive protective effects but not additive toxicity. However, it is planned to pursue

18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62A 1582
Box #: 44
File: 337 (West Point) N

this type of solution vigorously with the hope that a satisfactory procedure for certain situations will be developed in the relatively near future. For lasting benefit, it appears that entirely new agents, not now known or available should be developed.

We have decided to make a major effort in this area as it is our belief that the agents now known to be of value can and should be modified structurally to eliminate or reduce toxicity and possibly enhance their protective value. Already there is much known as far as chemical structure, protective effect and toxicity is concerned. By this same approach we feel confident that the relatively minor problem of limited duration of action will be overcome. We are engaged currently in contract negotiations with a number of chemical and industrial firms that have the capability to do such complex synthetic fabrications.

For example, reference to Table I will illustrate some facts already known. Each of the five compounds listed will, when given to rodents in the dose shown, reduce the injurious effect of any dose of radiation by about 50%. The protective dose differs markedly, from 85 to 1200 milligrams per kilogram of body weight. However, in all of these compounds the ratio between the therapeutic dose and the toxic dose remains almost the same so the toxicity is unchanged. Cysteine becomes mercaptoethylamine when the carboxyl group is removed, and the protective effect of the molecule is increased considerably. When three carbon atoms separate the amino and sulfhydryl groups an even more protective compound is obtained, as is shown by mercaptopropylamine. However, mercaptopropylguanidine is no more protective than mercaptoethylguanidine. Further separation of the amine and sulfur lead to an inactive molecule. Isocysteine, with the carboxyl alpha to the sulfhydryl is a radio-sensitizing compound indicating that the site of substitution is critical.

These are some of the examples of how toxicity and protection are known to be related to structure. Our first approaches to the problem will be to explore the changes brought about by substitutions on the carbon atoms of both mercaptoethylamine and mercaptopropylamine. In addition to aliphatic compounds we shall try to develop aromatic molecules containing the two basic structures mentioned above.

It is obvious many thousands of compounds could be synthesized in this development program. Our aim is to test representative compounds in the various families to establish what

18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62 A 1582
Box #: 44
File: 337 (West Point) U

changes have occurred in terms of toxicity and protective effect. By thus increasing the basic knowledge of the relationship between structure and function we hope to draw closer to our goal.

This method of investigation will also contribute to elucidating the basic pathology of radiation injury. Our optimism does not blind us to the tremendous task we have undertaken, but the goal desired is worthy of every effort expended. Prophylaxis of acute radiation injury is as far removed from an idle dream as it is from reality for human use. The major paths of investigation appear clear. We intend to explore them thoroughly.

actory
latively
new

as it
nd
ity and
uch
xicity
the
be over-
h a
lity to

some
, when
ect of
fers
ight.
ra-
e tox-
m the
mole-
arate
ound is
cpto-
idine.
ve mole-
l is a
situation

d pro-
roaches
by sub-
nd mer-
all try
tures

e syn-
pre-
at



18-22 July 1994
Washington Federal Record Center
RG 112, Office of the Surgeon General
Department of the Army
Accession #: 62 A 1582
Box #: 44
File: 337 (West Point) U