

Minutes of IPR, Ionizing Radiation Injury-
Prevention and Treatment, held 11 October 1965

1. References

a. AR 705-5

b. Letter, HQ, USAMRDC, 14 September 1965, file MEDDH-N, subject, In-Process Review, Ionizing Radiation Injury - Prevention and Treatment (Annex 1).

2. The meeting was convened at 0915, 11 October 1965, in Room 2029, Main Navy Building, 19th and Constitution Avenue, N.W., Washington, D. C. An agenda (Annex 2) and a list of attendees (Annex 3) are attached.

3. The Chairman, in his introduction, called upon Col Colin F. Vorder Bruegge, Commanding Officer, U.S. Army Medical Research and Development Command, who spoke briefly on the early history of the anti-radiation drug program. He said that in the early days, before much work had been done, people spoke of drugs that might produce a ten-fold, or even a hundred-fold decrease in the injurious effects of ionizing radiation. These hopes have proven to be unrealistic. It is now believed that a Dose Reduction Factor (DRF) of from 2 to 3 is reasonable, and may be attainable in the immediate future. He emphasized that the concern today is to learn what the "line" thinks of this. Specifically, the question asked by this IPR is, what is the Army Staff's attitude towards a DRF of from 2 to 3 as an interim capability.

4. The Chairman began by pointing out that the overall program is responsive to the QMDO in paragraph 1212b (9), CDOG. Further, he stated that this is a Priority I QMDO, which he interprets to mean that work should move forward without delay.

5. He said that in his presentation he would consider three matters:

a. The current status of the program.

b. The operational significance of a DRF of 2 to 3.

c. The implications of the decision asked.

6. The Chairman began his discussion of the current status of the program by offering definitions of several terms in common use in the program. "Survival" is always in terms of 100% lethal irradiation, which is recognized

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to be a rigorous criterion. "Dose Reduction Factor" (DRF) is a ratio of the radiation exposure dose to the protected animal to the exposure dose to the unprotected animal required to produce a constant effect, in this case the LD50. It must be noted that this is an LD50 determined by probit analysis, however, and not one estimated from the response of a few animals. "Safety Factor", which is also measured as "Therapeutic Index", is the ratio of the LD50 of the drug itself to the maximum tolerated dose.

7. Then the Chairman presented comparative data in which he contrasted current drugs with the best anti-radiation drug available when the program was just getting started in 1960.

<u>End Point Observed</u>	<u>1960</u>	<u>1965</u>
Dose Reduction Factor	1.53	>2
Safety Factor	1.5	12-15
Drug Dose Size	150 mg/kg	5 mg/kg
Duration of Action	½ hr	5 hrs

8. He described recent observations of potentiation of action in certain combinations of drugs, which are very encouraging. In one example, one drug was administered in a quantity 1/8th of the drug LD50, at which level it exhibited no anti-radiation activity, in combination with another drug at 1/13th of its LD50, again a level that exhibited no activity. The combination, however, produced 100% survival in the irradiated mice.

9. In another study, three drugs were administered in combination at 1/9th, 1/5th, and 1/20th of their respective LD50's, which levels separately gave no protection. This combination was determined to have a DRF of 2.89.

10. Lt Col O'Dell, representing the USA Combat Developments Command, asked if it was the intention of The Surgeon General to procure drugs now for immediate issue to troops. The Chairman stated that there was, of course, no such intention. Procurement, he explained, is the final step in a long process of study, testing, and evaluation.

11. The Chairman then turned his attention to the second of his three points, the operational significance of a DRF of 2 to 3. He stated that this significance could be expressed as a savings in morbidity, or as maintaining the effectiveness of combat troops. Using data from FM 101-31-1 he constructed the following table on the blackboard.

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<u>Dose in Rads</u>	<u>Symptoms</u>	<u>Effectiveness</u>
200	Headache Little nausea	No or slight impairment 5% hospitalized No mortality
400	Nausea Vomiting Malaise	Sustained combat hampered 6-24 hrs 90% hospitalized 5% mortality
600	Severe Nausea Vomiting and Malaise	No significant combat capability. 100% hospitalized 5% or more mortality

12. He then explained that a drug with a DRF of 3 would effectively transpose exposed troops from the manifestations of the higher exposure ranges to the lower.

13. Lt Col O'Dell asked how it was possible to extrapolate from empirical data based on "lethality" to such considerations of "effectiveness".

14. The Chairman acknowledged the dangers that are associated with such extrapolation, and said that dogmatism certainly was not intended in this presentation. He then explained that although the end-point measured in all tests is death, there are certain inescapable observations of animal response. In addition to this, he mentioned a specific program of behavioral studies in avoidance-conditioned monkeys, now being conducted.

15. In the development program there will be human drug tolerance studies, and, finally, studies in irradiated patients.

16. Mr. Sills asked for evidence that it was reasonable to use the DRF as an arithmetic divisor at various dose levels.

17. The Chairman replied that the observations made in dogs indicate that the DRF can be treated in this fashion.

18. The Chairman then discussed his third point, the implications of the decision that was sought in this IPR. He stated that if the Army Staff decides that a DRF of 2 to 3 is not acceptable as an interim capability, research will continue for a drug affording a DRF considered acceptable.

19. On the other hand, if the result of this IPR is a concurrence in the proposed DRF of 2 to 3, then a program of advanced development of some three-years anticipated duration will be initiated. At the same time, the long-range research program will be continued.

20. The Chairman said that it might of interest if he were to outline the existing long-range program for the information of those present. This long-range program encompasses four areas of investigation. These are:

- a. Mechanisms of drug action.
- b. The search for better drugs outside the aminothiols area.
- c. An investigation of therapeutic regimens for use after man has been injured by irradiation.
- d. A study of irradiation combined with wound-healing and infections.

21. Mr. Norris Sills, OACSFOR, stated that a DRF of 2, with a toxicity that was insignificant, would be acceptable to the Army Staff. Lt Col O'Dell agreed with him.

22. The Chairman said that if the DRF was accepted, the U.S. Army Medical Service would continue to make all efforts to take care of the toxicity.

23. Mr. Sills said that the U.S. Army Staff is concerned about toxicity. They have seen letters that imply a 20% death rate with a DRF of 2.

24. Col Sven Bach stated that the OCRD position was this: The program is excellent and progress has been good. The toxicity problem can be overcome. The only question is, is a DRF of 2 acceptable to the Army?

25. The Chairman stated that if the Army finds a DRF of 2 acceptable, the drug that will be developed will be no more toxic than drugs now in general use.

26. Lt Col O'Dell said that the U.S. Army Combat Developments Command will support the work that is required to produce a drug with a DRF of 2 or 3 and does not cause side reactions. Further, the necessary money should be made available.

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27. Mr. Sills said that, speaking for the Assistant Chief of Staff for Force Development and for the Army Staff, he would concur in Lt Col O'Dell's statement, and the need for funds.

28. Col William Smith said that the U.S. Continental Army Command would also concur and expressed satisfaction with the U.S. Army Medical Research and Development Command's planned approach to develop the drug for use in man, in radiation and combined injuries.

29. Col Sven Bach did not concur due to lack of information on which to base the Chief of Research and Development's position.

Submitted:


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APPROVED:


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Annexes

1. Letter of Notification
2. Agenda of IPR
3. List of Attendees
4. Concurrence Sheet
5. Distribution