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WORKSHOP
on
SHORT-TERM HEALTH EFFECTS OF REACTOR ACCIDENTS: CHERNOBYL

August 8-9, 1986

V.P. Bond and E.P. Cronkite, Editors

Held at
Medical Department
Brookhaven National Laboratory

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Introductory Remarks

Victor P. Bond

This Workshop, "Short-Term Health Effects of Reactor Accidents: Chernobyl," came into being as a result of a conversation between Drs. Jacob Thiessen of the OHER, DOE, and Victor P. Bond of BNL less than one month before the meeting. The Workshop was organized by Drs. V.P. Bond and E.P. Cronkite of the Medical Department, BNL, and Dr. W.W. Burr of the Medical and Health Science Division, ORAU, Oak Ridge.

Research on the acute effects of radiation and of radiation combined with other types of trauma (e.g., burns, mechanical injuries) and on approaches to therapy was popular during the 1950s and 1960s. This resulted in the development of reasonable diagnostic and therapeutic regimens, including bone marrow replacement. However, this kind of research was largely supplanted by studies on the effects of radiation at the cellular, subcellular, and molecular level. The high-dose early-effects research that has been continued has been done in the context of infrequent accidents with large radiation sources and the use of bone marrow transfusions for treating malignancies, especially leukemia. It thus seemed appropriate to bring together the rather small remaining group of those who have done research on and have had experience with massive whole-body radiation. The objectives were (1) to review what is known about the acute effects of whole-body irradiation, (2) to review the current knowledge of therapy, and particularly of the diagnostic and immunologic problems encountered in bone marrow therapy, and (3) to compare this knowledge with observations made to date on the Chernobyl accident radiation casualties. (Dr. Robert Gale, who had helped to care for these casualties, was present at the Workshop.) It was hoped that such a review would help those making continuing clinical and pathological observations on the Chernobyl casualties, and that these observations would provide a basis for recommendations for additional research that might result in improved ability to manage successfully this type of severe injury. This particularly under the conditions of an actual accident, whether the number of casualties be few or substantial.

Each session of the Workshop was organized around a Discussion Leader, who presented introductory material adequate to provide a framework for an extended period of questioning, commentaries, and exchanges of ideas. The degree to which the observations to date at Chernobyl did or did not follow extant views was discussed.

One participant was asked to serve as Principal Recorder for each session, and another to serve as back-up. The sessions were taped, and the relevant transcript was given to each Principal Recorder to permit verification of specific points made in summaries prepared from their notes. (Dr. Bari provided his own summary.)

The summaries were edited and in some cases supplemented with additional material by Drs. Bond and Cronkite, who are deeply indebted to Mrs. Margaret Dienes for her most capable assistance in this effort. All who attended appreciate deeply the excellent assistance of the Conference Secretary, Mrs. Bernice Armstrong, who personally looked after the

extensive preconference arrangements which had to be accomplished in a very brief period of time, who typed the material, and who took care of the necessary follow-ups required for early publication of the summary proceedings of the Workshop. All are indebted to Dr. Jacob Thiessen, Deputy Director of the Office of Health and Environmental Research of the U.S. Department of Energy, for his continuing aid and support in organizing the Workshop, and for his active participation throughout. Financial support was provided by the U.S. Department of Energy.

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Charge to the Workshop Group

Dr. J. W. Thiessen

This is the 10th international meeting since 1960 on the medical management of radiation accidents. The last one, held seven years ago at Oak Ridge, was organized by the Radiation Emergency Assistance Center and Training Site (REACTS). That meeting had, besides its stated objective of providing an international review of the medical aspects of radiation injuries, a strong connctation of information dissemination to physicians and scientists with a principal objective of increasing the ranks of such individuals who are knowledgeable in this important and neglected area. Let me express first the objectives of this gathering seen from the point of view of a DOE program manager and research administrator.

First, I believe that the reactor accident at Chernobyl, which so far has taken 30 lives, called for a meeting of the ever decreasing number of experts involved in the medical management of past radiation accidents and in the research on radiation injury in man and its treatment, in order to discuss recent experience and place it in the context of the knowledge base obtained in the past. It behooves us to look at what we know and don't know in order to determine what we should know. The Atomic Energy Commission had an extensive research program in these fields and of course had to address the consequences of rather severe accidents. Its demise in the early 1970s was soon followed by shrinking of the funding base for radiation biology research in general and for human radiobiology and treatment of radiation injury in particular. In hindsight, one can discern a number of reasons--some rational and some not--for the declining interest, at least among government officials, in such research. Among the rational reasons was that radiation accidents in the nuclear and weapons industry had become extremely rare. Among the less rational ones was the expectation that this would remain so.

The recent events in the USSR have made us once more aware that human and technical failures do occur. We may wish they wouldn't happen but they do. Whether scientists, physicians, politicians, or other members of the public, we all have to look at the world again and determine whether the nuclear option--and I don't mean just nuclear power production--is to be accepted at face value (I'm not saying: uncritically) or whether we will maintain a rosy view that ignores the realities of life; realities that we all have accepted in a great many other activities that we now take for granted. In the realistic mindset, accidents are a fact of life and there is no need to distinguish right from wrong ones.

Applications of nuclear technology in engineering, medicine, agriculture, and many other areas of human endeavor are with us and will be with us for centuries to come. That being so, we have to face situations resulting from human failure, including radiation accidents, and we must plan for their management. This implies that we have to analyze whether we are truly prepared organizationally (and I include manpower and other resources in this category) medically and in research

support. This meeting could make a substantial contribution to that analysis.

The second objective of this meeting relates to something that may also have been responsible for the downturn in funding of research on the treatment of radiation injury. I do not have the final word on this, but maybe the research has reached a stage of diminishing returns. Perhaps the attention of investigators was slowly diverted from what had been a fertile field of investigation into other areas that promised greater returns, such as transplantation biology, genetics of histocompatibility, and immunology. The fact is that even if we continue research on radiation injury in general and on bone marrow transplantation in particular, research into other radiation treatment modalities has faded whereas the newer areas of research have bloomed, most of them under funding from other agencies. The fact is also that the DOE Office of Health and Environmental Research, to which I belong, is no longer seen as the natural funding agency for this research area whereas the AEC Division of Biology and Medicine was perceived to be just that.

How is this situation to be turned around? Let me give a personal view of this, and let me promise you that I will attempt to get an official resolution of this issue given the results of this meeting. As I said earlier, radiation accidents will occur and human overexposures will happen again. I don't know how frequently, but they will. That being so, and given the predominant role of the Department of Energy in the further development of nuclear options and in the operation of facilities involved in this development, DOE has the responsibility for ensuring that it is prepared to take remedial actions when accidents happen. Such preparation, in my mind, cannot exclude caring for the most valuable asset in any human endeavor--people. DOE cannot discharge its responsibility without giving appropriate attention to research and education, to mention just two.

We all know that above a certain level of exposure, although we don't know the exact level, there is no effective treatment for radiation injury. Even below that level therapy can be extremely difficult and not without risks of its own. Only continued research into the nature of radiation injury in man and into the mechanisms of its production and repair can provide us with new insights, new approaches, and eventually definitive answers. Recent biological research has provided us with tools unheard of only a few years ago, especially molecular methods such as DNA probes and monoclonal antibodies. Such new approaches to the study of radiation injury have enormous implications for future treatment strategies.

Both the occasion, however tragic in its consequences, and the opportune time are now. The Department of Energy, with its extensive resources in science and technology and with a proven record of performance in project management, appears to me to be the natural agency to lead the research effort of this kind. This in addition to its responsibilities in this respect which I mentioned earlier.

Finally, I see this meeting as an opportunity to look into training and information dissemination--education if you will. A glance around this room makes at least one point clear--those of us involved in

radiation injury research and care are getting older. It is thus necessary to look into building up our human resources as well. That in itself is adequate reason to get new people, new minds, the study of the short-term efects of massive exposure to ionizing radiations.

This meeting is an important one to all of us. I consider it less of a conference than a colloquy. I think we are all fortunate to have with us many of those who stood at the cradle of the nuclear era, whether at the Universities of Rochester, California or Chicago, at the large laboratories such as those at Oak Ridge and Los Alamos, or in the Pacific. Together they represent a base of knowledge that is phenomenal, and to see them together here is a real thrill--and I mean that from the bottom of my heart. I especially welcome our foreign guests, all of them eminent in their fields and in their country.

I wish you success in your discussions and look forward to your conclusions and recommendations. I can assure that they will be very carefully considered.

Chairman's Remarks: I should like to reinforce only one of Dr. Thiessen's very thoughtful remarks: the subject matter of this Workshop is early effects. We do not have time to deal with the possibility of late effects, i.e., cancer and genetic effects. Thus carcinogenesis is, so to speak, off limits at this meeting.

Design and Safety Comparison between Chernobyl Reactor and U.S. Commercial Light Water Reactors

Chairman's Remarks: Although it was said earlier that the subject matter is limited to early (medical) effects, this will now be violated to a degree by inviting discussion of the precipitating physical happenings that resulted in biomedical effects. A principal reason for this as follows: The material given out at this meeting included three articles taken from the August 1st issue of the Journal of the American Medical Association. One of these gets into the question of types of reactors. It is important to understand the differences between different types of reactors. Even though we are interested in radiation effects independent of source, the types of injury likely to be seen in an accident are somewhat dependent on reactor characteristics. Therefore, we have asked Dr. Robert Bari, a leading engineer in our Nuclear Energy Department at BNL, to discuss briefly the designs of reactors in the Soviet Union vs those in Western countries.

Robert A. Bari: In the BNL Department of Nuclear Energy, for the last decade or so we have been involved in core meltdown accident analysis for both light water reactors and liquid metal fast breeder reactors. Since the accident at TMI in 1979 we have focused more on possible accidents at U.S. commercial light water reactors, and we have done many studies that are follow-ons to the so-called Rasmussen study (Wash 1400), in which we calculate the likelihood of accidentsand analyze both the in-plant physical processes and the off-site consequences to get an overall perspective on risk in terms of health effects and property damage.

The design of any reactor covers three general categories: (1) the design for normal operations; (2) the design for anticipated transients--the routine things that happen maybe once a month or once a year or once in the lifetime of a reactor; and (3) the design from the point of view of severe accidents--catastrophic accidents such as those at Chernobyl and TMI and some accidents in research facilities over the years.

My subject today is reactor design from the severe accident perspective, and my main message is that, in looking at Chernobyl (and what we now know about its design), the severe accident analysis that would have to be done for Chernobyl would be quite unlike any analysis that we have done for U.S.-designed commercial reactors. I think it would be very wrong to infer that, because the Chernobyl accident happened, therefore this has direct implications for U.S. reactors, and it would be wrong to say that we should increase our focus on severe accidents in the U.S. because of it, at least at this time. I will restate that main message at the end of my presentation, which will be brief. The major points are outlined in Figures 1 to 3, and the Chernobyl reactor is shown in Figure 4.

Figure 5 is a schematic drawing of the Chernobyl reactor. The thing to keep in mind is the reactor core. This is where the nuclear heat is generated, and this is where the graphite is that everycne has heard about, and also the pressure tubes, the fuel rods, and so forth. The heat transport piping removes heat from the reactor core by taking hot water out of the core. It produces steam, which goes through a steam separator to a turbine, and then to the electrical generator--this is how the plant produces

REACTOR CORE	REACTOR CONTAINMENT
CHERNOBYL	CHERNOBYL
- 1693 PRESSURE TUBES	- HIGH PRESSURE CONTAINMENT ENCLOSES LARGE DIAMETER PIPES AND PUMPS
- GRAPHITE MODERATOR	- LOW PRESSURE CONTAINMENT ENCLOSES REACTOR CORE (& VESSEL), SMALL DIAMETER PIPES, STEAM DRUM
- POSITIVE REACTIVITY COEFFICIENT	- VERY LIMITED CONTROL/PREVENTION OF HYDROGEN COMBUSTION
U.S. LWRs	U.S. LWRs
- INTEGRAL CORE	- HIGH PRESSURE CONTAINMENT ENCLOSES REACTOR CORE (& VESSEL) AND ALL RELATED PIPING
- WATER MODERATOR	- CONTROL/PREVENTION OF HYDROGEN COMBUSTION
- NEGATIVE REACTIVITY COEFFICIENT	

Figure 1.
A listing of the major differences between U.S. light water reactors and the graphite moderated reactor at Chernobyl.

RBMK-1000 STRUCTURES

- High pressure containment
  - Encloses large diameter piping (300-900 mmϕ)
  - 4.5 bar, ~15,000 m^3 volume
  - Vents to suppression pool
- Low pressure containment
  - Encloses small diameter piping (50-100 mmϕ)
  - 0.8 bar, ~2,000 m^3 volume
  - Vents to suppression pool
- Reactor vault
  - Encloses reactor
  - 1.8 bar, 1,600 m^3 total volume (500 m^3 free volume)
  - Vents to low pressure containment or suppression pool
  - Vent designed for 1 pressure tube failure

Figure 2.
Characteristics of a RBMK reactor of the size used at Chernobyl.

CONCLUSIONS

- CHERNOBYL'S POSITIVE REACTIVITY COEFFICIENT AND GRAPHITE MODERATOR CAN LEAD TO ADDITIONAL ACCIDENT FEATURES NOT FOUND IN U.S. LWRs.
- CHERNOBYL'S CONTAINMENT UNLIKE ANY U.S. LWR CONTAINMENT DESIGN FROM THE VIEWPOINT OF MELTDOWN ACCIDENT MITIGATION.

Figure 3.
How differences in design between the U.S. and U.S.S.R. designed reactors can affect safety.

1 - reactor
2 - water pipelines
3 - steam-water pipelines
4 - loading machine
5 - separator drum
6 - main circulation pump

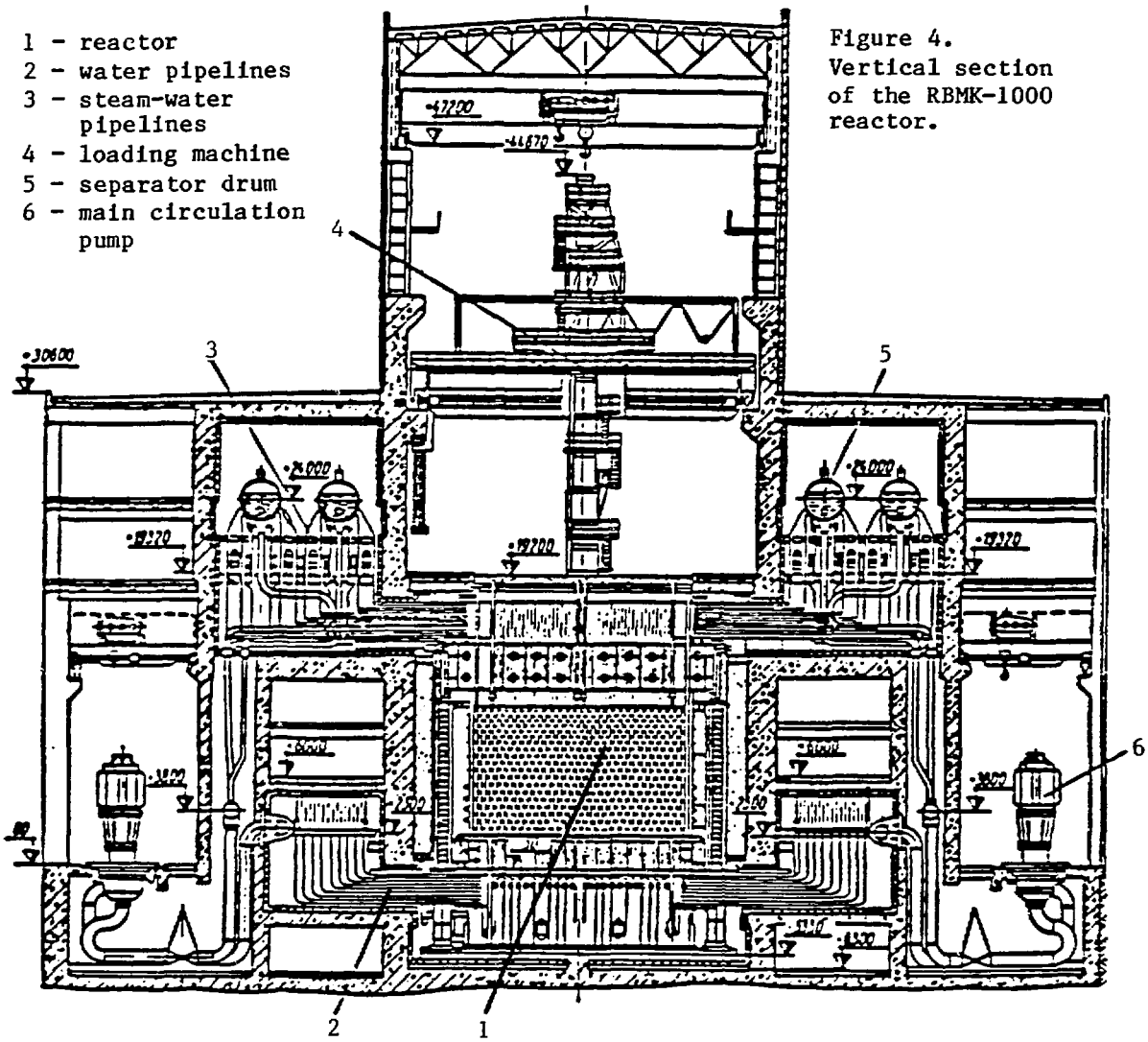

Figure 4.
Vertical section of the RBMK-1000 reactor.

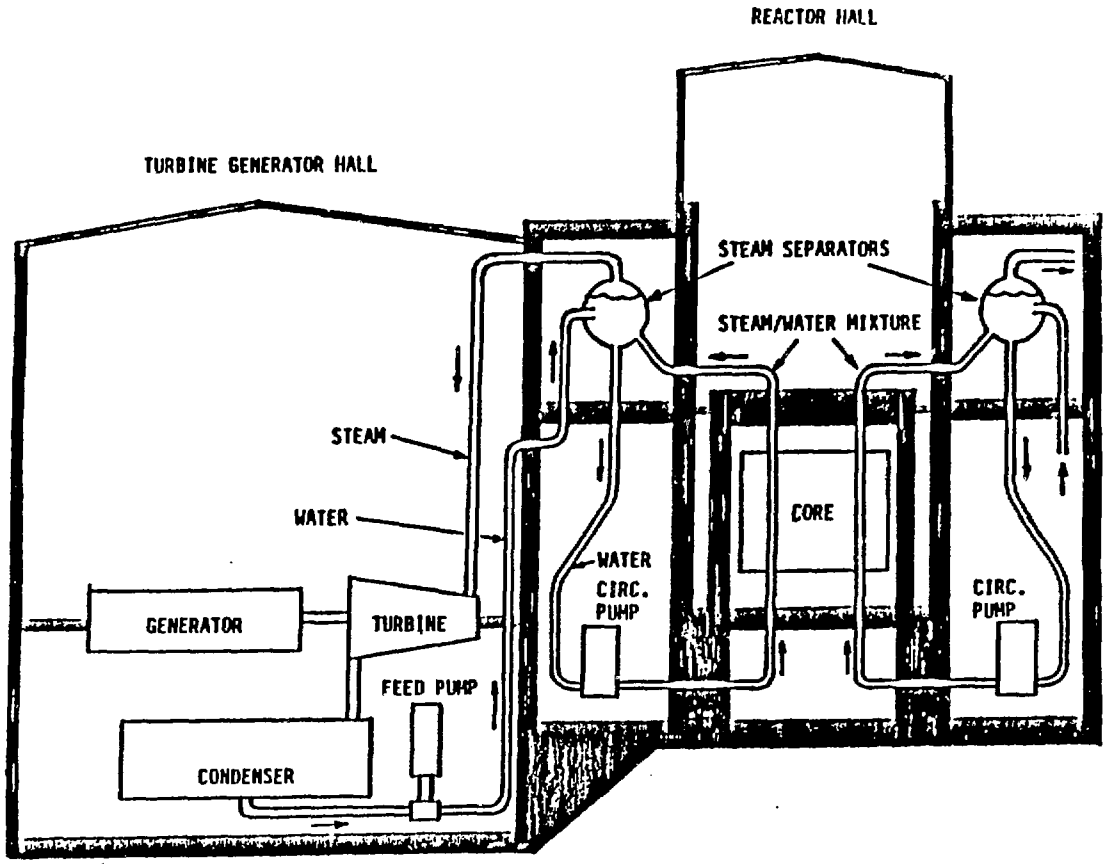

Figure 5. Chernobyl RBMK-1000 reactor. Reference information for this sketch applied specifically to the Smolensk power station, which uses the same type of reactor and which is believed to have the same plant configuration.

electricity. The rest of the drawing shows, more or less, the hardware connected with the thermodynamics of the plant. The structure around it is the so-called containment or confinement building, which I will discuss later in more detail.

In the first approximation, this is what almost all reactors look like. There is a localized core which generates heat, nuclear heat. There is piping that carries away the heat in hot water and eventually steam, and there is a turbine and generator. This could also be said of fossil fuel plants: a local core burns oil or coal, and piping carries away steam which then cranks a turbine.

In looking at the design differences between U.S. commercial reactors and Chernobyl, let's focus on major differences--based on what we know now--and I should caution again, our knowledge of the Chernobyl reactor is still very limited. Quite a bit of speculation is still going on, which we hope will be reduced after the meeting in Vienna later this month.

The core of the Chernobyl reactor is comprised of ~1700 pressure tubes whereas the U.S. light water reactors have an integral core. The main implication of this is that the reactor physics--the control of thereactivity in the reactor--is quite different. It is much more complex in the Chernobyl case because of the loosely coupled core. As we understand it now, complex computer controls are required to manage the reactivity in this core. There could be large spatial variations in the reactor power, quite unlike the behavior of the type of core we have in U.S. light water reactors.

The second major difference is in the moderator, i.e., the means of slowing down neutrons in the core to make the reactions go in their proper way. In the Chernobyl reactor the moderator is graphite; in U.S. light water reactors it is water. The other very important thing that we soon found out from reading the Russian literature, was that the Chernobyl reactor has a positive reactivity coefficient whereas the U.S. reactors have just the opposite, a negative reactivity coefficient. If a reactor with a positive coefficient gets into a transient situation such that it heats up, and if the water in the pressure tubes starts to void and the steam content increases, the nuclear reactions increase and this produces more power. On the other hand, in U.S. reactors with negative coefficients, as more water boils or is lost because of a loss-of-coolant accident, the nuclear reactions decrease. Such reactors are forgiving in that sense. The Chernobyl reactor, from our present limited information, has a positive reactivity coefficient so that transients tend to become aggravated as they progress.

The containment was highlighted in the AMA papers you received from Dr. Bond as a feature that is similar in Chernobyl and in U.S. reactors. The reactor containment at Chernobyl is, however, quite unlike anything we have in the U.S. in the commercial sector. First of all it has, as we understand it, three distinct containment compartments. The first is a high pressure compartment to enclose large-diameter pipes and pumps which comprise the main heat transport system going to the turbine. Two other compartments which are rather lower pressure containments enclose the reactor core and the vessel. Each of the ~1700 pressure tubes has a pipe coming off it, and these pipes then join together into one massive header. Thus a tremendous "spaghetti wire array" of pipes goes into this type of reactor, and the part where they join is enclosed in a separate lower pressure capacity containment which also houses the so-called steam drum where the steam is separated out.

Another important consideration is that the Chernobyl plant, as we understand it, has very limited capability for control and prevention of hydrogen combustion; the Russians have said (perhaps they are speculating right now) that there was a large hydrogen explosion or burn.

In contrast to the Chernobyl design, in U.S. light water reactors all the components analogous to those listed above are confined in one containment vessel of relatively higher pressure capacity. Furthermore, U.S. reactors are provided with the capability to control or prevent hydrogen combustion. For example, for the Mark I and Mark II type of boiling water reactors, the atmosphere in the entire containment building is continuously kept inert by nitrogen, which prevents combusion of

hydrogen because the oxygen content is much too low. Other types of containments have deliberate ignition systems which burn hydrogen at low concentrations and thereby prevent catastrophic burns.

Figure 5 shows what these differences mean. Around the reactor core and the heavy piping that I mentioned, the containment is relatively strong and is comparable with U.S. standards. Here the Russians seem (I'm just speculating) to have followed a design basis safety philosophy which protects this piping; throughout the consideration of reactor safety over the last 20 or 30 years, a major concern has been large piping ruptures, and this part of the piping has been well protected. The region above the core, however, is rather less protected. In fact, going back to my major conclusion, from the point of view of severe accident analysis as currently done in the U.S. for commercial light water reactors, if I encountered a design like this I would give virtually no credit at all for having containment. In contrast, in the analysis for U.S. reactors, a rather strong containment has to be dealt with. An example is the large dry containment of the Indian Point or Zion type of design (Figure 6). The reactor vessel and the reactor core, the steam generators, and the associated piping and pumps are all within the containment. The volume of this containment is 2.5 million cubic feet. The large piping portion of the Chernobyl containment is ~0.4 million cubic feet. The most vulnerable part, surrounding the core--the part that is of interest for core melt considerations, is only about 40,000 to 50,000 cubic feet. This shows the big difference in terms of containment concepts and philosophy.

Let me return to my conclusions. In terms of design, Chernobyl's positive reactivity and graphite moderator are two elements which, in an accident analysis in the U.S. of a reactor of that type, would add two very complicating features: (1) the positive reactivity coefficient leads to the possibility of an autocatalytic transient, which is absent in U.S. reactors, (2) since graphite can burn, the possible interactions of graphite with air, with steam, and directly with the fuel material would have to be considered. The other point is that, as I said, the Chernobyl containment is quite unlike anything in the U.S. in the commercial sector with regard to severe accident mitigation.

Are there any questions?

Q. Could you explain why they have a positive reactivity coefficient vs. the negative one? Or is it too complicated?

Dr. Bari: It is complicated. I'll start with U.S. reactors because they are easier to understand. The neutrons from the chain reaction come out with a wide distribution of speeds, but we want to get neutrons into a certain narrow band of speeds so that they can be used in the subsequent chain reaction to produce additional fissions. That is the whole idea of a nuclear reaction. In a bomb we have an uncontrolled nuclear reaction and in a reactor we have a controlled reaction. In U.S. designs for light water reactors, normal everyday water plays the role of moderator. It also plays the role of coolant, conveniently, so it plays two roles. It slows down the neutrons to the correct speeds and it removes heat from the reactor. In such a reactor if you have a loss of coolant, you also have a loss of the mechanism for directing neutrons

LARGE DRY CONTAINMENT (ZION)

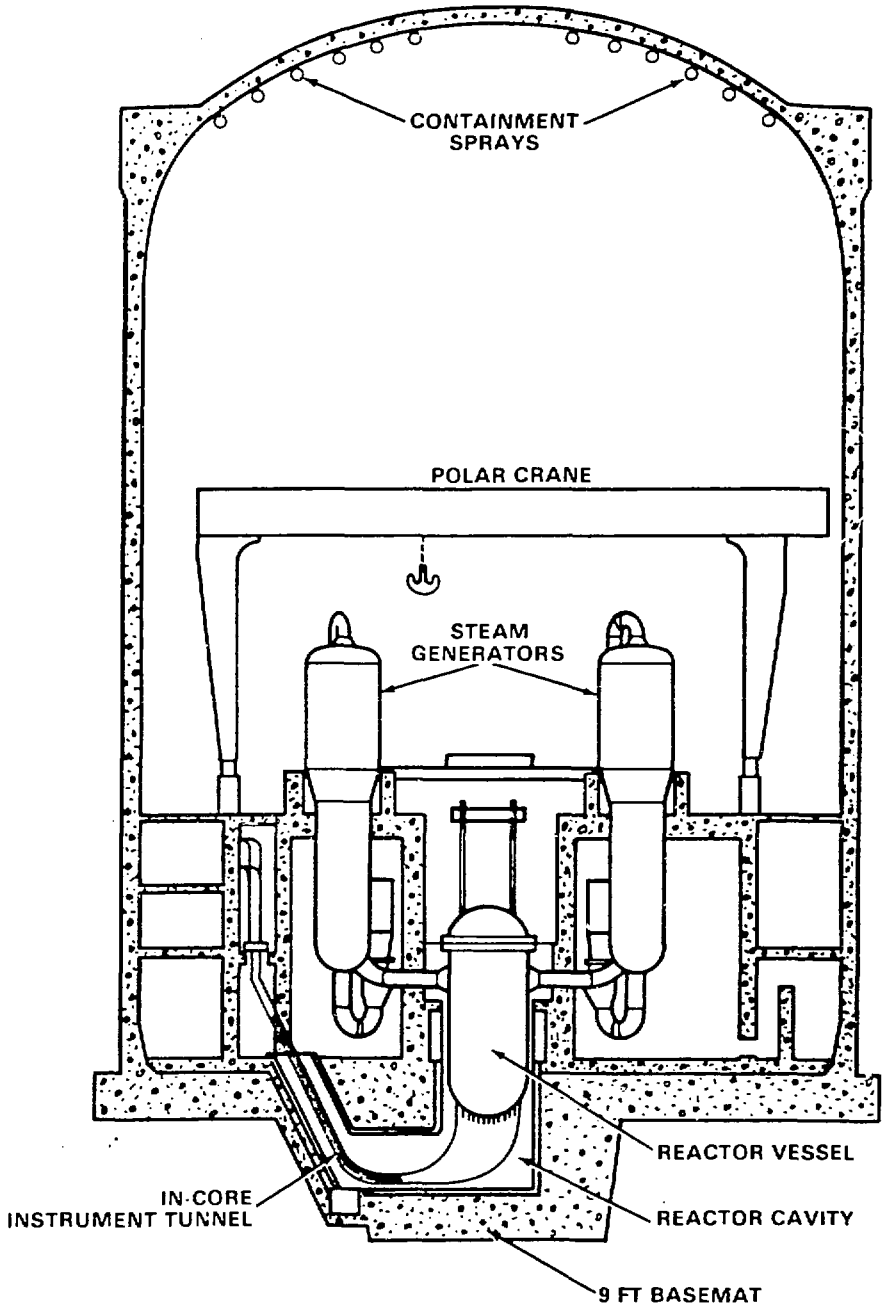

Figure 6.
Schematic of the containment design for the Zion plant.

into the right range of speeds for subsequent nuclear reactions, so that there is a negative feedback effect. The reactor gets into a transient but then corrects itself--it is no longer producing fissions.

In the graphite design, it is the graphite--in big heavy stationary blocks--that plays the role of neutron moderator, slowing down the neutrons into the right energy band. The water is there only as a coolant. It does have nuclear characteristics, as all materials do, but it is there mainly as coolant. One of its characteristics is that of a poison, so there is a balance between its slowing down and its poisoningroles. If you lose the coolant in a Chernobyl type reactor, you still have the moderator, and, since you have lost the poisoning role of the water, you have a net positive gain. This is a highly schematized description. You have a positive effect, without self-correction, which aggravates the accident.

Q: In the Chernobyl type of reactor, is it necessary occasionally to carry out the annealing process which brought on the Windscale accident, because of the Wigner energy problem? Is it possible that they were in such a process?

Dr. Bari: As far as we know now, the answer is no, and we looked very hard at this. I should add that the work we do here is sponsored by the Nuclear Regulatory Commission, and right after the accident we were asked to support their tracking team at the Emergency Response Center in Bethesda on the accident. We studied this question very hard and tried to get information on it. We know the Russian designers are keenly aware of the Windscale issue, and they run their graphite at higher temperatures to avoid and circumvent the so-called Wigner effect.

Q. Do you have enough information from the U.S.S.R. to do a source term analysis or to give some idea of dose rates in the neighborhood of the reactor and in off-site areas?

Dr. Bari: The key word is "enough"--I don't think we have enough information to do a hard and fast calculation that we would feel confident about, as we might about a calculation in the U.S. A major effort is being made in the U.S. right now to get an understanding of the source term and its magnitude. We did a limited analysis, and made limited estimates of what the source term might be from Chernobyl, given what we know about it, but I don't think that at this point we would want to make predictions. Certainly there is tremendous difficulty in trying to verify on the basis of the data, say, from Sweden, what the source term was because there are so many imponderables in between what happened in the reactor and what was observed in Sweden. We would need much more documentation on the reactor even to start a calculation.

Dose Injury Assessment and Medical Effects at Chernobyl

Robert P. Gale

Recorders: Clarence C. Lushbaugh
A. Bertrand Brill

The medical emergency response to the Chernobyl disaster began when the on-site medical team of eight physicians was alerted within 15 minutes of the accident on the morning of April 26, 1986. The local response was expanded within six hours to include three thousand M.D.s and several thousand nurses and paramedics, who were organized under the leadership of the medical staff of Moscow Hospital No. 6. This Soviet Institute, which is devoted to the therapy of hematologic disorders and clinical aspects of human radiation biology, was the site where Dr. Robert Gale and his team from UCLA Medical School went on May 2 to assist the Russian staff headed by Drs. Guskova and Barbarnov.

Ultimately 135,000 persons who were found to have been exposed to environmental radiations were evacuated from a 30-km-radius area around the towns of Chernobyl and Pripyat and the nuclear power plant No. 4 where the steam explosion and fire occurred. Immediate medical care was given to 29 persons who were considered the most irradiated and were severely burned, some having up to 90% of the body involved. About 203 persons were hospitalized later in Moscow Hospital No. 6.

The triage team used the time of onset of nausea and vomiting and lymphocyte depression as determined on site as the first criterion of radiation exposure and dose estimation. Later the fall in granulocytes and platelets was used in establishing the level of total-body (bone marrow) dose. Of the 203 hospitalized persons, 154 were selected for cytogenetic chromosomal analysis in which 50 mitotic spreads were analyzed per case. About 29 persons were considered candidates for bone marrow transplantation. Severe difficulties were encountered in obtaining adequate lymphocyte cultures for typing and then in finding sufficient numbers of related donors for selection by tissue typing. In all, 6 persons at Moscow and 2 at Kiev received fetal liver transplants (all died) and 13 others at Moscow received allogeneic bone marrow transplants. The U.S. team participated in 7 of these; all but 4 of the 13 had died at the time of Dr. Gale's report at BNL.

The apparent conclusions from this experience from the point of view of the radiation-induced bone marrow syndrome include the following:

1. Thermal injury combined with both local and total-body irradiation exposure determines the severity of expected deleterious clinical responses to an unknown extent.
2. In the absence of reliable external physical dosimetry and biologic extrapolations, the value of allogeneic bone marrow transplantation as a life-saving procedure is questionable.
3. State-of-the-art antibiotic therapy, platelet, blood and serum (gamma globulin) transfusions, and good hospital nursing practices produce remarkable amelioration of the acute hematopoietic syndrome in even the estimated 600- to 1000 rad (6- to 10-Gy) TBI range.

4. At the level of 200 rads or less, good hospital and medical care is not required as long as secondary infections do not occur and other forms of trauma are not present.

5. The complexity of caring for 50 critically irradiated and burned accident victims, amidst 150 others exposed to less radiation, requires an accident response capability that is in place and ready to react.

6. It is questionable that a comparable response could be mounted in America as rapidly and efficiently as was done in the U.S.S.R.

7. It is very probable that in a nuclear holocaust of any size, the medical community of any country would prove to be inadequate for the job.

The Bone Marrow Syndrome: Signs, Symptoms, Time Course of Hematological and Pathological Findings, Dose-Response Functions, Replacement Therapy

Discussion Leader: Theodor M. Fliedner

Recorders: Eugene P. Cronkite

The Chernobyl accident presented the medical care organization with combined traumatic injuries, thermal burns, and radiation burns, principally from radioisotopes deposited in the clothing and on the skin, in addition to inhomogeneous whole-body irradiation. This galaxy of injuries presented physicians with extremely difficult and complex medical problems. In general, we have tended to be concerned with pure whole-body radiation injury, and in fact much of past research has been devoted to study of uncomplicated radiation injury. The very early injuries resulting from criticality accidents involved intense damage to skin with edema, necrosis, and pain complicating the sequelae of depression of marrow function. It has always been recognized that the military use of nuclear weapons would involve combined injuries like those seen in the Japanese casualties exposed to the nuclear bombs at Hiroshima and Nagasaki. A summarization of our knowledge on the bone marrow syndrome should precede consideration of the superimposition of traumatic injuries and burns upon the course and lethality of whole-body radiation injury.

The symptomatology associated with injury to the gastrointestinal tract precedes the sequelae of marrow effects. The gut syndrome is characterized by nausea, vomiting, and diarrhea of varying degrees, the severity being a function of the dose of radiation to the gut. Management involves intensive fluid and electrolyte replacement, symptomatic management by drugs, and use of antibiotics to forestall and hopefully prevent bacterial invasion of the denuded areas of the gut as neutropenia develops. Within certain limits of dose the gut will regenerate, GI function will return, and the individuals will experience an interval of well-being before the sequelae of marrow suppression threaten life in successive order by susceptibility to infection from neutropenia, hemorrhage from thrombopenia, and anemia from blood loss and cessation of new cell production.

For all practical purposes the probability of survival depends on the number of hemopoietic stem cells surviving and the probability that the survivors will undergo self-renewal and differentiation into the major blood cell lineages. This can be studied directly only in the mouse and the rat, hence one must be guided clinically by changes in the peripheral blood. Fragmentary studies on human hemopoietic precursor cells show a close similarity in the D_0 of human and murine early progenitor cells. It is assumed without proof that the D_0 of human stem cells will be similar to the murine D_0 of 80 to 100 rad low-LET radiation.

Lymphopenia occurring in a few hours and becoming maximal within 48 to 72 hours indicates there has been significant exposure to radiation (homogeneous or inhomogeneous). Up to perhaps 200 to 300 rad the degree of lymphopenia is dose dependent, and when it is maximal lymphocyte levels become very low, approaching zero. Hence a lymphocyte level has no prognostic value for radiation doses >200 to 300 rad and is thus of limited clinical value. Lymphocyte levels can be misleading because inhomogeneous exposure produces a rapid decline, but in a few days rapid recovery occurs from areas of the body that received lesser amounts of radiation.

How does one predict the outcome? If there is early and persistent nausea, vomiting, and diarrhea, survival is improbable because of severe injury. If there is early but transient nausea, vomiting, and diarrhea with a period of well-being, the gut has probably repaired itself but one must face the sequelae of hemopoietic depression, and survival is possible. If there is trivial and short-lived nausea and vomiting, and lymphocytes do not bottom out close to zero, survival is probable. These are general rule of thumb guidelines that will be helpful when one is confronted with large numbers of casualties, and in a general sense they apply to uniform whole-body irradiation and inhomogeneous exposure. In individuals surviving the GI phase, the most valuable early predictors are the granulocyte and platelet counts.

In some cases of human radiation injury, the neutrophil count plummeted to near zero in 4 to 5 days. In the Japanese casualties survival was near zero when neutrophil counts were below 1000 in the first week, but in these cases there may have been combined injuries since the records are not very detailed. It is clear that the percent mortality in the Japanese and in homogeneously irradiated dogs is correlated with the depression in the neutrophil count. The earlier the depression the more serious the prognosis. If the granulocyte count precipitously drops in the first week to $<250/mm^3$, the prognosis for spontaneous survival is nil. Marrow transplantation along with antibiotics and transfusion of platelets and red cells are indicated. The factors related to successful marrow transplantation will be discussed elsewhere. It is pertinent to point out the necessity of irradiating blood or platelets with about 2500 rad to kill T-cells and minimize sensitization of the recipient to allo-antigen.

When granulocytes approach their nadir in the second to third week after exposure, marrow transplantation is less likely to be successful and useful. Management by antibiotics and transfusion therapy will rescue a large fraction of the exposed individuals. If the nadir is attained in the fourth to sixth week after exposure, the mortality will approach zero and therapy will be dependent upon the clinical signs and symptoms. To this point the value of the platelet count has not been considered. A rapid fall to a nadir within 10 days is a very serious prognostic sign. When platelet counts fall below $50,000/mm^3$, platelet transfusions of irradiated concentrates should be considered to prevent fatal hemorrhage into vital organs or exsanguination by diffuse purpura. The value of platelet transfusions has been well established in thrombopenic humans and animals.

Fliedner has cogently emphasized that the persistence of even a low level of granulocytes is a favorable prognostic sign: since a mature granulocyte's mean lifespan is <1 day, the presence of any granulocytes in the second week after exposure clearly indicates that granulopoiesis is under way somewhere in the body, thus improving the prognosis and suggesting that stem cells may be undergoing self-renewal and differentiation into functional cell lineages.

Since the human platelet mean lifespan is about 10 days, a thrombopenia approaching near zero levels by 10 days indicates that most thrombopoiesis has been eliminated and is a bad prognostic sign. When a low platelet level is maintained for 3 to 4 weeks, it is a clear indication that thrombopoiesis is proceeding somewhere in the body. This has been well demonstrated in the slowly developing thrombopenia maximum at around 30 days in the Marshallese and other accidentally exposed persons. The clear indications for marrow transplantation are severe initial symptoms, a rapid decline of lymphocytes and granulocytes to near zero in the first week, and a thrombopenia approaching near zero levels by 10 days. Of course, the sooner transplants are performed the earlier there will be a reconstitution of hemopoiesis, hence the granulocyte count is the earliest and the best clinical guide for making a decision as to whether transplantation is indicated.

The question of dose of radiation cannot be ignored. If the unlikely situation arose that the dose was well-documented uniform total-body exposure by 500 rad or more from high-energy gamma radiation, one should promptly collect the patient's lymphocytes and perform HLA typing and mixed lymphocyte cultures to select a compatible donor. Even if the exposure is known to be highly inhomogeneous, it is prudent to type the patient, identify donors, and observe the patient clinically before making the decision to transplant.

In addition, multiple bone marrow aspirates from different anatomic sites may indicate sites of aplasia and sites of some marrow proliferation.

When there are combined injuries and/or third-degree burns with open wounds, the development of neutropenia and thrombopenia may be accelerated, increasing substantially the probability of death from sepsis and/or hemorrhage. Gram negative infections may precipitate diffuse hemorrhage in the presence of thrombopenia that is otherwise being well tolerated; thus prompt debridement, closure of wounds, protection from infection, and intensive symptomatic therapy must be used.

A subject brought up in the discussion was the possible use of cytogenetic analysis to determine whether there had been inhomogeneous exposure, by utilizing the relative frequencies of one-hit and two-hit aberrations. These frequencies are rather strong functions of dose, and different ratios of these aberrations are therefore seen after significantly non-uniform vs uniform exposure.

Dr. Wald proposed the use of the Thoma and Wald index based on multiple hematologic and clinical signs and symptoms. Whereas this index appears to quantify severity and may correlate with mortality, it seems

to offer little in addition to what can be gained from careful observation of the sequence of events in blood lymphocyte, granulocyte, and platelet counts and of the clinical course.

In conclusion, one must make decisions promptly. As soon as possible lymphocytes should be collected from the casualties for allo-typing and identification of a compatible donor. The granulocyte count must be followed daily along with platelet counts. If both are falling precipitously and the former approaching zero by the fifth to sixth day, transplantation is indicated, the techniques for which are to be discussed later.

If the hematologic changes develop more slowly, watchful waiting is indicated, with use of antibiotic, platelet, and red cell transfusions as needed.

The GI Syndrome

Discussion Leader: Clarence C. Lushbaugh

Recorders: E. Donnall Thomas
Thomas MacVittie

Dr. Lushbaugh summarized the radiation accident at Los Alamos many years ago in which a very large exposure of total-body irradiation was received by one individual in a few seconds. The principal clinical problem was ileus, requiring Wangensteen suction during the few days that the patient survived. Dr. Lushbaugh also presented the histological changes. The gut showed denudation of the epthelium and extensive bacterial infection.

There was a discussion of the role of sodium and potassium disturbances in various compartments that might be a major component of the so-called GI syndrome. It was agreed that nausea and vomiting after 300 to 400 rad was probably not due to gut damage. It might be due to nerve damage in the solar plexus, but Dr. Saenger pointed out that there was no difference in upper vs. lower half-body irradiation.

A major question arising from Dr. Lushbaugh's presentation concerns the existence of a separate set of radiation effects and consequences that can be termed the "GI syndrome."

Dr. Lushbaugh presented evidence indicating that "loss of electrolytes" was not the cause of lethality in animals irradiated with doses sufficient to cause "GI syndrome" lethality. His protocol made use of whole-body and specific-organ retention of radiolabeled sodium and potassium. The main result cited was the plateau of the sodium retention curve, where retention existed, with increasing dose over the the "GI range." Questions were raised as to the significance of this protocol in distinguishing between the various "pools" within which the critical electrolytes exist. These were identified as being relevant in establishing "electrolyte imbalance" as a consequence post irradiation. An imbalance or translocation in the intracellular, intravascular interstitial, and/or intraluminal pools may have significant consequences. Dr. Lushbaugh indicated that an "imbalance" certainly exists but whether "loss" occurs and results in the "GI syndrome" is in question. It was noted that the "imbalance" can be corrected by appropriate use of fluid therapy, which permits time for bowel regeneration and improves the survival rate.

The discussion did not resolve the question as to the existence of a "GI syndrome," whereby the actual cause of death is related to electrolyte loss rather than to infection by opportunistic pathogens and hemorrhaging in a granulocyto- and thrombocytopenic host. What is the pathogenesis of the "GI syndrome"? Can it be distinguished from the pathogenesis of the hematopoietic syndrome, or is lethality the consequence of disrupted mucosal cell integrity, electrolyte loss, and death of stem cells?

The answers to these questions could have an impact on design of more effective treatment regimens post exposure.

The CNS Syndrome

Discussion Leader: Niel Wald

Recorders: Arland L. Carsten
Shirley A. Fry

The main question under discussion was whether or not there was evidence for the presence of the central nervous system syndrome (CNSS) in exposed individuals at Chernobyl. From the available data, the consensus was that the exposures were likely in the 400- to 600-rad range and therefore would not be high enough to elicit the CNSS, which requires an exposure somewhere in the range of a few thousand rads. It was noted, however, that, in view of the large margin of error in estimating the doses, the exposures could have been several times the estimates now available (figures up to 1200 rads or more have been suggested). The clinical observations reported by Dr. Gale indicated no symptoms characteristic of the CNSS, but it was noted that our knowledge of CNS effects in man is minimal for the reported doses and dose rates. The bulk of the available knowledge on CNS effects is dependent upon animal studies, as described below. It was also emphasized that an attempt should be made to correlate Chernobyl autopsies and clinical findings with what is known from animal studies and the few previously reasonably well-documented human exposures.

With the above observations in mind, the question was presented as to whether or not there is an acute radiation syndrome that can rightfully be called the central nervous system syndrome. The human experience related to this question can be considered only on the basis of six acute high-dose exposures--three to the whole body and three to the head--together with the cases at Los Alamos, NM, Providence, RI, and possibly the Italian case. Reference was also made to the patient at Lockport, NY, who received a significant x-ray exposure from a Klystron tube (this case, although involving a high dose, did not show the CNS symptomatology until much later, about one month post exposure.) With these scant data on humans, it was agreed that defining the CNS was quite difficult.

Experience with a close relative of man, the rhesus monkey, however, does supply some additional information. In animals receiving doses of 15,000 rads at 1000 rad/minute, two specific observations were made: (1) Although the purpose of the studies was to determine the doses that would produce incapacitation due to impairment of the nervous system, incapacitation--or rather, performance--was found to be relatively radioresistant, and the monkeys performed until death even after these high doses. (2) Related findings at autopsy were primarily of increased edema, perivascular cuffing, and migration of granulocytes around blood vessels in the meninges, the only specific change being in the base of the granular cell area of the cerebellum as evidenced by pyknosis of cells. While there is an impairment which is clearly lethal in a very short time, there is also very little functional impairment of the cerebrum. The pathologist sees very little in the way of change. It

appears that the focus should be on the impairment of membranes which account for edema. It is apparent that impairment of the operations of the nervous system and particularly of the vegetative center that controls respiration, blood pressure, etc., is affected by the edema. However, its effects remain invisible to the pathologist and perhaps do not interfere with functions of the cortex itself. The observation of limited early impairment in casualties at Chernobyl described by Dr. Gale seems to parallel earlier experimental observations in monkeys.

It was suggested that perhaps some information might be obtained from data on transplant patients given large whole-body priming doses involving the central nervous system. After some discussion, however, it was agreed that this dose is too low, or the dose rate is too low, or the syndrome is (as generally conceded by the audience) an ambiguous one, and that a gap exists between the 1000- to 1200-rad dose given pretransplant and the ~5000-rad or higher dose received by the accident case victims. Whether or not Chernobyl information will fill this gap is not yet known.

The role of the blood-brain barrier was also considered, since it has been shown that doses in the critical range of several thousand rads break down the blood-brain barrier in rats and monkeys, but, interestingly, doses as high as 40,000 rads have no effect on the shark blood-brain barrier and almost no effect on the shark brain as evidenced by light or electron microscopic examination.

The early recognition of irreversible radiation-induced functional changes is desirable, especially in a triage situation such as that following the Chernobyl accident. The symptomatology of generalized paresthesia and hyperexcitability alternating with depression of consciousness has been a reliable predictor of early radiation-induced death among human accident victims.

The EEG may be another method of evaluating early CNS impairment since its depression is evidenced rather early after doses as low as 2500 rads and is evident essentially immediately after ~28,000 rads to the brain of rhesus monkeys. In the whole-body irradiated animal, effects could be seen at ~10,800 rads. The EEG changes were even more evident in a sleeping animal than in an awake one.

To summarize, the effects seen on the central nervous system after large high-dose-rate exposures involve primarily membrane effects leading to edema; microthrombi due to the action of platelet activating factor (PAF) in regions of the epithelial cells; non-uniform slowing of cerebral blood flow, which is reversible by antihistamines and allopurinol; and a transient, regional hypotension that coincides with the time of early incapacitation and loss of autoregulation, which may be regained for a period of time before death. The consensus was that the central nervous system syndrome, as described on the basis of the few human observations and a number of animal studies, might better be given the descriptive title of neurovascular syndrome, since it has little to do with immediate direct damage to the central nervous system but is a combination of vascularly mediated factors resulting in the symptomatology observed.

The diagnosis of this syndrome in humans is best made by the clinical observation of changes in behavior, i.e., decreased alertness,

apathy, etc. Results of animal studies indicate that early EEG changes may be an indicator of exposure in the >2500-rad range, but until measurements are made on exposed humans, together with the necessary follow-up observations, the value of early EEG's remains unknown.

Data from the Chernobyl accident may yield little information related to the CNSS as it may exist in humans, since the doses received were probably too low to elicit what has been considered the classical CNSS. In addition, clinical observations on the Chernobyl victims revealed none of the symptoms usually ascribed to the CNSS.

Cytogenetic Analysis as a Technique for Determining Magnitude of Exposure and Injury

Discussion Leader: Michael A. Bender

Cytogenetic evaluation is a practical technique that may be of help to the clinician in discriminating between those victims who need treatment and those who do not. Considerable confidence can now be placed in the estimations of radiation doses obtained from cytogenetic analysis of the chromosome aberrations in peripheral lymphocytes, provided the exposure was acute, homogeneous, to the whole body, and to low-LET radiation. Also, samples must be obtained in the early (<2 weeks) post-exposure period. In the case of exposure to nonhomogeneous, partial-body, or high-LET radiation, there are distortions in the pattern of aberration distribution among the cells and also in the distribution between types. However, if one knows whether it is a whole-body exposure or a high-LET exposure, one can estimate the dose in either situation. Large distortions from the expected Poisson distribution will indicate nonhomogeneous exposure or high-LET radiation exposure, as will the ratio of single-break to two-break aberrations. The time factor in using these techniques should be considered, since at least two days' incubation of a peripheral blood culture is necessary before slides can be made, and it may then be necessary to analyze as many as 500 metaphases to measure low doses accurately, making the determination quite work-intensive.

It was noted that the protocol described above is one that makes it possible to determine rather low doses, whereas in the high-dose triage situation the evaluation of perhaps 10 to 15 cells would allow categorization of the dose in a particular case as (1) "too low to worry about" or (2) "too high to worry about" or (3) in the range worthy of accurate dose estimation, which might be deferred for a few days in order to get more cells scored so that better information upon which to base clinical decisions could be obtained.

Dose estimation by cytogenetic analysis may be expedited by automated procedures. Automated metaphase location can be 3 to 5 times as fast as visual location, but the technique for automated scoring of metaphases presents a much more difficult problem and current developments are not impressive. Dr. Bender urged support for work in this area to expedite chromosome analysis for dosimetry.

It was noted that available information indicates that cytogenetic techniques were used at Chernobyl, but details as to exactly what was done, or as to their usefulness, are not yet available.

The Lung Syndrome

Discussion Leader: E. Donnall Thomas

Recorders: Roger E. Linnemann
James J. Conklin

Our experience with the lung syndrome comes from observations of lung effects seen after the use of radiation and chemotherapy in the study of bone marrow transplants of leukemia patients. We have been able to classify our interstitial pneumonias as either idiopathic or agent-induced, i.e., cytomegalic virus, pneumocystic, other viruses, or unknown when an autopsy was not obtained.

In earlier years, when our diagnostic acumen was not as acute, 40 to 50% of interstitial pneumonias were classified as idiopathic. Today, with lung biopsy we can identify more specific causative agents. About 10% are still idiopathic immunosuppression. Most disease increases in allogenic grafts. In HLA matched siblings, the incidence of cytomegalic virus pneumonia increases.

It is possible that the remaining 10% of idiopathic pneumonias may be a form of radiation pneumonitis. The group in Toronto (Bacquine, Van Dyke, etc.) have shown that radiation pneumonitis begins at about 800 rads and is about 100% at 1200 rads for partial-body high-dose acute exposure. In some of our recent studies 1575 rad fractionated over 7 days or 200 rad per day for 6 days did not result in lung effects. In our dog studies single exposures of 2000 rad have not resulted in radiation pneumonitis.

About 5% of our marrow graft patients developed acute adult respiratory distress syndrome (ARDS). It is usually seen in patients who have had much chemotherapy and then received Cytox and total-body radiation. It develops 5 to 10 days following marrow graft. ARDS, however, is also seen in severe burn and trauma patients who have normal bone marrows. Inhalation of radionuclides might also produce this picture. ARDS after marrow grafts typically appears with a peak incidence at about 30 to 40 days, whereas radiation pneumonitis à la Van Dyke peaks at somewhat more than 100 days. Since radiation pneumonitis tends to appear later, I would assume a radiation dose large enough to produce radiation pneumonitis in accidents that would result in severe damage to other organ systems, e.g. bone marrow and GI tract. Consequently, in the management of such patients, lung injury would not really be important. Any pneumonias could be due to immunosuppression by the accidental high dose exposure and not due directly to radiation effects on the lung.

The use of immunoglobulin against CMV: Our group has been able to demonstrate some protective effect against cytomegalic virus pneumonitis with high-titer antibodies. We are continuing these studies with higher-titer antibodies. Pneumocystic pneumonia in immunosuppressed patients can be treated with Bactrim. This could be helpful in patients immunosuppressed as a result of accidental high dose exposure who develop similar pneumonias.

Bacterial endotoxin and ARDS: Bacterial endotoxin is a well-known mediator of ARDS. Perhaps severe radiation damage to the GI tract could result in an increase in endotoxin levels, and therefore lead to ARDS.

Vascular damage and pulmonary fibrosis: Pulmonary fibrosis as a late sequela of radiation may well be due to vascular damage to lung tissue rather than direct damage to pulmonary interstitial tissue. This is particularly so with partial-body lung exposure. With total-body exposure lung damage can result from direct effects as well as secondary effects of damage to other organ systems, e.g. infection resulting from decreased granulocytes or endotoxins from gut damage.

Lung lavage: Lung lavage has been used successfully in plutonium inhalation cases to reduce long-term cancer risks. There is little or no experience with lung lavage for inhalation of fission fragments. In the latter case one would consider earlier and aggressive lung lavage to prevent beta burns of the trachea and bronchial tract. However, the estimated dose would have to be considerable (>1000 rads) because of the risks of pulmonary lavage. Other factors to consider are the age of the patient, lung function, and other pulmonary damaging agents such as smoke, heat, and chemicals as seen in Chernobyl.

Early Effects from Radioisotope Dispersion

Discussion Leader: William H. Adams

Recorders: Fred A. Mettler, Jr.
Robert A. Conard

Two main problems will be discussed: thyroid hypofunction and skin effects. Prior to Chernobyl, experience was gained in 1954 when 253 natives were exposed in the Marshall Islands. Twelve of these were exposed *in utero*. Dose ranges were 11 to 190 rem whole body and 150 to 5000 rem to the thyroid. These individuals have been followed for 32 years by Dr. Conard and colleagues.

Dr. Maxon, summarizing the experience in man of hypothyroidism secondary to ^{131}I, suggested a threshold for induction of hypothyroidism to be 20 rad (Maxon, H. R. et al., Am. J. Med. 63: 967, 1977), with a risk of about 4.5×10^{-6} per rad per year. With external radiation, the risk factor may possibly be twice as high. Fourteen of the Rongelap natives became hypothyroid (some subclinical). All of the exposed Rongelap individuals are currently on thyroxine suppression and some have had thyroidectomies. If short-lived iodines are considered, the thyroid dose in some of the children probably exceeded 4000 rad. The spontaneous hypothyroidism rate in the United States is estimated at 0.02% per year. At this rate 1.3 cases would have been expected in the combined exposed groups of Rongelap and Utirik (253 persons). Two additional cases have just been found in the Utirik population, raising the total to 16.

Benign (adenomatous) nodules have also appeared as a nonstochastic event related to dose. Of those individuals who received 4000 to 5000 rem to the thyroid, ~75% (7 of 9 individuals) developed benign nodules, and 45% of them became hypothyroid. These adenomatous nodules do not appear to have malignant potential but are particularly important for the following reasons: (1) They represent the most important cause of morbidity in these patients. (2) They are the most common cause of hypothyroidism. In many cases, surgery for benign nodules resulted in hypothyroidism. This morbidity may be a reason to give potassium iodide. Adenomatous nodules appear as late as 25 years post exposure at levels of 150 rads to the thyroid. The risk factor appears to be 4.7×10^{-6} cases per rad per year. If there is a threshold, it appears to be below 150 rads to the thyroid.

Forty-eight of the Marshallese have had thyroid surgery and 32 of those are currently hypothyroid, most apparently on an iatrogenic basis. There are also two cases of hypoparathyroidism which are also iatrogenic.

It may be beneficial to give potassium iodide immediately upon exposure or thyroxine at a later date to prevent adenomas. In addition to the above-described effects, there is a suggestion that pituitary tumors may be related to the thyroid irradiation. Currently, two cases of pituitary tumor have been found in the Marshallese. Consequently, thyroxine suppression may decrease the incidence of pituitary tumors. Patients involved in irradiation incidents should be followed to find subclinical hypothyroidism. No statistically significant study has yet

been done to determine the value of KI or thyroxine in preventing or decreasing the number of benign nodules.

Dr. Gale indicated that during the Chernobyl accident dose levels to the thyroid may have been ~400 rem as far as 100 km from the accident site, and to the best of his knowledge potassium iodide had not been given in an organized fashion to individuals out this far. He said that thyroid burdens have been measured in thousands of persons to date and that the Soviet Union is well aware of possible effects such as hypothyroidism. Thyroid measurements were made directly rather than by urine sampling. Dr. Saenger suggested that he would give potassium iodide to prevent hypothyroidism and benign nodules, but that he would not give thyroxine unless there was clinically evident hypothyroidism in exposed individuals. He also indicated that the short-lived radionuclides of iodine are gone within two weeks and that inclusion of these would be important in the calculation of the thyroid doses at Chernobyl.

Skin effects were also discussed. It was mentioned that one case of basal cell carcinoma was diagnosed this year in a Marshallese Islander at Rongelap. Dr. Conard stated that the fallout had a high beta-to-gamma ratio and that the Marshallese took no precautions. Most of the beta dose was within the first mm of epidermis, but many natives did undergo epilation. Dr. Bond said that little infection occurred with beta burns in the Marshallese and questioned what happened at Chernobyl. Dr. Gale replied that there were severe beta burns in patients at Chernobyl, that these were associated with Gram negative sepsis, and that there were several subsequent deaths. He added that most of these patients also had neutropenia, and that the cause of the sepsis (whether due to thermal injuries, beta burns, or internal flora) is still uncertain. Dr. Cronkite mentioned that, in the Marshallese, skin lesions occurred predominantly at 10 to 30 days, with epilation in up to 50% of the population of Rongelap. Dr. Jammet pointed out that skin burns are predominantly beta burns rather than gamma burns, and that there should be no real problem distinguishing between thermal burns and rdiation "burns" since thermal burns are present immediately but blistering from irradiation rarely occurs in less than 7 to 10 days. Dr. Gale replied that in many cases he was uncertain whether the burns observed were due to thermal injury or to irradiation, and that many of the patients at Chernobyl had pain, occurring within two weeks, with what appeared to be radiation burns. He also related a case of a woman who was gardening on her hands and knees, unaware of the accident and subsequent fallout, apparently for ~3 hours, who subsequently developed significant beta burns over the anterior aspect of both lower legs. Dr. Linnemann questioned whether these could be gamma burns, but Dr. Thiessen replied that burns due to contamination on the skin are beta burns and that gamma burns occur only after substantial external irradiation.

The important points from this session appear to be the following:

1. Thyroid hypofunction and benign nodules may occur in a large population sample following the Chernobyl accident. Most of the discussants thought that use of potassium iodide would have been valuable, but opinion was divided concerning the value of thyroxine suppression to prevent the possible occurrence of benign adenomatous nodules.

2. At Chernobyl as many as 100,000 people may have gotten significant thyroid absorbed doses, but the magnitudes of the doses are uncertain because of the limited data concerning the administration of potassium iodide to the public and the amounts of short-lived iodine radionuclides involved.

3. Beta burns are well described in the previous literature. The fallout, at least locally near Chernobyl, appears to have been sufficient to cause beta burns in several individuals after several hours of direct contact with it.

Combined Effects
(External radiation plus thermal or beta burns, trauma, or internal emitter damage)

Discussion Leader: James J. Conklin

Recorders: William W. Burr
Eugene L. Saenger

Combined injury (CI) may be defined as the symptom complex found in individuals injured by thermal burns, blast, or other forms of trauma combined with exposure to ionizing radiation in various degrees. In the Chernobyl accident, from all accounts, CI appears to have been a major cause of increased morbidity and death. Although accounts of the Japanese bombings suggest that some of the immediate circumstances at that time were probably little different, the presence of blast effects close in and the absence of beta burns in the Japanese may be significant to the total health consequences.

Studies in a variety of animal species and the observations made following the nuclear bombings of Hiroshima and Nagasaki indicate that CI can result in the following:

1. The characteristic latent period of the acute radiation syndrome may be decreased.
2. Resistance to infection is impaired.
3. Wound healing is delayed and impaired.
4. Leukopenia is accelerated.
5. Hypochromic anemia is accelerated.
6. Frequency and intensity of shock are increased.
7. Lethality is increased.

Early studies in mice demonstrated that the combination of burns and ionizing radiation had an increased effect on both early deaths and deaths occurring after three days. X-irradiation doses at levels that caused no mortality alone, when combined with burns, caused excess deaths over the number anticipated from burns alone. Other studies in mice and dogs have shown a synergistic increase in mortality when burns are associated with radiation.

Injuries that alone would be expected to be benign, in combination with whole-body radiation may become lethal. Initial exposure of sheep to mixed neutron and gamma radiation followed by abrupt overpressure resulted in increased mortality. Studies of skin wounds in mice have shown delayed healing, reported to depend partly on the timing of the irradiation. In animal experiments, early closure of such wounds has been reported to be beneficial. In other CI investigations, in rats, excision of burn injured tissue lessened the combined injury effect.

Mice infected with K. pneumoniae in association with radiation and trauma have shown a marked increase in mortality when both trauma and radiation occur.

Studies have continued aimed at modifying the response to CI as well as learning more about the basis of the CI response.

With regard to the clinical observations at Chernobyl, the evaluation of CI was complicated by the confusion immediately following the accident. Apparently some persons reentered the building as many as 5 to 10 times in attempts to control the catastrophe.

The lethality in individuals was apparently greater than expected from burns or radiation alone in those suffering CI, although these relationships may not be clarified until the analysis of clinical data and of autopsy material is completed. The skin burns resulted from thermal burns, beta and gamma radiation, radioactive particulates, and radioactively contaminated water. Scoring these burns was extremely difficult. Differentiating beta burns from thermal burns was also most difficult, particularly if they were combined.

The degree of injury to workers at the accident scene from inhaling noxious chemical fumes in addition to large quantities of radionuclides added to the complexity of the problem. Fumes from burning of the plastic coating on the tremendous number of pipes added to these CI effects. Substantial pulmonary and liver damage was seen, apparently resulting from these several factors.

The 13 individuals on whom the bone-marrow transplants were done had burns over substantial portions of the body. The efficacy of transplantation has not yet been determined (August 1986).

The importance of CI is clearly recognized. Nevertheless methods for determining the relative proportion of trauma due to radiation are by no means well developed, and more precise analysis will have to await the evaluation of available data. Continued study and observation of CI should be encouraged to provide important information useful in both civilian and military catastrophies.

Bone Marrow Transplantation

Discussion Leader: E. Donnall Thomas

Recorders: E. P. Cronkite
V. P. Bond

Lorenz and Jacobson in the late 1940's described the beneficial effect of marrow transplants in fatally irradiated mice. If there were a genetic difference, the mice developed a wasting illness first described by Trentin and now known as graft versus host (GVH) disease. In the late 1950's Ferrebee and Thomas showed that one could transplant bone marrow in fatally irradiated dogs with some degree of success. The discovery of the histocompatibility antigens, tissue typing, and mixed lymphocyte culture enabled clinical investigators, notably Thomas and associates, to ablate bone marrow and malignant cells in patients with leukemia and successfully transplant bone marrow, thus saving the lives of many individuals with this disease. World-wide, about 10,000 bone marrow transplants have been performed on human beings with leukemia refractory to chemotherapy or with idiopathic aplastic anemia (AA) or AA induced by drugs or chemicals. Very few marrow transplants have been performed on individuals who have been exposed to potentially lethal doses of irradiation. The known attempts were those of Mathé in treating the Yugoslavians exposed in a criticality accident, and in a radiation accident in Pittsburgh in which an identical twin was available as a donor. In the former incident it was never established satisfactorily whether the marrow transplants were successful. In the latter case the marrow transplant from the identical twin was almost certainly life-saving.

Thomas and associates in studying transplants in dogs given 400, 500, and 600 rads showed that allogeneic, untyped marrow is of no value, but also apparently not harmful since transplanted and control animals died at the same time. When autologous marrow was used, there was a dramatic increase in survival rate and rapid recovery of granulocyte and platelet counts.

Allogeneic, DLA-compatible bone marrow transplants significantly increased the survival of dogs receiving almost certainly fatal doses of radiation. Whether T-cell depleted allogeneic DLA-compatible bone marrow will be beneficial to dogs in the lethal range of 300 to 600 rads has never been tested. Will GVH disease be prevented? Will hemopoiesis be maintained by transplants or host marrow? This is an area that needs study. Specifically, will marrow that is matched for major histocompatibility complexes be of any value in the 0 to near 100% mortality range of radiation exposure, when there is not sufficient immunosuppression to allow engraftment?

Another question that arises is whether an increment of radiation should be given to bring total exposure to the level where immunosuppression will be sufficient to allow allogeneic engraftment. An additional increment of radiation in such cases may be logical in principle, but will not be attractive to the casualty or the clinician.

Whether one should use immunosuppressive drugs, antithymocyte globulins, or monoclonal antibodies directed against subsets of T cells needs to be addressed. The canine is an appropriate animal to use for such a needed study although mice with known histocompatibility differences might be more desirable for initial studies since the murine monoclonal antibodies are available commercially.

It is clearly established in human beings that allogeneic bone marrow matched for major histocompatibility complex with negative mixed lymphocyte cultures will engraft in a high percent of individuals who are adequately immunosuppressed by lethal radiation exposure and administration of cytotoxic immunosuppressive drugs. These individuals are benefited by a protective environment and require platelet and red cell transfusions in addition to extensive antibiotic therapy to weather the period between marrow transplantation and development of functioning marrow that is producing an adequate number of red and white cells as well as platelets. Mild GVH is managed by immunosuppressive drugs, Cyclosporin A, antithymocyte globulins, and monoclonal antibodies. High-dose irradiation of a platelet preparation for transfusion will eradicate immunologically competent cells without harming the platelets.

Histocompatibility typing requires adequate numbers of lymphocytes as do mixed lymphocyte cultures. The rapid disappearance of radiosensitive lymphocytes after large doses of ionizing radiation mandates the collection of blood lymphocytes as early as possible after exposure to radiation. One should also consider the histocompatibility typing of individuals who may be at risk. Autologous marrow transplants are known to be effective and harmless in man and are being used extensively in the therapy of some diseases. This requires the collection and freezing of bone marrow before an accident or collection of peripheral blood mononuclear cells as done by Fliedner and associates. The former has the hazard of general anesthesia and the latter the minor hazard and discomfort of prolonged leukopheresis. There is no doubt that collection and freezing of autologous marrow or blood stem cells could be life-saving. It would be impractical on a large scale, but should be considered if one can identify a group of individuals at high risk. Both procedures are expensive. A cost-benefit analysis should be made.

These considerations also apply to HLA, B, and DR typing of individuals at risk before an accident.

It is to be noted that individuals who volunteer as platelet donors have their HLA typing done. Several thousands of such potential marrow donors exist in Seattle, Minneapolis, Milwaukee, Los Angeles, and other centers. The International Bone Marrow Register would be of great help in finding compatible donors.

In treating casualties with combined thermal and radiation burns, trauma, and heavy whole-body radiation exposure, it is unlikely that marrow transplantation would be of much value. Chernobyl appears to have demonstrated this, as well as the expected lack of efficacy of fetal liver transplants. On the other hand, if the Chernobyl casualties had had histocompatibility typing prior to the accident, an earlier marrow transplant thus might have been made possible. This might have resulted

in a better therapeutic result. T-cell depletion of bone marrow to minimize the probability of GVH disease must also be considered.

In all cases, even if bone marrow transfusion is done, the need for a protective environment, platelet transfusion, superb general medical care, fast bacteriologic diagnosis, and antibiotic administration after sensitivity tests will continue to be mainstays in the management of combined injury.

American power reactors do not have air or water-cooled graphite moderators; hence the probability of fire and explosion is much less than at Chernobyl. It is probable, should an accident occur in a Western-type reactor, that combined injuries would not occur. Thus, in cases of "pure" whole-body radiation injury, marrow transplantation, with all the caveats mentioned earlier, might well be life-saving. Accordingly, an inventory of laminar air-flow rooms, private clean rooms, etc., that are now available in the United States should be made with an estimate of how many may be in use at any one time and thus not available for radiation casualties. Attempting marrow transplantation in any hospital or clinic that is not already operating a marrow transplantation program should be discouraged.

Patient categorization will be the key to any treatment program: selection of individuals who need no special therapy, those who need supportive therapy (i.e., antibiotics and platelet transfusions), and those who may benefit from marrow transplant. The last would be individuals in whom there has been a precipitous drop in blood lymphocytes, granulocytes, and platelets as described in another section. In the unlikely event that there are accurate personal dosimeter readings, individuals with less than 200 rads need only observation and rarely will require therapy. Individuals exposed to 200 to 500 rads are believed to be in the lethal range and will need antibiotic therapy and platelet and red cell transfusions as clinically indicated (not prophylactically). Individuals receiving 500 to 1000 rads are in a grey zone in which they probably need more immunosuppressive therapy to facilitate engraftment of matched allogeneic marrow. Individuals receiving 1000 to 2000 rads are definite candidates for matched allogeneic marrow transplants and may not need additional immunosuppressive therapy. Individuals receiving greater than 2000 rads probably will not benefit from marrow transplant and should be given supportive and humanitarian therapy.

Regulation of Hemopoiesis, Its Perturbation by Ionizing Radiation and New Therapeutic Approaches Involving Recombinant Molecular Regulators

Discussion Leader: E. P. Cronkite

Radiation-induced perturbation of hematopoietic regulators was a recurrent theme throughout the Workshop. It is well established that steady-state hemopoiesis requires pluripotential stem cells and activation of the appropriate gene(s) to self-renew and to produce differentiated cells of the different cell lineages [erythropoietic, granulopoietic, megakaryocytic, and lymphocytic (B and T cell lines)]. Two factors are essential for modulating the rate of proliferation or regeneration. Receptors for the molecular regulators must be synthesized and incorporated into the plasma membrane of the precursor cells. In parallel the regulatory molecules must be produced and transported to the receptors on the plasma membrane of the early, undifferentiated progenitors. Ionizing radiation perturbs hemopoiesis first by killing radiosensitive hemopoietic precursor cells in a dose-dependent manner. It also kills, in a dose-dependent manner, T-lymphocytes, which occupy a key role in initiating and accelerating production of diverse molecular regulators. In addition, through gene rearrangement, deletion, or translocation, the ability of cells to produce receptors and molecular regulators may be impaired by ionizing radiation.

Several molecular regulators of hemopoiesis have been identified. These are IL-3, M-CSF, GM-CSF, M-CSF, Meg-CSF, and Ep. IL-3 is required for proliferation of pluripotent stem cells. Present thinking indicates that differentiation into the different cell lineages is a stochastic process. The cells produce receptors for the molecular regulators and in synergy with IL-3 expand the population of the given lineage. For example, a cell develops receptors for the regulator, GM-CSF, which can then attach to the receptors and induce cells to go into cycle. The frequency of successive mitoses is dependent on the number of receptors and their saturation. The number of progeny produced is a function of the number of mitoses before unidentified factors switch off cycling, perhaps by suppressing new receptor production.

The production of the molecular regulators may also be controlled by a radiation-dose-dependent mechanism. For example, IL-3 is produced by radiosensitive T-cells. If these are killed or rendered inoperative, availability of this regulator for "self-renewal" is impaired. Il-1 and IL-2 products of the radiosensitive T-cell are also involved in nonimmunological functions. IL-1 is also produced by radiosensitive monocyte-macrophages. This agent then stimulates bone marrow fibroblasts and/or endothelial cells to produce GM-CSF. IL-2 maintains T-lymphocytes in culture, which also produce regulators. It is seen that a whole network of radiosensitive cells, their molecular regulators, and the target cells and their receptors are involved in radiation damage to hemopoiesis. Much research on the interrelationships involved is ongoing. Prostaglandins, lactoferrin, interferons, and cachechitins (tumor necrosis factors) have roles in inhibiting various aspects of hemopoiesis.

From this brief description of hemopoiesis, its regulation, and the effect of ionizing radiation in killing the radiosensitive stem cells, early progenitors, T-cells, and monocytes, and perhaps interfering with the functions of accessory cells that produce the molecular regulators, it is clear that one must consider the possible beneficial or even detrimental effect of exogenous administration of the molecular regulators produced by recombinant DNA. The molecular regulators now available are IL-3, GM-CSF, M-CSF, G-GSH, erythropoietin, IL-1, and IL-2.

One can visualize, after whole body irradiation, a situation in which the radiosensitive precursor cells and the radiosensitive T and B lymphocytes and monocytes, producers of the molecular regulators required for stem cell self-renewal and amplification, are drastically diminished in number. Will substitution of the recombinant molecular regulators now available accelerate restitution of hemopoiesis? Will their administration kill stem cells undergoing repair? To test the preceding experimentally, the recombinant molecules should be administered at different times after different lethal doses of radiation. Since the marrow endothelial and fibroblastic cells are relatively radioresistant compared to stem cells, it would be logical to see if IL-1 will stimulate production of endogenous marrow GM-CSF and thus perhaps accelerate regeneration of granulocytes. Will IL-3 accelerate the regeneration of the stem cell pool? This could be easily tested by assaying the bone marrow for stem cell content by the spleen colony assay and survival rate. There are many permutations and combinations when one is concerned with seven separate known regulators and more being discovered at regular intervals.

Evaluation of these factors in the irradiated mouse should commence promptly and precede attempts to use them in human beings.

Early Fetal Effects
(Emphasis on Cell Killing Leading to Mental Retardation)

Discussion Leader: William J. Schull

Recorder: Seymour Abrahamson

Dr. Schull's presentation centered on studies of three associated end points of the in utero exposed survivors of the Hiroshima and Nagasaki atomic bombing. The observations are on severe mental retardation, I.Q. test scores, and school performance. These end points are different measures of the general population character called intelligence, which has a normal distribution in a large population sample, and is primarily under the control of the cerebrum portion of the brain. The cerebrum growth and the setting of the specific architectural pattern (neuron distribution) occur predominantly during weeks 8 to 15 post conception. Schull and Otake have demonstrated 15 cases of severe mental retardation associated with exposures during the critical stage of development. The data could be fitted by a linear regression analysis, although other functions could be accommodated as well. Exposure during the other stages (1 to 8 weeks and 26 weeks and beyond) had no significant effect, although possibly a less sensitive critical stage existed during weeks 16 to 25. Both the I.Q. and school performance data (as yet unpublished), based on a much larger study sample, also showed significant decrease with increasing dose in the critical 8- to 15-week exposure group. Clearly the consistency in results implies that radiation, through cell killing and/or derangement in neuron migration and structure formation, shifts the intelligence distribution unidirectionally away from the mean, increasing the proportion of retardation and lower performance scores.

Studies in Japan did not begin for three or more years after the bombings: Chernobyl offers the opportunity to strengthen the information base without a corresponding delay. Since time is critical it is urgent that the following studies be undertaken immediately.

1. All abortuses be maintained for brain histology and evaluation.
2. All living fetuses be thoroughly studies with non-invasive techniques by pediatric neurologists (a double-blind study would be preferable if exposure can be established).
3. All live born exposed in utero be given a complete neural workup by pediatric neurologists and neurobiologists, along with their siblings.
4. An extensive workup on parents' intellection qualities be developed in order to establish whether any aberrant neurological features result from hereditary influence rather than exposure.
5. Records be maintained and follow-up studies continued on the group exposed in utero throughout their schooling experience along with an appropriately chosen control group.

Note that all of these approaches should allow both earlier and finer-scale analyses of the effects of radiation on the developing

fetus. Some questions that still need answers are the following.

1. Do the phenomena observed above result from a threshold or true linear dose response, and do dose rate differences influence the effect on cerebral function?
2. Lower-dose information is needed: will Chernobyl provide any more information in the $\leq$ 15-rem range?
3. Will more sensitive techniques, in conjunction with earlier results, unearth more sensitive neurolgical end points?

Discussion; Recommendations

Discussion Leader: Stuart C. Finch

Recorders: Ludwig E. Feinendegen
Victor P. Bond

Rather than trying to summarize the many observations and opinions of each speaker, I will outline some of the major points of agreement and disagreement and will make some broad recommendations. The discussions made it apparent that much information about radiation injury remains unknown, that a uniform opinion is lacking with regard to many issues, and that much future planning and research is needed.

Dr. Thiessen defined the challenge and set the tone of the conference in his introductory remarks. He emphasized that, if we are to accept the nuclear option, then we must be prepared for the eventual occurrence and consequences of future nuclear accidents. This will require bringing young people into the field, increased training and education, wider information dissemination, greater application of the modalities of research, and increased radiation injury research--despite the practical problem of a shrinking financial base. His recommendations appear to be as cogent and as pertinent at the end of the conference as they were at the beginning.

Dr. Gale's lucid and graphic description of the Chernobyl accident illustrated the many problems of practical application of current principles regarding population evacuation, dose assessment, patient triage, utilization of medical facilities, and administration of various forms of therapy. He emphasized the multiplicity of medical problems for the most seriously injured and especially the difficulty of identifying persons with varying degrees of severity of acute radiation injury. The major problems here included (1) the recognition of thermal, beta, and gamma burns, (2) the effects of ingestion and/or inhalation of toxic or radioactive substances, (3) the difficulties in early establishment of the severity of the injury, due to the interactive effects of multiple injuries on the various types of biological indicators, and (4) the side effects of the multiple medications being administered. Evaluated were time until nausea and vomiting developed, the slope of the decline of peripheral blood lymphocytes, the time to the depletion of granulocytes, and peripheral blood cytogenetic changes. Some data were conflicting, but both lymphocyte changes and cytogenetic data were found to be most useful. Notable was the absence of rapid decline in peripheral blood granulocytes. Difficulty was encountered in identifying persons with irreversible stem cell damage. Major focus was on the 19 patients with probable irreversible bone marrow damage who received transplants of either bone marrow or fetal liver. Dr. Gale noted that--because of the complexities of the multiple medical problems, the wide age span of the patients, and the difficulties with tissue typing and identifying suitable donors--probably no more than 20% of heavily irradiated patients can be salvaged by means of marrow transplantation. Other major problems

encountered were body contamination of patients and subsequent contamination of hospital personnel, management of thermal injuries, potential thyroid effects, and central nervous system complications.

For the next day and a half discussions of many of the problems encountered by Dr. Gale and his Russian colleagues at Chernobyl made it clear that much more research and planning must be undertaken if such problems are to be properly managed in the future. Recommendations suggested during the Workshop are summarized as follows.

1. Specific site plans should be set up for rapid triage of injured persons to primary and secondary medical centers, depending on the degree and type of radiation injury and other medical problems.

2. The capability must be established for early and continuous application of the best clinical and biological indicators of radiation injury in order to expedite early decision regarding patient triage to appropriate support centers and early institution of the proper therapy modalities.

3. From recent investigations at Lawrence Livermore National Laboratory glycophorin A and B, a somatic mutation demonstrated in human red cell membranes, may become useful as a biological dosimeter. Further investigations are needed before its use can be recommended. Murine GM-CSF, G-CSF, M-CSF are now available from recombinant DNA. The full potential of this approach should be explored in mice. ESR signals in teeth should be explored for use as a dosimeter.

4. Chernobyl demonstrated that large amounts of radioactivity can be released over several days, so that the potential exists for high doses to man protracted in time. Additional studies are needed to determine the degree to which the LD_{50} changes, and perhaps the mode(s) of death, as a result of such protraction.

5. Injured persons must receive early and vigorous treatment in view of the realization that with moderate support systems mortality may be $\leq$5% for up to 28 days.

6. Physicians, ancillary medical personnel, radiation workers, and the general public require more extensive education concerning appropriate behavior during and after a radiation accident.

7. Specific protocols should be developed in local and regional medical facilities for applying biological tests to assess the severity of injury (i.e., rapid and sequential blood counts, cytogenetics, assessment of bone marrow function, etc.).

8. Consideration must be given to adequate preparation for possibly providing bone marrow transplants to large numbers of persons at high risk of lethal injury. This might include autologous bone marrow storage and HLA typing of all radiation workers. Plans also might be made for using HLA registries, identifying potential HLA matched donors, transporting patients and donors, and identifying all bone marrow transplantation centers and establishing communication with them.

In particular,

1. The best practical biological indicators for the prediction of survival should be determined. Particular attention should be directed to the evaluation of bone marrow function, cytogenetic changes, and both qualitative and quantitative changes in lymphocytes, granulocytes, and

platelets. Areas of erythropoiesis in non-uniformly irradiated casualties could be detected readily by means of the positron-emitting isotope, ^{52}Fe. Better methods should be identified for determining potential reversibility or irreversibility of damage to bone marrow stem cells.

2. Studies are needed on the therapeutic potential of recombinant molecules for modifying biological response, including IL-1, IL-2, IL-3, M-CSF, GM-CSF, G-CSF, and Ep (see Session III-1a). Selective decontamination; indications for bone marrow transplantation and optimum timing; the use of transient bone marrow grafts and of grafts from unmatched donors; the application of T cell depletion techniques to donor marrow, including the use of monoclonal antibodies specific for different T-cell types; and the possible use of cytotoxic agents or other methods of immunosuppression prior to bone marrow transplantation, must be investigated further.

3. More research is needed regarding the best techniques for predicting the clinical outcome of patients with multiple and complex medical injuries. The usefulness of integrated information from multiple sources should be evaluated. Guidelines should be established for the management of patients who have extensive burns and multiple injuries, who inhaled or ingested toxic or radioactive substances, who show side effects of various medications, and who were exposed to radiation with different qualities.

4. Research in the prophylaxis of thyroid injury from radiation should be expanded, with emphasis on the optimal use of potassium iodide and thyroxine. Cutaneous application of iodine for thyroid blocking should be explored further.

5. During the discussion at this meeting reference was made to alterations of cellular metabolism following irradiation in the low dose rate range, over a period of several hours; this raises the question of altered vulnerability of the organism to pharmacological, biochemical, and physical interventions during low dose rate exposure. Research into this area might provide improvements in the therapy of radiation injury.

Finally, I again call attention to the lessons of Chernobyl, which serve to emphasize our urgent need for renewed and more vigorous research and planning for a possible major radiation accident in the United States. I also note that most of the experts in the field of radiation injury are getting older--new blood must be brought into the field. An infusion of additional research funds is urgently needed for the study of complex radiation injury problems if we are to be adequately and properly prepared for the inevitable consequences of possible future radiation accidents.

I think everyone in this room is to be complimented and thanked for making this a very successful meeting. The participation has been excellent, and I also want to thank BNL for hosting this meeting. We couldn't ask for a better opportunity to get together and discuss this topic.

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