I

THE NUCLEAR REACTOR AS AN INSTRUMENT OF MEDICAL RESEARCH AND THERAPY

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for
1957 Nuclear Engineering and Science Congress

Research Supported by U. S. Atomic Energy Commission

II

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ABSTRACT

This paper describes reactor equipment and procedures employed in medical experimentation, with specific examples of the use of radioactive materials and instantaneous induced radiations. Limitations met in six years' experience with the research reactor are also listed. Utilization of facilities of the new Medical Research Reactor is outlined.

Numerous expressions of widespread interest in the Brookhaven Medical Research Reactor make pertinent a review of the special features of that device. These special features arose from needs demonstrated in the prosecution of research at Brookhaven by the Medical Department, at the present large BNL research reactor. The major considerations which dictated the design features can perhaps best be illustrated by descriptions of typical projects from past and present efforts. The future program can be roughly outlined by considering the function of the reactor's several facilities.

Lines of medical research directly utilizing the nuclear reactor have generally fitted into two categories. One covers the effects of radiations on living systems and their fuels, the other includes the gamut of radioactive tracer applications. Under the first category falls the studies on induced activities mediated by reactor neutrons, the effects of inherent reactor radiations, and the production of high activity materials for experimental radiotherapy. The second category includes the usual radioactive tracer techniques, exploration for new tracers or new carriers for tracers, and other special procedures of high analytic power. Some of this work uses the type of facility and service routinely provided at a research reactor, as in ordinary radioisotope production and irradiation services. Others have been constructed to special requirements in varying degree.

Although the full research program of the Brookhaven Medical Department extends broadly into many fields of bio-medical investigation, actually a large part of the work is based on the unique facilities available at the large research reactor. These special circumstances make it practical to use procedures which employ induced instantaneous radiations and radioactivities of short half-life. For instance, it has been possible to make therapeutic trials with such agents as radioactive chlorine, with a half-life of only 38 minutes. In this instance there are important advantages related to the short period of irradiation, in that the area of exposure follows the early distribution pattern of the material, which is usually quite different from the distribution obtaining some hours later, by which time the radioactivity has decayed away. As far as the use of the reactor is concerned, this is a straight-forward application of routine isotope production methods. Here, the special circumstance is simply that emphasis is placed on rapidity of handling and application, which makes possible an unusual application of special physiological knowledge of pathways and rates of distribution.

Another example in which the early distribution of a radioactive agent is utilized is the experimental application of the 2.6 hour activity of manganese-56 for radiotherapy in metastatic and primary malignancy of the liver. To draw a comparison with a more familiar situation, the distribution of radioactive iodine in the body might be considered. This widely known agent of "atomic medicine" is used in certain diseases of the thyroid gland, sometimes to destroy cancerous follicular material, sometimes simply to cause reduction of thyroid activity to control Graves' disease as an aid in managing cardiac complications. The rationale for radioiodine therapy is based on the accumulation of radioactive material in the gland. It requires many hours to reach the peak concentration but thereafter the material is carried off slowly. Most of the radiation is thus delivered to the gland itself, the remainder of the body being spared by virtue of this avidity of the gland for iodine and the gradual nature of its manufacture into products to be distributed and subsequent dilution in the body. In contrast with this picture, an experimental study of the behavior of manganese in the body showed a rapid accumulation in the liver and [illegible]. The rapidity of this concentration can be used to effect a [illegible] treatment in these [illegible]. These distribution characteristics were studied with Mn[illegible] and Mn[illegible], pointing the way to the possibility of using Mn[illegible] [illegible]. Subsequent studies have used yet another approach [illegible] distribution of manganese has been followed by application of activation analysis to tissue specimens.

The neutron capture therapy experiment should be brought in at this point. This rationale is based on the instantaneous production of energetic heavy particle radiation throughout a brain tumor mass, under slow neutron exposure after accumulation in the tumor of a target element of high neutron capture cross section. Here the time scale is determined by the way in which normal and tumor brain concentrations differ during the first few minutes following injection. The neutron exposure is scheduled to take advantage of a transient favorable tumor to brain capture element concentration ratio, to spare the surrounding normal tissues as much as possible. In these studies the dynamic differences in concentration of target or radioactive elements have been termed selective kinetics. Knowledge of the pattern of movement or distribution of any agent in the body is basic to the understanding and improvement of investigative and therapeutic modalities based upon it.

A simple enumeration of the reactor facilities we have used proceeds as follows, with some typical agents indicated in each case:

(a) regular isotope production conveyor for radioactive gallium, sodium, etc.

(b) short exposure pneumatic tube irradiations to make Cl^{38}, Mn^{56}, ...

(c) water cooled facility for activation of thermally unstable compounds such as sodium citrate and chloroform.

(d) special exposure tank to make radioactive gases, e.g., krypton 87.

(e) a special cave with a two-inch collimated neutron beam for studies of neutron penetration patterns in tissue.

(f) the Medical facility on top of the reactor, where experimental therapy and related programs are carried out.

(g) the Biology Department's facility, also on top of the pile, for thermal or fast neutron exposures in a chamber about one foot cube.

(h) and an important accessory—the laboratory assigned to the Medical Department in the reactor building has served variously as a staging area for reactor experiments or as an operating space where in vivo experiments have been carried out using short lived isotopes.

This enumeration defines the outline of the work which has been done and which is possible to do. Some further detail on a few of the projects may be of interest, since not all can be described to any satisfactory degree of completeness in this paper.

A varied group of experiments revolve about the radioactive inert gases. These are prepared by neutron activation in a 2 liter tank situated in one of the vacant fuel element sites. This tank is loaded to 3 atmospheres pressure, producing a sufficient quantity for convenient tracer and even therapeutic trials. The gaseous media require much more searching; the experiments done so far have merely pointed the way. Already they have contributed in the study of the mode and site of action of anesthetic agents, [illegible] excellent practical possibilities. Therapeutic [illegible] argon have been made to reduce serous effusions in [illegible] cavities, somewhat after the manner of radioactive [illegible] procedures, but with the hope of achieving more uniform and extensive irradiation of the serous surfaces by virtue of the greater fluidity of gas with respect to liquid. Another therapeutic possibility is irradiation of body cavities such as bladder or stomach with gas delivered in a thin walled "balloon." An advantage here is that the body tissues do not retain these gases to any great extent.

Experimental studies on anesthesia have provided two striking examples of the application of short-lived materials. The agents used were xenon and chloroform. This program was carried out in collaboration with a research team from the State University of Iowa. A quantity of activated xenon was mixed with stable xenon and then administered to animals by the anesthesiologist. Studies were carried out to determine where the material localized as a function of time, with special attention to various glands and nervous tissues, followed by parallel studies to establish corresponding rates of loss at termination of anesthesia. The few hours' working time which the effective half life of xenon allowed were quite adequate for this work. Similar experiments with neutron activated chloroform were also begun. Here the reactor facility had to maintain the chloroform at near room temperature during activation, because of the volatile nature of the compound. In both instances it was necessary to carry on the work in an operating room set up in a laboratory immediately adjacent to the reactor.

Energetic heavy particle effects on bacterial cultures and other microbiological systems have been studied using the neutron [illegible].

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with facilities modified to accommodate test tubes. This is a modality which provides a distribution of the heavy particles throughout the specimen, a situation which cannot be effected to any great depth using external particle beams such as are provided by accelerators.

Another phase of the work based on neutron capture radiation involves radioautography of a special type. This procedure is used to determine—on a microscopic scale—in which parts of the organisms the capture target element concentrates. The injected tissue sample is prepared and mounted in contact with a special photographic emulsion and the assembly inserted into a special bismuth shielded exposure holder adapted to the medical facility. Development of the tracks made by the induced heavy particles provides the desired localization information. This technique requires great pains to minimize the effects of other radiations which are present, including the radioactivity from both silver and bromine induced during the exposure. Plastic slides are used in place of glass. In addition to our own work in this field, cooperative projects have been carried out with research groups of the University of Illinois and the Massachusetts General Hospital. Both of these projects have already been described in the literature.

In all of these experiments special regard must be given to [illegible] customary laboratory materials. Glass test tubes become radiation [illegible] suspension media for materials under irradiation must be generally screened for unwanted radiation as well as chemical effects. In the application of induced radioautography for iodine in electrophoresis paper strips, care must be taken to select a paper of low chlorine residue, since that activity could mask the effects which are being sought.

Throughout this broad program certain limitations continue to recur. In a way, these limitations are really expressions of the eagerness to rush further into possibilities revealed by the earlier investigations; they are the result of a completely natural growth of ideas and techniques. Two types of limiting factors are essentially based on (1) quantity and quality of external neutron beams, (2) adaptability of facilities to the special needs of experiments as they arise.

The need for greater quantity and for control of the quality or energy of the neutron beam is felt especially in the neutron capture therapy experiment and its ancillary investigations. The first medical facility in the roof of the reactor provided a flux of about 2×10^8 neutrons per second-square centimeter. This we now know to be the lowest level at which such work can be carried out. An improved facility was contrived and has been used extensively. The flux was increased to about 3×10^9 neutrons/sec·cm^2. But the increased convenience through having a shutter and suitable shielding arrangements allows many kinds of experiments to be carried out during routine working hours. Without this improvement the screening of procedures and materials in developing this technique might be literally interminable. The further improvements we hope to obtain from the new Medical Research Reactor include another increase in slow neutron flux and some measure of control over the energy of the neutrons, with consequent improvement in their penetration through the tissues of interest.

While a great variety of special facilities have been provided, either by invention or by borrowing from other projects, some desirable applications have been beyond our reach. We have been able to utilize short-lived radioactive gases, but we now look forward to using even briefer activities in gaseous and liquid form by recirculating the medium through reactor exposure loops and directly into treatment room or laboratory touching the reactor wall itself. Also there are frequently substances of interest which must be maintained at room temperature or even refrigerated during exposure. This is already possible, but the demands on and limitations of present equipment preclude any extensive investigation of reactor thermal and radiation influence on these substances.

There is need for more study of the way in which neutron beams of various qualities penetrate tissue. Collimated beams are of special value in such work. The therapeutic experiments have demanded fluxes which cannot be delivered except by diffusing orifices, however. Nevertheless, some instrument studies with ionization chambers in tissue equivalent phantoms have been carried out with neutron intensities only one-thousandth as strong as the situation used for experimental therapy, and these have been correlated with phantom studies set up to duplicate the therapeutic situations. Better collimation, higher flux levels, and control of neutron beam energy would combine to make this type of investigation much more valuable.

Another limitation in the present situation is the inconvenience of programming for experiments which require massive external neutron beams. These experiments of necessity raise the background in the vicinity, putting out of business many experiments dependent on delicate radiation measurements. Any experiment involving human patients requires converting considerable space into an appropriately controlled hospital area, another requirement in conflict with contingucus experimental sites, only partially satisfied by evening schedules. But one important experimental area is not accommodated at all--the rate-sensitive characteristics of radiation affecting biological experiments over a suitable range of exposure rates are not at all compatible with the over-all uniform operation program of a large general purpose research reactor.

The design of the experimental facilities of the Medical Research Reactor is itself the result of extensive study. Each phase of the work to date and each proposal for a future project has been considered in arriving at the plan which is now taking concrete shape. Briefly stated, the specifications are these: the MRR is capable of providing external thermal neutron beams at intensities about 10 times those we have used, with the fast neutron and gamma ray contaminations well below limits acceptable for the experimental situation. It provides a patient irradiation facility with a widely adaptable treatment port incorporating both gamma ray and neutron shutters and with an auxillary preparation room. Means are included for modifying the character of the neutron flux, in order to explore the enhanced penetration of epithermal neutrons. An identical exposure facility is provided for animal irradiations. In addition, a large cell directly exposed to a bare face of the reactor is available. A collimated neutron beam hole for irradiation of microbiological specimens and for study of radiation effects or neutron depth dosimetry in tissue or equivalent media is available. Our work also includes the application of radioactive materials of very short half life, for which there are irradiation tubes inside the reactor arranged for direct delivery into the treatment rooms or laboratories.

From our experience with the experiments using the Brookhaven research reactor, specifications for the proposed reactor designed exclusively for biomedical research were based on a slow neutron flux of 10^{11} neutrons/ $cm^2 \cdot sec$ delivered at the treatment port. This level is to be achieved by a reactor core utilizing enriched fuel elements of the MTR or BSF type in a water-cooled arrangement surrounded by an air-cooled graphite moderator, operated at one megawatt. Details of the reactor, shielding, and layout of 198-11 research facilities have been worked out in collaboration with the Nuclear Engineering and Reactor Departments and the Architectural Planning Division of Brookhaven National Laboratory. Preliminary design for the reactor and specifications for the special shielding were developed cooperatively with the Advanced Technology Corporation under contract with Brookhaven National Laboratory.

Architect for the Medical Center is Eggers and Higgins. Contractor for building the reactor is Daystrom, Incorporated. The radiation shutters for the treatment facilities have been fabricated by Baldwin-Lima-Hamilton. Medical Center Buildings are being erected by the Malan Construction Company.

In speaking of medical research at our reactor it is impossible to point out all that has been done without telling the large contribution by personnel outside the Medical Department. Full cooperation of the reactor operations staff has always been completely given. On questions of shielding design, radiation measurements, or other physical, chemical and engineering details arising in our work, we have had competent assistance on request from those working around us who are specialists in these matters. The interest and aid of the entire staff has been a factor of basic importance in the progress of our work.

[illegible] summarise in broad terms, the nuclear reactor has been used [illegible] in medical investigations utilising activation analysis, the preparation of special radioactive materials for tracers and therapeutic agents, and directly as an instrument of radiation therapy. The experiment for delivering energetic heavy particles for radiation therapy throughout a disease site was begun within the first month of operation of the Brookhaven Research Reactor, and this experiment was indeed one of the important early uses of the machine. This particular experiment continues to be our most important single effort using the reactor and is expected to continue so for a long time to come.