The Cyclotron and Cancer

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"Now what the speed to matter's atom given . . . Outstrip in speed, and be more swiftly borne than light of sun . . ."
—De Rerum Natura, Lucretius ca. 58 B.C.

The discovery of the principle of cyclotron acceleration represents another contribution of the university physics research laboratory which has important applications in cancer research, diagnosis and treatment. A cyclotron can produce specific radionuclides which are essential for metabolic research studies of cancer as well as others which are unique labels of biologically significant compounds for diagnostic studies. It also can produce radioactive gases which have tumor localizing properties and which permit unique pulmonary function studies. In addition, it can produce some radionuclides suitable for the treatment of cancer and radiations which can be used directly for treatment as well as for diagnosis. This review is intended to describe briefly the facilities and research associated with the Institute's cyclotron, as well as their application in the Hospital.

THE CYCLOTRON

The principle of the cyclotron, conceived by E. O. Lawrence in 1929, provided for sequential electrostatic acceleration of charged particles held in circular orbits by a magnetic field. In 1932, Lawrence reported the first successful operation of his machine, which accelerated protons to energies slightly above one million electron volts. Our cyclotron contains an evacuated chamber located in a specially shaped magnetic field. Inside this circular and evacuated chamber are two hollow electrodes, approximately semicircular in shape, called "dees." An alternating difference of potential is applied between these "dees" so that positive ions created in an arc source situated at the center experience an accelerating force each time they cross the gap between the "dees." Since we are accelerating positive ions to relativistic energies, their mass changes during their acceleration which changes the frequency and field requirements for acceleration. This relativistic problem is overcome by the design of our magnetic field poles which have radial sectors with decreasing separation at larger radii. Also, the ion in a circular orbit experiences alternatively strong and weak fields as it progresses to larger radii. Since the magnetic field varies with azimuthal position, as well as increasing with radius, such a cyclotron is often referred to as an azimuthally varying field (AVF) machine: the term "isochronous" is also used because the time of rotation is constant despite the relativistic increase in mass. The ability to accelerate helium-3 ions to relativistic energies is particularly advantageous for certain nuclear reactions.

RESEARCH OBJECTIVES

The major purposes in a biophysical cancer research program for a cyclotron installation include the following:

(1) Production of radionuclides such as
carbon-11, nitrogen-13 and oxygen-15. These elements are the only radionuclides of these biologically important elements which produce penetrating radiation that permits detection external to the human body. They are produced conveniently by bombardment with positive ions.

(2) Many radionuclides produced by the cyclotron have short half-lives, which results in decreased radiation exposure of patients and permits extension of some diagnostic procedures to children.

(3) Some charged particle reactions result in radionuclides that emit positrons. Positron emission is followed by two annihilation quanta which facilitate external localization by coincidence detection methods.

(4) Fast neutrons are produced by a variety of nuclear reactions and are of interest for neutron activation (both in vivo and vitro) for radiography and possibly also for cancer therapy.

(5) Charged particle activation analysis is feasible for the detection of specific elements in trace amounts in tissue sections, or oxygen-18 can be used as a stable tracer and subsequently determined by proton activation analysis.

Although the importance of cyclotron-produced radionuclides was recognized many years ago, such use of cyclotrons for medical purposes has not been general. This has been due to the limited number of cyclotrons, their complexity and expense, size and scarcity of staff, and scheduling problems. The authorization by the British Medical Research Council for the establishment of a cyclotron at the Hammersmith Hospital over a decade ago was an early recognition of the need for locating a cyclotron explicitly for biomedical use. The second machine exclusively for such use was installed at the Washington University School of Medicine in 1966. Both of these machines were of conventional design. The third machine used exclusively for biomedical research and application was the one installed in our institution; it is of the isochronous type to permit acceleration of more different particles to relativistic energies in a compact machine. (Fig. 1.)
TABLE 1 – MEASURED OPERATIONAL PARAMETERS OF THE SLOAN-KETTERING INSTITUTE CYCLOTRON.

| Accelerated Particles | Beam Energy (MeV) | Internal Beam Intensity (µA) | Beam Intensity (µA) |
|-----------------------|-------------------|-----------------------------|--------------------|
| Protons               | 14.5              | 60                          | 100                |
| Deuterons             | 8                 | 60                          | 125                |
| Helium-3 ions         | 23                | 55                          | 120                |
| Helium-4 ions         | 15                | 50                          | 100                |

Extraction Radius .......... 13.5 inches
Magnetic Field Strength (average) 16.5 kilogauss
Operating Frequency:
Protons ...................... 25 MHz
Deuterons ..................... 12.5 MHz
Helium-3 ions .............. 16.7 MHz
Helium-4 ions .............. 12.5 MHz

INSTITUTE BIOPHYSICS ISO TOPE LABORATORY COMPLEX

In the early 1960’s when initial planning for the Kettering Laboratory and for the new Division of Biophysics was being carried out, provision for the accelerator necessary to the research program was planned. Acquisition of the cyclotron was made possible by a grant from the Atomic Energy Commission. The cyclotron and “hot” target radiochemistry laboratory were located at the subcellar level to simplify shielding and weight problems. The associated research isotope facility was placed at the cellar level, one floor above, in order to be sufficiently distant from the cyclotron to avoid radiation interference, and yet sufficiently close to permit convenient access to the short-lived radionuclides, including radioactive gases. This location was also dictated by the location of the tunnel connecting the Institute with the Hospital to permit convenient access for patients. (Fig. 2.)

The scanning laboratory houses both the

High Energy Gamma Ray Scanning (HEG) system and the Total Organ Kinetic Imaging Monitor (TOKIM) system. The HEG system has been in use since 1959. It was our initial scanning system on which we initiated both quantitative and computer-analyzed scanning procedures. After more than a decade of continuous use, it has recently been modernized with improved mechanical and electronic features. The TOKIM system consists of two 13½ inch diameter sodium iodide scintillation gamma cameras (Anger type) which were designed and constructed here with digital electronics and coincidence circuitry, and interfaced directly with an IBM 1800 computer. The HEG system is also used extensively with the computer. Adjacent to the scanner is the computer, isotope laboratory office and associated isotope work areas.

\*The IBM 1800 was funded by an N.I.H. Biomedical Computer Research Project Grant which was obtained to facilitate research on the application of mathematical and computer methods to biomedical research problems. It is a descendant of earlier automatic computation equipment acquired by the Institute in 1954.
Automatic methods for our radiation treatment planning procedures were originally carried out in the Institute, and have been under continuous development since that time. Complex computer programs are now regularly in use for both the external and internal use of radiation. An outgrowth of this activity was the computerization of our isotope scanning procedures. All scanning equipment in both Memorial Hospital and Sloan-Kettering Institute is fully compatible with this computer installation. A large variety of sophisticated programs has been developed for many different research projects, and a systems program has been developed which allows the simultaneous online processing of data by an IBM 1800 computer with off-line batch processing of data without any interference between these simultaneous uses.

The staff of this laboratory complex collaborates with many other investigators in the Institute and Hospital. The whole radioactive isotope research complex is efficiently and integrally designed to make optimum use of space, equipment and staff.

PROPERTIES OF CYCLOTRON-PRODUCED RADIONUCLIDES

Fluorine-18

Fluorine-18 is particularly useful for bone function scanning. Its rapid clearance from serum, rapid uptake in areas of bone remodeling and its energetic annihilation quanta make it possible to obtain skeletal scans with superior resolution than is possible with other bone-seeking nuclides. Its short half-life (1.9 hours) permits large doses with consequently improved statistics in scanning, and also allows repetitive studies. Sodium fluoride (\(^{18}\text{F}\)) is deposited in bone by an exchange for hydroxyl groups and perhaps for other anions in the surfaces of the mineral phase of bone. Kinetic studies carried out here a few years ago, with different bone-seeking radionuclides employed simultaneously in patients, permitted the quantitative determination of the best methods for its use and exploitation of its potential for cancer diagnosis. It not only provides skeletal function information of diagnostic importance, but in cancer diagnosis it also reveals skeletal lesions long before they are radiographically demonstrable.

High purity carrier-free fluorine-18 in isotonic saline solution is regularly prepared for clinical investigative use. The production procedure involves a 22 MeV helium-3 irradiation of water contained by means of a thin metal foil in a cylindrical recess in a titanium target plate.

The present research protocol calls for a total body search scan which is performed at 1-3 hours after injection of 1 mCi of fluorine-18. Analog output is in the form of a mini photoscan, having a reduction factor of 1/5. Incremental digital output is stored on magnetic tape for computer analysis. A computer program is used for smoothing by linear interpolation and the limits of count rate levels are calculated so that their midpoints are separated by any desired number of standard deviations. A line printer designates these levels alphabetically. This computer manipulation provides evaluation of the statistical reliability of the data which inherently contain count rate fluctuations.

The program is also capable of correcting the count rate for physical decay during the scan time as well as permitting certain low level counts depicting soft tissue areas to be omitted. One such scan is shown in Figure 3. This case was diagnosed as Ewing's sarcoma and the fluorine-18 skeletal survey demonstrates areas of increased uptake in the left orbital and temporal parietal regions, and the distal portion of the right femur.

The investigation of the role of fluorine-18 is now being carried out on a large scale.

Iron-52

Iron-52 has been of interest for many years for erythropoietic studies because of its reasonably short half-life (8.5 hours) and its gamma rays of conveniently detected energies. More of its energetic gamma rays come from the subsequent decay of manganese-52 with a half-life of 5.7 days. It is being employed in erythropoietic function studies.
Iodine-123

Iodine-123 is of great interest because its relatively short half-life (13.1 hours) permits the employment of much larger doses and avoids the restriction on the use of iodine-131 to nonpregnant adults. It can be produced by several different reactions, including helium-3 bombardment of antimony.

Chromium-48

Chromium-48, with a half-life of 23 hours, is advantageous for spleen scanning. It is produced by irradiation of titanium with the helium-3 ions with adequate yield.

Oxygen-15

Oxygen-15, as $^{15}$O$_2$, C$^{15}$O$_2$ and C$^{15}$O, has been used extensively in lung function and oxygen metabolic studies. It is produced by deuteron bombardment of nitrogen either in air or in more concentrated nitrogen-oxygen mixtures. The short half-life of 2 minutes requires that the gas be used either "on-line" during cyclotron operation or immediately after production. It is now being employed in a series of pulmonary investigations.

Nitrogen-13

Nitrogen-13 is of particular interest for regional pulmonary ventilation studies as well as for lung-blood flow measurements. For ventilation, it can be used alternatively with xenon-133 in either the single breath, or wash-in, wash-out equilibrium method. Its lower solubility in blood and fatty tissues makes its use preferable to xenon, and it gives less ambiguous results. A recent finding in the Institute was that nitrogen-13 in the form of ammonia is particularly useful for myocardial scanning and that it may also prove to be a good carcinoma scanning agent. It is usually produced by deuteron bombardment of carbon. Its short half-life of 10 minutes requires that it be used on an "on-line" basis.

Fig. 3. Computer analyzed display of an anterior total body search scan performed at two hours postinjection of one millicurie fluorine-18. Count rate levels are designated by letters and symbols and are separated by intervals of two standard deviations.
Carbon-11
Carbon-11 has a half-life of 20.3 minutes and is the only isotope of carbon with associated penetrating radiation due to its positron emission. Carbon-11 is also used in $^{13}$CO for red cell volume measurements. Despite its short half-life (20 minutes) it is potentially important as a label for organic metabolites and extensive research is under way to achieve this by recoil labelling, biosynthesis and by exchange reactions.

Rubidium-81
Rubidium-81 is of interest because of similarities in its metabolism with potassium. It has also been used to label red blood cells in spleen function studies.

Cesium-127
Cesium-127 has been produced in our cyclotron with good yield and is of great interest because of its localization in myocardium. Extensive research is planned to develop its role in the study of myocardial lesions as well as for a soft-tissue tumor indicator.

Indium-111 and Gallium-67
Indium-111 and gallium-67 are also produced with substantial yield on our machine and are of great interest as potential indicators for the location of cancer in nonosseous tissue.

Development of the methods for production of these nuclides has required investigation of alternative nuclear reactions, investigation of target design and measurement of yield as a function of target thickness, bombarding particle, energy, etc. Sterility and pyrogen-free conditions have to be maintained and are continually checked. Once the details of a procedure have been developed, repeated production runs are tested for pyrogenicity and sterility. After F.D.A. approval, use in patients is initiated.

A further medical application is the use of fast neutrons for direct irradiation of patients with cancer. This was initially investigated at the University of California by Dr. R. S.

### TABLE 2 – YIELD OF RADIONUCLIDES WITH THE SLOAN-KETTERING INSTITUTE CYCLOTRON

| Radio Nuclide | Half Life | Target | Production Reaction | $\mu$Ci/$\mu$A† | $\mu$Ci/$\mu$A at sat‡ |
|---------------|-----------|--------|---------------------|----------------|---------------------|
| N-13          | 10 m      | H$_2$O | $^3$He,2n           | 6.1x10⁴        | 6.1x10⁴            |
| F-18          | 110 m     | H$_2$O | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| P-30          | 2.5 m     | CaSi   | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| S-37          | 5.1 m     | Ar     | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| K-43          | 22 h      | Ar     | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| Cr-48         | 23 h      | Ti     | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| Cr-51         | 28 d      | V      | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| Fe-52         | 8 h       | Cr     | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| Ga-67         | 78 h      | Zn     | $^3$He,2p           | 1.5x10⁴        | 1.5x10⁴            |
| Se-73         | 7.1 h     | Ge     | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| Rb-81         | 4.7 h     | NaBr   | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| Rb-82m        | 6.3 h     | NaBr   | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| In-111        | 2.8 d     | Cd     | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| I-121         | 2.0 h     | Sb     | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| I-123         | 13 h      | Sb     | $^3$He,2p           | 3.4x10⁴        | 3.4x10⁴            |
| Xe-123        | 2.0 h     | $^{125}$Te (80%) | $^3$He,2p | 670             | 670             |
| Cs-127        | 6.2 h     | NaI    | $^3$He,2p           | 922            | 922             |

*E.O.B.=End of Bombardment
†$\mu$Ci=microcuries
‡$\mu$A=microamperes hours
¶For a saturation bombardment
Stone who concluded that the effects on normal tissue were unacceptably severe. More recent developments have indicated why the early study may have shown unnecessarily severe reactions and interest has been rekindled in the possible therapeutic use of neutrons. Unlike X-rays and electrons, whose therapeutic effectiveness is dependent on the state of cell oxygenation, the response of tissue to neutrons is much less dependent on oxygenation and this may make them more effective in tumor therapy. The physical and biological bases of this are being investigated with our neutron reactions, as is being done with other neutron sources in other laboratories.

The neutrons from the cyclotron can also be employed in a variety of reactions for both in vitro and in vivo activation. For example, the total amount of calcium in the skeleton can be determined by neutron activation of calcium-48 to radioactive calcium-49. This may provide a method of gaining knowledge of the amount of calcium in patients, a factor which is not obtainable by other methods.

The cyclotron presents us with a challenging weapon in the fight against cancer. Its versatility and promise for the future are shown by the varied applications described above. In the immediate years ahead, we hope continuing research effort will enable us to exploit to the full the great potential offered by this facility and thus contribute toward the ultimate resolution of the cancer problem.

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