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Medical Applications of Synchrotron Radiation at the National Synchrotron Light Source*

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Introduction

In the short time that synchrotrons have been available to the scientific community for X-ray and VUV science, they have been used in virtually all areas of medicine which use ionizing radiation (Thomlinson, 1992a). The research has not been confined to any one facility, but is being carried out throughout the world. The overriding features of the synchrotron beams which make them applicable to medical research are their extremely high intensity and broadband energy spectrum. Several orders of magnitude separate the smooth, continuous spectrum of the synchrotron from the sharply peaked characteristic emission spectrum of a conventional source. Basically, the high intensity and tunability allow monochromatic beams to be generated at virtually any energy. The standard problem of beam hardening in both medical imaging and therapy is eliminated by the monochromatic beams since the energy spectrum does not change with passage through tissue. The tunable spectrum allows enhancement of images and therapeutic dose by selection of the most effective energy for a given procedure.

The beams are very highly collimated in the vertical direction and are thus ideal for research programs such as protein crystallography, small angle scattering and computed tomography. The radiation is plane polarized in the plane of the storage rings where the radiation is produced. This feature is exploited by researchers studying the helicity of DNA with a technique known as circular dichroism.

A summary of the current medical research areas at the National Synchrotron Light Source (NSLS) is given in Table 1. Surveying the table, it is obvious that the research already

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covers all dimension scales from the atomic and molecular level (EXAFS and structuralbiology), up through DNA (photon activation therapy and structural biology), chromosomes and cells (X-ray microscopy), to tissues and organs (angiography, computed tomography, and mammography). The research is directed at brain and breast cancer imaging and therapy, development of new drugs, evaluation of cellular function, and coronary artery imaging in a manner which is safer for the patient than conventional means. In some cases like structural biology and EXAFS the research will only be in-vitro due to the basic research nature of the subject matter. This manuscript will discuss the research presently underway at the NSLS with the exception of structural biology and EXAFS. References to those technologies, and to work being done at other laboratories, will be found in the proceedings of this conference as well as in a previous summary article (Thomlinson, 1992a).

NSLS Medical Research Facility

Medical research programs have requirements which are different than those of standard material or chemical science synchrotron beamlines. At the NSLS, the X17B superconducting wiggler beamline meets all of the requirements. With a high critical energy of 20 keV, the photon spectrum extends to sufficiently high energies to satisfy the need for high flux at energies at and above the iodine K-absorption edge (Thomlinson et al., 1988). The high energy spectrum is essential for imaging at the iodine K-edge, imaging of the human cerebrum and thorax, and for radiotherapy programs.

Human studies should be done in a clinical research environment. In parallel with the development of the wiggler beamline, the NSLS developed the Synchrotron Medical Research Facility (SMERF) as an end station on beamline X17B (Thomlinson et al., 1992b). SMERF is

an ambulatory health care facility with full clinical support for patients in the coronary angiography project and, in the future, in the multiple energy computed tomography and radiotherapy programs. At present, SMERF is the only synchrotron facility dedicated to human research. In addition to the human studies area, X17B supports a materials research area in which many prototype medical programs are being developed.

Basic Research Programs

X-ray microscopy

The X-ray microscope has been developed to image, on a scale of microns or less, the elemental distribution in tissues and cells. The intent is to supplement existing technologies such as the electron or light microscopes. There are two distinct types of instruments, differentiated by the photon energy range over which they operate and, to some degree, the spatial resolution of the images. The first type of microscope is the scanning X-ray microscope which uses X-rays in the wavelength range between the carbon and oxygen K-edges (2.5-4.0 nm) where water is relatively transparent. Wet biological specimens can be imaged with high contrast, especially in systems employing the technique of K-edge digital subtraction imaging. There are a number of soft X-ray microscopes operating around the world. The present generation of microscopes has been constructed on undulator lines to take advantage of the extremely high brightness of the sources. The NSLS soft X-ray microscope can be configured to operate in the scanning transmission mode, the photoelectric emission mode, or holographic imaging mode (Rarback et al., 1990).

In order to image dense, high Z materials or to study trace elements of high Z materials in a matrix such as bone, it is necessary to turn to the hard X-ray microscope. In the present

context that means an instrument operating on a hard X-ray line at energies greater than 3 keV. An example of such a beamline is one built at the NSLS (Jones et al., 1990). Images can be produced by measurement of fluorescent X-rays or of the attenuation of the incident beam by the specimen. Maps of the elemental distributions or linear attenuation coefficients can be made by scanning of the specimen past the beam. Because of the higher energies of this instrument, computed microtomography can be used for nondestructive images through the specimen in either fluorescence emission or absorption mode.

Photon activation therapy

Photon Activation Therapy (PAT) is a system being investigated as a therapeutic modality for the treatment of malignancies. The PAT process involves the incorporation of a target halogen atom in the immediate vicinity of a cell's critical site (DNA), followed by the activation of this atom with photons of energies suitable for the induction of the photoelectric effect and its concomitant Auger cascades. The Auger electrons impart significant damage at the critical site. The effectiveness of PAT for radiotherapy lies in the fact that the malignant cell pools are often rapidly dividing relative to the surrounding tissue cells. It is therefore possible to incorporate stable halogens such as bromine or iodine into the cellular DNA. Radiation would then preferentially damage the malignant cells since they have incorporated the halogen. Previous results have failed to show any substantial enhanced sensitivity due to Auger processes resulting from the photoelectric absorption of photons above the K-edge of bromine. However, a recent study has been done at the NSLS in which iodine has been incorporated into the DNA of V-79 Chinese hamster cells (Laster et al., 1992). The iodine was in the form of stable I-127 in the halogenated pyrimidine 5-iodo-2'-deoxyuridine (IdUrd) and was incorporated into the

cellular DNA during cell replication as an analog of the natural base thymidine. Monochromatic photons above (33.4 keV) and below (32.9 keV) the iodine K-edge were used to determine if any additional biological damage would accrue from the Auger cascades. The total therapeutic gain (relative to non-iodinated controls) was a factor of 3.1. PAT has been described as a potential clinical modality for the treatment of malignant brain tumors (Fairchild et al., 1987).

Applied Research Programs

Transvenous coronary angiography

Certainly the most advanced of the applied medical research programs at synchrotron facilities are those doing transvenous digital subtraction coronary angiography. The field traces it origins back to the proposal that the intensity of the synchrotron X-ray beams would be high enough to allow imaging of the coronary arteries following venous injection of an iodine containing contrast agent (Hughes et al., 1983). The goal is to reduce the risks associated with the conventional arterial catheterization technique.

The most advanced of the human coronary angiography projects is that at the NSLS. It was first developed at Stanford University and the early human studies were done at the Stanford Synchrotron Radiation Laboratory (Rubenstein et al., 1986). In 1989 the project moved to the NSLS where the hardware was installed in SMERF. In this technique an iodinated contrast agent is injected into the venous system. Once the contrast agent reaches the coronary arteries, a series of dual energy images is taken in the line scan mode as the patient is traversed through the fan X-ray beams. A digital subtracted image is obtained with very high iodine contrast. The present spatial resolution is 0.5mm with each line of data acquired in 4 msec. Since October 1990, human patients have been studied in SMERF. Thus far, excellent images of the right

coronary artery and preliminary images of the left anterior descending coronary artery have been obtained (Thomlinson et al., 1991; Thomlinson et al., 1992b).

Multiple energy computed tomography

Monochromatic synchrotron X-rays have two distinct advantages over the wide-energy band bremsstrahlung radiation obtained from X-ray tubes for radiology in general and for computed tomography (CT) in particular. The monochromatic X-rays do not "beam harden", an effect in which the low energy end of the photon spectrum attenuates more than the high energy end. Second, the tunability of the spectrum allows both dual-photon absorptiometry (DPA) and K-edge subtraction (KES) imaging. A system called Multiple Energy Computed Tomography (MECT) has been developed at Brookhaven National Laboratory which will utilize synchrotron radiation beams for DPA and KES of the human cerebrum (Dilmanian et al., 1991).

DPA is an imaging method in which the attenuation of X-rays at two greatly different energies (e.g. 40 and 100 keV) is measured to obtain two different images of the subject. One mainly represents the concentrations of low Z elements and the other mainly the intermediate Z elements. The DPA image of the low Z element groups will emphasize concentrations of H, C, N, O, and Na while that of the intermediate Z group will emphasize P, S, Cl, K, Ca, and Fe. In particular, the second group includes the neurologically important elements K and Ca. KES utilizes the large rise in the photoelectric absorption cross section at the K-edge of elements. The introduction of a contrast agent and imaging with two energies on either side of the k-edge can give high contrast images of the vasculature in the brain.

The MECT system being developed at the NSLS employs monochromatic and tunable 33-100 keV X-rays from the superconducting wiggler beamline. The CT configuration is that

of a fixed, horizontal fan beam and a subject seated in a rotating chair. The KES studies will image the brain, large blood vessels of the head and neck, and arteriovenous malformations. DPA will obtain images that map the low Z and intermediate Z elements. The system is expected to provide 0.25 mm spatial resolution with unprecedented image contrast and accuracy of elemental quantification.

Radiotherapy

The development of dedicated high energy monochromatic and geometrically well controlled synchrotron beams almost immediately gave rise to ideas directed at increasing the amount and effectiveness of X-ray dose to tumors and decreasing the dose to the normal surrounding tissues (Larsson, 1983). As discussed above, photon activation therapy is one way of increasing the effective dose to the malignant cells since they preferentially incorporate the halogen in the DNA relative to the non-proliferating normal cells. Coupling that to the ability to tune the highly monochromatic synchrotron radiation beams (which are inherently collimated) to the relevant K-edge should provide a very efficient tool for some forms of external beam therapy.

The monochromatic synchrotron radiation beams can be very highly collimated in either planar or cylindrical beam geometries and can be either focusing or non-focusing. With the development of high energy synchrotron sources it is now possible to have beams with energies in the range of 50 keV and above. These are excellent for targeting tumors deep in the brain. The geometry is ideal for stereotactic radiosurgery and the monochromatic beams will not beam harden. Hence, the radiation dose to the patient will be efficiently delivered. With the development of high Z element complexes which can be bound to tumors, the tunability of the

source will allow selective targeting of the tumors.

Mammography

For many years, researchers have discussed the possible use of the intense, monochromatic X-rays in the range 1 - 30 keV for enhanced contrast in the images of breast tumors. The enhancement over present radiation sources may come from better spatial resolution and greatly enhanced tissue differentiation (dense tumor mass vs. surrounding soft tissue) due to the monochromaticity of the beams. Preliminary studies have been performed at the NSLS (Price, 1991). Several groups are planning advanced programs to compare the radiography of excised breast tumors taken with both conventional X-ray sources and the synchrotron beam.

Conclusion

The near term future of synchrotron based medical programs is clearly along the lines of basic research in which drug development may take place, new radiotherapy techniques may be developed and tested, and advanced imaging systems may become successful. These will all certainly continue on existing first and second generation synchrotron sources and tomorrow's third generation sources. Whether or not any programs reach the level of clinical diagnostic or treatment centers will depend on the success of the present research programs and the acceptance of these technologies by the medical community.

Table 1

Medical Research at the NSLS

	TYPE OF IMAGE OR THERAPY	PRIMARY ANATOMY	RESEARCH STATUS
Angiography	Projection Image	Coronary Arteries	Human Studies
Computed Tomography	CT Image	Head and Neck	Animal Models
Radiotherapy	External Beam	Brain Tumors	Animal Models
Mammography	Projection Image	Breast Tumors	In-Vitro
Photon Activation Therapy	Internal/External Beam Therapy	Brain	In-Vitro
X-Ray Microscopy	CT or Projection Image	Cells and Tissues	In-Vitro
Structural Biology	Crystallography	Protein Structure	In-Vitro
EXAFS	Absorption Spectroscopy	Local Molecular Structure	In-Vitro

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