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DEPARTMENT OF ENERGY

FINAL REPORT

GRANT NO. DE-FG02-87ER60519

NEW IMAGING SYSTEMS IN NUCLEAR MEDICINE

DISCLAIMER

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JANUARY 1, 1993 - DECEMBER 31, 1995

1.0 Project Overview

The broad aim of this program has been to improve the performance of positron emission tomography (PET) to achieve high resolution with high sensitivity. Towards this aim, we have carried out the following studies:

1. Explored new techniques for detection of annihilation radiation including new detector materials and system geometries. Specific areas that we have studied include:

   Exploration of factors related to resolution and sensitivity of PET instrumentation including geometry, detection materials and coding.

   Exploration of techniques to improve the image quality by use of depth of interaction and increased sampling.

2. Complete much of the final testing of PCR-II, an analog-coded cylindrical positron tomograph, developed and constructed during the current funding period.The following specific areas were investigated:

   Demonstration of the performance of PCR-II in phantoms and animal models. Resolution, sensitivity, count rate capability and scatter coincidences have been measured.

   Evaluation of existing software for reconstruction of the three-dimensional data set and correction for uniformity and other factors.

3. Developed the design of a positron microtomograph with mm resolution for quantitative studies in small animals. A single slice version of this device has been designed and studied by use of computer simulation.

4. Continued and expanded our program of biological studies in animal models. Current studies have included imaging of animal models of Parkinson's and Huntington's disease and cancer. These studies have included new radiopharmaceuticals and techniques involving molecular biology.

2.0 Background and Significance

Our work has contributed significantly to the recent growth and wide application of PET in biological and medical imaging. We have developed a number of positron imaging instruments (1-7) and have the distinction that every instrument has been placed in operation for basic research and/or clinical study. At the present time, PCR-I remains in continuous demand for animal studies in neurology and oncology. This instrument also served as a prototype for PCR-II, a volume sensitive tomograph with 3 mm spatial resolution. PCR-II is entering its evaluation program.

As PET instrument resolution improves, physical limitations become more significant in instrument design, becoming major effects at 3 mm resolution and dominant effects as 1 mm is approached. To better understand how to incorporate such effects into instrument design we have studied the limitations of PET imaging imposed by them. Positron range is one of the most important effects, small angle deviation of the two annihilation quanta is a second important effect.

Achievement of resolution for human imaging beyond that predicted for PCR-II will require major innovations. This could take the form of new scintillators or solid state detectors or improved geometry of detection. We have studied many of these areas. The further evolution of PET instrumentation requires a careful study of new detector materials and new photo-sensors as well as methods to improve sampling, sensitivity and data rate capacity. The use of depth-of-interaction information has been explored to increase off-axis sampling and to permit use of thicker detectors without loss of resolution.

Another area of major effort by our laboratory has been the development of three dimensional reconstruction algorithms to fully exploit the data produced by PCR-II (8-10). Accurate reconstruction of truncated 3D data sets produced by our instrument as well as all other current 3-D designs is required to preserve the quantitative nature of PET imaging as the transition is made from instruments using only transverse or small divergence coincidence rays to the use of wide divergence rays in instruments such as PCR-II. A further issue resulting from the use of wide divergence data is the fact that the very large data sets generated result in the need for much faster computational hardware and software in order to maintain tractable imaging protocols.

The use of Fourier domain reconstruction results in an order of magnitude decrease in computer time in comparison with convolution backprojection (11). These algorithms are being applied to the processing of data from PCR-II. We have recently initiated a study on the use of super-computers and in particular multi-processor super-computers for the rapid reconstruction of the large datasets resulting from imaging with PCR-II. A second area of development at our laboratory, which impacts the ability to produce fully quantitative results, has been in the study of approaches to dealing with the incomplete datasets generated by truncated 3D detector systems and other corrections (12).

Another important aspect of our development program has been the use of computer simulation to study aspects of instrument design and data processing prior to construction of instruments (13). All of our instruments during the past 15 years have

been designed using this approach. Recently we have applied it to the design of a 1 mm PET system specifically for imaging small animals. We believe that this instrument could have a great impact on the field of biological research, especially with small animals, permitting studies to be carried out in vivo that can now only be carried out using carbon-14 or tritium labeled compounds and autoradiography following sacrifice of the animal. It should be noted that studies carried out at different time points which normally require the sacrifice of multiple animals, could with a small animal imager, be done with fewer animals and improved data since each animal could be its own control.

One of the most important aspects of our program is that instrument development has been carried out in a setting rich in biological and medical research so that new instruments and concepts have been rapidly tested in real biomedical applications. For example, PCR-I has been in almost continuous operation for over 5 years obtaining useful biological information in animal models. This experience has been useful in the development ofdesigns of even higher resolution PET devices.

We have pursued a number of new applications of PET imaging particularly in the areas of cancer research (14-16) and research related to the brain (17-28). Studies in monkey models of Parkinson's and Huntington's disease have indicated the potential of this area of research. The applications that we are addressing are extremely important to the wider utilization of PET imaging in biological and medical research.

3.0 Progress Report

Our work during the current grant period has led to progress in four specific areas related to the overall aims of the program. These areas include: (1) Basic limitations to high resolution PET, (2) Completion of software and evaluation of performance of PCR-II, (3) Preliminary design studies for a mm resolution small animal PET and (4) Biological applications. Each of these areas is discussed in more detail in the following sections.

3.1 Basic Limitations to High Resolution PET

Resolution in positron tomography is limited by positron range, small angle deviation, and sampling. Each of these factors must be considered in the optimization of an instrument design. The ideal detector material for PET systems stops all photons that enter the detector and provides high spatial, temporal and energy resolution for the recorded event. These parameters cannot be optimized simultaneously in a single detector material or geometry since the optimal PET device must be matched to the source geometry and imaging requirements.

Scintillators

High-Z inorganic scintillators (such as NaI(Tl) and BGO) have been widely used as PET detectors, providing high stopping power and photofraction adequate for scattered photon rejection. However, both of these scintillators have limitations, low mass density in the case of NaI(Tl) and lower light output in the case of BGO. Both are relatively slow. Table I lists properties of these two scintillators as well as a number of

other candidates. A number of these scintillators - particular rare earth scintillators - are very promising (29,30,38). However these scintillators are not yet available in adequate quantities and at reasonable cost.

Crystal Scintillator			BGO	NaI(Tl)	GSO(Ce)	CWO	CeF3	CsI(pure)	BaF2	LSO	LUALO
Density		g/cm2	7.13	3.67	6.71	7.9	6.16	4.53	4.89	7.4	8.34
Radiation length		cm	1.11	2.6	1.38	1.06	1.68	1.86	2.06	1.2	1.05
Decay constant	fast	ns	300	230	50	5000	10	10	0.6	12	17.9
	slow	ns			600			1000	620	42	
Light yield	fast	relat.	10	100	20	35	4.5	4	5	75	39
	slow	relat.						4	16		
Peak emission	fast	nm	480	415	430	480	300	305	210	420	365
	slow	nm					340	400	310		
Radiation hardness		log(rad)	6	3	8		7	5	7	7	7
Hygroscopicity			no	yes	no	no	no	slight	no	no	no
Melting point		oC	1050	65	1950	1300	1443	621	135	1000	1000

Table I. Properties of High Density Scintillators

Positron range

Positron range degrades resolution since an annihilation event occurs at the end of the positron track rather than at the location of the radioactive atom. This effect provides a physical limit to resolution and has been studied by a number of investigators. Derenzo observed the range of positron emitters in polyurethane foam absorbers (31). Measurements were made using a line source in air and a line source in aluminum casing. The latter measurements was used to deconvolve the effects of small angle deviation and source and detector size from the overall line spread function. Using

range-energy data and various assumptions concerning the diffusion of positrons in matter, we developed a model that fits the data from Derenzo's experiment (32) and permits the estimation of the range effect. The combined LSF is given by the two-dimensional convolution of these terms.

$$L_t(r) = L_c(r) * S(r)$$

where L_t is the combined LSF, L_c the camera's LSF describing all systematic effects other than positron range, and S is the LSF due to positron range blurring. We have carried out these calculations over a range of beta end-point energies and three hypothetical isotopes having atomic numbers 10, 25 and 40. The camera LSF has been taken to be Gaussian in form, and we have calculated combined LSF's for camera resolution of 1 mm, 2 mm, and 3 mm FWHM (Figures 1a and 1b). As expected, the degree of image resolution loss is strongly dependent on the end-point energy. For a camera possessing an intrinsic spatial resolution of 1 mm FWHM the positron range effect degrades the resolution by only a small amount for positron energies less than 1 Mev. The two isotopes most suitable for high resolution imaging are F-18 and C-11 with end point energies of 0.63 and 0.98 Mev.

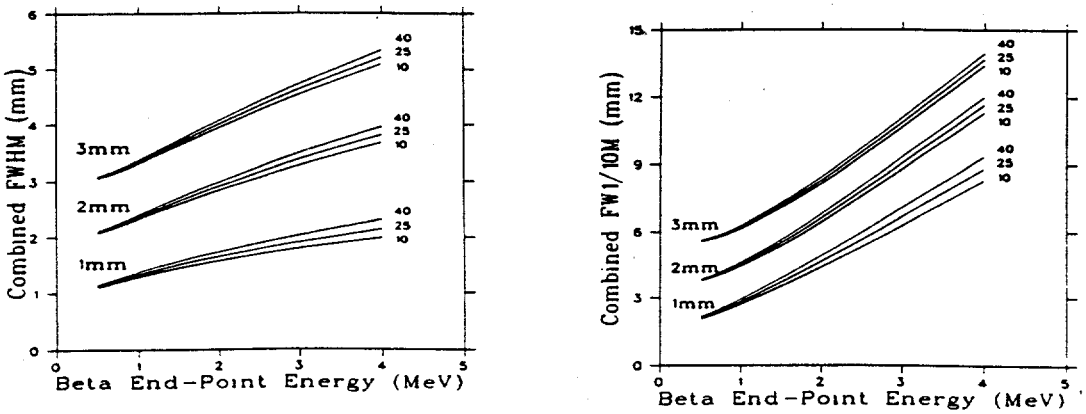

Figure 1(a) shows FWHM and 1(b) shows FW10M as a function of beta end point energy in Mev and atomic number of the source.

Angular deviation

Although the two annihilation quanta emerge nearly back-to-back, there is a small angular deviation that depends on the material within which the annihilation events occur and the temperature. For positron tomography the shape of the distribution is not of interest since tissue is nearly equivalent to water, but the spread of the distribution (approximately 0.25°) does degrade the resolution. The effect on the FWHM of a point source at the center of a tomograph will be a function of its

diameter. This effect will range from 0.5 mm for 25 cm diameter to 1.0 mm for a 50 cm diameter detector array.

We have studied the combined effect of range and angular deviation for a high resolution animal imaging systems by simulation and measurement. We studied the effect of range on a high resolution animal device as described below. Figure 2 shows simulated data for line sources spaced at 2 mm. Figure 2a shows the image of this source including range and angular deviation, assuming a ring of 11.5 cm diameter and 1 mm BGO detectors, for F-18 having a mean energy of 0.2025 Mev. Figure 2b shows the effect of angular deviation and range when using C-11 having a mean energy of 0.326 Mev. The effect of the increased range of C-11 is clear but the two lines are still clearly defined, showing that 1 mm resolution can be achieved with low energy beta emitters such as F-18 and C-11. Higher energy beta emitters such as N-13 would have significantly lower resolution.

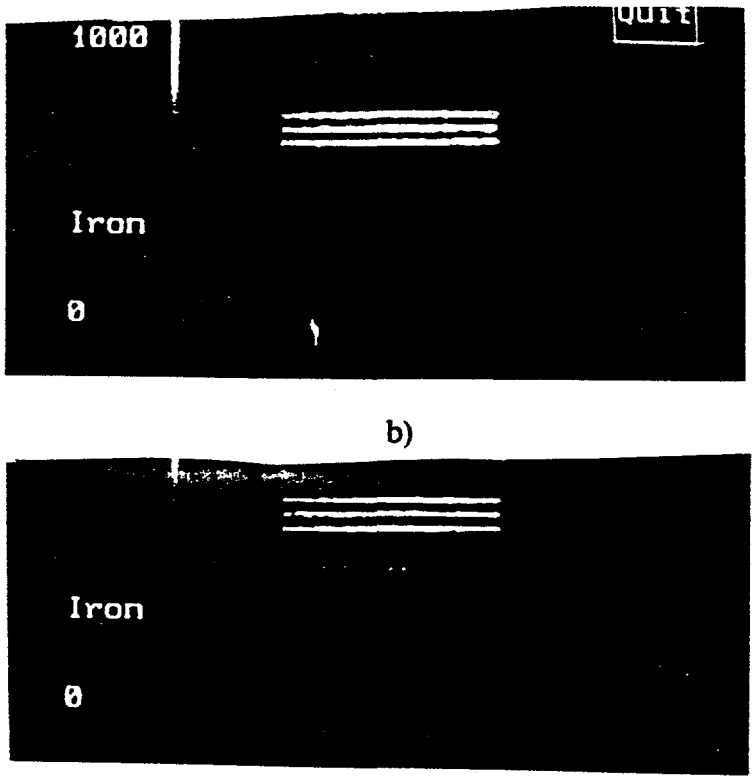

Figure 2. Simulated images of two line sources spaced at 2 mm with (a) F-18 and (b) C-11.

Sampling

In a device that samples a volume with discrete detector elements, the image "signal" is in effect filtered (or smoothed) by the detector response or aperture function. High spatial frequency components in the signal are thus attenuated by this filtering process.

The Nyquist theorem states that an analog signal can be reconstructed from a set of discrete samples, provided that the sampling frequency (reciprocal of the sample spacing) is at least twice the highest frequency present in the signal. Sampling signals at rates below this critical frequency result in a form of error called aliasing. In practice, some aliasing error is always present for signals of finite spatial extent. In a static PET system, the sampling requirement limits the resolution to the crystal width.

A second sampling requirement is present in tomographic imaging in order to assure that the desired resolution is available throughout the field of view. To support resolution (r) over the field of diameter (d) with the diameter of the detector array (D), it is necessary to acquire ($2\pi d/r$) angular samples. A ring of contiguous detectors provides adequate angular sampling over the inner one-half of the ring (i.e. for $d < (D/2)$).

Sensitivity

The factors discussed above provide limits on the resolution of a PET system. They impose an upper bound for the FWHM resolution of a single point source imaged by a PET instrument. Most "real" imaging experiments do not consist of resolving isolated point sources, but require distinguishing hot (or cold) regions within a field of activity, or quantitating activity concentration in a region of interest. Other factors impose practical limits on the useful resolution of a PET system in an imaging situation. These include detector geometry which determines detection efficiency, prompt and random coincidence rates and related factors.

The statistical requirements for tomographic imaging are particularly important for high resolution imaging. The signal-to-noise ratio (SNR) at the center of a three-dimensional image of a spherical object (diameter d) is related to the total counts obtained (N) and the effective resolution element size (r) by the formula:

$$SNR = [3N/4]^{0.5} (r^2/d^2)$$

Thus, the maximization of the true coincidence rate and minimization of the random and prompt scatter coincidence rates is a complex process involving many aspects of the design of the positron imaging system.

3.2 Evaluation of PCR-II

PCR-II is our current generation of PET imaging devices, the design, construction and evaluation of which has been supported from this program. PCR-II is a volume imaging device and uses a detector array of 12,800 3 x 5.7 x 30 mm BGO elements forming a continuous cylinder consisting of 20 contiguous rings each with 640 detectors (Figure 3). The design employs 1760 phototubes, each with its processing logic. The operating conditions are established by 20,000 computer controlled registers. In bringing the system on line, no major design flaws were encountered. However, a great deal of effort went into identifying and elimating system bugs. Our efforts are now aimed at determining the detailed performance of the device while its evaluation is underway.

The innovative optics for this design has resulted from simulation studies. No reflector is used between the detectors, reducing the light loss and improving uniformity. The camera does not use mechanical motion simplifying rapid sequential imaging and reducing artifacts. Software is now available to perform the reconstruction of three-dimensional data from the camera. Programs to manipulate and view the three-dimensional images are being tested. Data is currently being obtained in list mode. A block mode interface has been built and will be implemented. Uniformity studies have commenced and we expect detailed phantom studies to begin shortly.

The advantage of a PET cylindrical camera that uses cross-plane rays is its high sensitivity, which can be an order of magnitude greater than traditional designs using only transverse rays. However, the cross-plane rays present a set of challenges for data processing. We have been and are continuing to study and solve these challenges as outlined below.

The first problem is the increased data processing time due to the greatly increased size of the data set. Without cross-plane rays, the number of coincidence pair channels in the data set is approximately equal to the number of pixels or voxels in the reconstructed image. Since the cross-plane data is redundant and is only used for increased sensitivity, the number of data channels with cross-plane rays is an order of magnitude greater than the number of voxels. The solution is to do the reconstruction in the frequency domain, and thereby avoid the time consuming process of back-projection. The time saving factor is approximately M/8 where M is the number of voxels in one in-plane direction.

A second problem results from the fact that the ends of the cylinder make the data set non-stationary in the sense that the shape of the fan of possible coincidences from a crystal near the camera center is different from the shape of the fan from a crystal near a camera end. Also, the missing cross-plane data at the ends of the cylinder must be considered. (Figure 4) We have successfully implemented the following two different solutions in the frequency domain. The first solution is to reconstruct the missing data from the in-plane rays. The second solution is to process the data in such a way that the effect of the missing data does not blur axially into the region where there is no missing data and thereby cause artifacts.

The third problem concerns calibration of detector sensitivity. The lack of stationarity prevents the direct extension to a cylindrical camera of the filtering method for detector calibration used on our single ring camera. The solution is to artificially force stationarity by modifying, in the computer, the collected sensitivity calibration data.

We have had experience using parallel implementation of several competitive 3D reconstruction algorithms (3D filtered backprojection and 3D inverse Fourier transform of the Fourier space matrix) pertaining to high-resolution PET on the 512-node Connection Machine system CM-5. Techniques for vector and parallel architectures have been studied. We expect to reduce the reconstruction time for the competitive algorithms to under one minute.

We have been reluctant to publish definitive papers on PCR- II until the results

of the evaluation program are available. We are now preparing two papers, one on the design and performance of PCR-II and the second on preliminary results of phantom and animal studies.

3.3 Design of High Resolution PET for Animal Study

Biological applications have driven a continuing interest in the development of high resolution PET. Several papers have appeared recently aimed at high resolution for animal studies (33-35) but none have aimed at mm resolution instruments. Also a number of high energy detection systems such as scintillating fibers have been proposed but are not likely to compete with more conventional systems in the near future. We have studied a number of aspects related to the design of a high resolution animal PET (36,37) tentatively to be called a microtomograph.

Scintillator material: Table I presents data on a number of scintillators that could be considered candidates for the microtomograph. The properties that impact the performance of a scintillator for the microtomograph include stopping power, quantum efficiency, light output and decay time. In particular, the rare earth scintillators offer great promise in light output and decay time, both important in achieving the ultimate resolution. However, at present these materials are not available in adequate amounts or if available are extremely expensive. For example the cost of LSO is almost two orders of magnitude greater than BGO.

Optics: The design of the optics that conducts the light from the scintillators is extremely important in achieving high resolution. The amount of light that leaves the detector array depends on the nature of the optical surface. This is a particularly important factor with block detectors. We use a program that traces light photons from scintillator to phototube. The variables that have been studied are scintillator dimensions, surface treatment, light coupling and dispersion in the light pipe. The output of this analysis is the light spread function (LSF).

Analog coding: In general, most positron tomographs use either a continuous ring of detectors or blocks of detectors. Both approaches are valid and depend crucially on the LSF and on the treatment of the reflecting material at the ends of the blocks and on the surfaces of all detectors. The photon tracing program mentioned above can be used to study these and other geometries.

Light detectors: Phototubes still remain the most sensitive and fastest light detectors although solid state detectors are making rapid improvements in both of these areas. The most promising of these, avalanch photodiodes, are currently not widely available with the specifications needed for PET. Phototubes still remain the light detector of choice because they have the advantage of reliability and are relatively inexpensive.

Front end electronics: The design of circuits for front end detection is relatively complex since coincidence circuits typically run at 5 - 10 ns. In addition provision

is usually made to introduce test pulses at the phototube output to adjust the timing. Automatic gain control is almost essential for complex multiphototube systems.

Coincidence and single channel electronics: Both single channel and coincidence signals are required to process the coincidence data. The single channel data can be used to balance the phototube gain and to estimate dead time effects. The coincidence circuits must be capable of receiving the high data rates encountered when large amounts of activity are seen by the detectors.

Data Storage and analysis: The data is initially received in random list mode. The coincidence data is usually derandomized by a FIFO circuit before transfer to the computer where the reconstruction analysis is performed. The uniformity correction can be made by using data from a uniform source. Alternatively, a number of ingenious techniques for correcting for nonuniformity are available. We anticipate that a number of computer programs will be available to carry out the primary reconstruction either using back-projection or filtering in Fourier space.

Display: We have available a number of sophisticated display programs such as SimVIEW, developed at MIT, and various commercial programs. The problem in using packaged programs is that a number of modifications must be made to use the data from the tomograph and to apply it to the biological tasks.

We have carried out a number of design studies, primarily through the use of computer simulation to evaluate the properties of various detector geometries and materials for a 1 mm resolution animal PET device. The detection properties of BGO and LSO were calculated using Monte Carlo techniques. A uniform beam of 511 Kev photons, 1mm wide and 5 mm high was directed towards the center of a bar shaped detector. The fraction of photons interacting and the fraction of various events that exceeded an energy threshold were recorded for increasing bar thickness and energy threshold. Events recorded included photoelectric, single interaction and all interactions within the beam profile. The results of these simulations, shown in Figure 5, indicate several useful properties. First, the detection efficiency using either of these materials is greater than 30% and secondly that more than 70% of events will be single interaction events. The predominance of such events would enhance the ability to make depth-of-interaction corrections for PET. This would significantly increase the sampling rate.

Several experimental measurements to test the feasibility of BGO, LSO and LUAO as detectors for a 1 mm system were also carried out. Figure 6 shows the relative quantum efficiency for these materials measured in the geometry illustrated. The results indicate that LSO and LuAO have respectively 4.5 and 1.8 times the quantum efficiency of BGO.

A block detector with light sampling similar to that proposed by Wong (39) was used to estimate spatial resolution for BGO and LSO. Because only six LSO crystals were available, the space between crystals was filled with lucite spacers. The width of the elements was uniformly 1 mm with 13 elements per phototube. Reflective optical boundries were used at the ends of the block and transparent boundries between

elements to optimize uniformity of light collection. Note that this choice does not optimize the spatial resolution. Measurements were carried out using a 125 Kev energy threshold.

Figure 6 also shows the results of this study. It is clear that the larger light output of LSO improves the ability to resolve 1 mm elements. However, BGO also can resolve the elements although not as clearly as LSO and remains a viable candidate for the 1 mm PET.

Figure 7 shows a schematic drawing of a possible design for a microtomograph capable of producing 1mm resolution images over a region of 5 cm diameter. This would be adequate for imaging of brain and body organs of small animals and imaging of brain in monkeys.

3.4. High Resolution Techniques in Biological Applications

We have carried out a number of studies in small animals brain, heart, tumor and other tissues using PCR-I to demonstrate the need for high resolution and sensitivity to obtain quantitative physiological information. These studies indicate the necessity for higher resolution in animal imaging such that images yield the same relative detail in small animals as that in humans.

The goal of positron emission tomography is to measure analytically and noninvasively the radioisotope concentrations in local regions of anatomical structure. There are many physical factors which affect the accuracy of these measurements. The relationship of these physical factors to known anatomical structures can provide insight into quantitative errors occurring in a specific study. All imaging systems experience quantitative measurement inaccuracies as object size is reduced below the spatial resolution of the imaging device. Inaccuracies exhibited by such small objects are a function of their size, shape, and position in the image plane and relationship to neighboring regions. An understanding of these interactions provides the basis for avoiding errors in interpreting quantitative data pertaining to small objects and possible correction factors that can allow for more accurate quantitation of these structures. Table II shows biological data of brain size in small animals and Table III shows average radioactivity concentration for 2FDG. Table IV shows the effect of partial volume to the detection efficiency at different coronal planes of striatum and cerebellum in cynomolgus monkey brain when different resolutions of imaging system are used. This data show that using PCR-I with spatial resolution of 4.5 mm (FWHM) we can obtain accurate data at two levels of putamen and at one level of caudate in cynomolgus monkey. If the resolution is 1 mm, accurate data will be observed at all levels. We have found in biological studies in Huntington's and Parkinson's disease models that different part of striatum have different characteristics for degeneration process as well as for cell implantation induced recovery.

To demonstrate the resolution of PCR-I, a series of bone studies in rabbit head was carried out. Fluorine-18 ion in water was injected i.v., and serial images with 2 mm axial intervals were obtained 1 h postinjection in coronal section of the rabbit head using a computer controlled imaging table connected to PCR-I. Transverse and sagittal slices were processed afterwards from the coronal data (Figure 8). High resolution images of

blood flow and glucose metabolism in dog heart were obtained using PCR-I in the gated data collection mode. Cardiac gating was used to obtain time-resolved transverse sections at 40 msec intervals throughout the cardiac cycle. Eight to ten transverse sections acquired with a thickness of 5 mm were sufficient to span the heart. In cooperation with Dr. Derek Rowell at MIT gated volumetric images of glucose metabolism in dog heart have been prepared. High resolution PET imaging techniques were used to study glucose metabolism in rat stroke model. The PET imaging results had a good correlation with autoradiographic and magnetic resonance images (17). High resolution PET imaging has made possible to determine the phenotypic effects of oncogenes. Studies were performed to estimate tumor glucose utilization in human tumor xenografts and in genetically defined tumors implanted into immunodeficient mice. Glucose consumption was significantly different in various cell line tumors, and the metabolic rate of glucose utilization correlated with the tumor growth (14). Receptor studies have been done to study dopamine D_1-receptor binding and dopamine terminals in primate brain (Figure 9). These imaging techniques are applied in animal models to study degeneration of dopamine terminals in Parkinson's disease model (18, 19, 27) and degeneration of neurons in Huntington's disease model (23, 26). In addition, these imaging techniques are used to follow recovery after transplantation with fetal porcine cells (Figure 11) (21, 25).

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26. Brownell A-L, Hantraye P, Wullner U, Hamberg L, Shoup T, Elmaleh D.R, Frim DA, Rosen B, Brownell GL, Isacson O: Study of glucose utilization, dopamine receptors and hemodynamics in a primate model of Huntington's disease. Exper. Neurology 125: 41-51, 1994.

27. Wullner U, Pakzaban P, Brownell A-L, Hantraye P, Burns L, Shoup T, Elmaleh D, Spealman RD, Brownell G.L, Isacson O: Dopamine terminal loss and onset of motor symptoms in MPTP treated monkeys - a positron emission tomography study with ^{11}C-CFT. Exper. Neurology 126: 305-309, 1994.

28. Madras BK, Elmaleh DR, Meltzer PC, Liang AY, Brownell GL, Brownell A-L: Positron emission tomography of cocaine binding sites on the dopamine transporter. In: Imaging Techniques in Medications Development: Preclinical and Clinical Aspects. pp. 57-69. NIDA Research Monograph 138, 1994.

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31. Derenzo SE: Precision measurement of annihilation point spread distribution for medically important positron emitters. In: Positron Annihilation, Hasiguti RR, Fujiwara, Eds. Japan Institute of Metals, Sendati, Japan, pp. 819-823, 1979.

32. Palmer MR, Brownell GL. Annihilation density distribution calculations for medically important positron emitters. IEEE Transactions on Medical Imaging. II:373-378, 1992.

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34. Murthy K, Thompson CJ, Lin-Hinz C, Jolly D: A study of the light output and energy resolution of small BGO crystals. Nucl. Sci. Symp. & Med. Imag. Conf. Vol. 3:1352-1356, 1994.

35. Daghighian F, Lovelock DM, Eshaghian B, Shenderov P, Willins JD: Design considerations of an animal PET scanner utilizing LSO scintillators and position sensitive PMTs. Nucl. Sci. Symp. & Med. Imag. Conf., 3:1343-1346, 1994.

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37. Burnham CA, Elliott JT, Kaufman DE, Chesler DA and Brownell GL. Single interaction PET detectors. IEEE Nucl. Sci. Symp. Conference Record, 2:1332-1336, 1990.

38. Ficke DC and Ter-Pogossian MM, Miyaoka RS and Lewellen TK: A GSO(Ce) block type detector for high count rate PET applications. Nucl. Sci. Symp. & Med. Imag. Conf.,

4:1859-1863, 1994.

39. Wong W-H, Uribe J, Hicks K, Zambelli M: A 2-Dimensional detector decoding study on BGO arrays with quadrant sharing photomultipliers. IEEE Trans. Nucl. Sci. Vol. 41, No. 4. 1453-1457. 1994.

40 Hoffman EJ, Huang S and Phelps MM: Quantitation in positron emission computed tomography. I. Effect of the object size. J. Comput. Assist. Tomogr. 3:299-308, 1979.

4.0 PERSONNEL

See attached CV's.

5.0 Equipment

There is no non-exempt equipment (See Property Certification).

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Gordon L. Brownell	Physicist, Professor Emeritus

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Bucknell University Lewisburg, PA	B.Sc.	1943	Physics
Massachusetts Insitute of Technology Cambridge, MA	Ph.D.	1950	Physics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1950-1951 Assistant Physicist, MGH, Boston, MA
1951-1961 Associate Physicist, MGH, Boston, MA
1950-1956 Research Associate in Physics, M.I.T,, Cambridge, MA
1956-1961 Assistant Professor, Nuclear Engineering, M.I.T.
1959-1980 Associate, Retina Foundation, Boston, MA
1961-Pres. Physicist, MGH, Boston, MA
1961-1970 Associate Professor, Nuclear Engineering Dept., M.I.T., Cambridge, MA
1970-1994 Professor, Nuclear Engineering Department, M.I.T., Cambridge, MA
1994-Pres. Professor Emeritus, Nuclear Engineering Dept., M.I.T., Cambridge, MA

Honors

Honorary Member: Argentina Medical Association
Fellow: American Physical Society; American Nuclear Society
American Association of Physicists in Medicine
Member: Radiation Research Society; American
Association of Physicists in Medicine;
Society of Nuclear; Biophysics & Health Physics Society

Awards

1987 The Coolidge Award, AAPM, Detroit, Michigan
1985 Honorary President, Second International BNCT Conference, Boston, MA
1983 President, 3rd Symposium of Med. Appl. of Cyclotrons, Turku, Finland
1983 Co-chairman of the First International BNCT Conference
1979 Director and Fellow of the American Nuclear Society
1979 George VonHevesy Memorial Award, Innsbruck, Austria
1975 Paul C. Aebersold Award of Society of Nuclear Medicine

Selected Publications:

Brownell G.L., Burnham C.A. and Chesler D.A.: High resolution tomograph using analog coding. Chaper 2 in The Metabolism of the Human Brain Studied with Positron Emission Tomography, edited by T. Greitz et al., Raven Press, Medical and Scientific Publishers, 1985.

Kairento A-L., Brownell G.L., Elmaleh D.R. and Swartz M.R.: Comparative measurement of regional blood flow, oxygen and glucose utilization in soft tissue tumour of rabbit with positron imaging. The British Journal of Radiology, 58, 637-643, 1985.

Stearns C.W., Chesler D.A., Kirsch J.E. and Brownell G.L.: Quantitative imaging with the MGH analog ring positron tomograph, IEEE, NS-32 (1), pp. 989-890, February 1985.

Burnham C.A., Bradshaw J., Kaufman D., Chesler D.A. and Brownell G.L.: Positron source position sensing detector and electronics, United States Patent, Patent Number 4,531,058, July 23, 1985.

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Stearns C.W., Burnham C.A., Chesler D.A. and Brownell G.L.: Simulation studies for cylindrical positron tomography. IEEE Trans. Nucl. Sci., NS-35 (1) 708-711, 1988.

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Burnham C.A., Kaufman D.E., Chesler D.A., Stearns C.W., Correia J.A., Brownell G.L.: A low Z PET detector. IEEE Trans. Nucl. Sci., NS-37(2), 832-834, 1990.

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Brownell A-L., Kano M., McKinstry R., Moskowitz M.A., Rosen R., Brownell G.L. PET and MR studies of experimental focal stroke. J. Comput. Assist. Tomog. 15:376-380, 1991.

Burnham C.A., Kaufman D.E., Chesler D.A., Gregoire M-C. and Brownell G.L.: MGH cylindrical PET operational characteristics. IEEE Nuclear Science Symposium, Orlando, FL., October 27-31, 1992, (Abstract).

Hantraye P., Brownell A-L., Elmaleh D.R., Madras B.K., Spealman R.D., Wullner U., Brownell G.L., Isacson O. In vivo assessment of dopamine fiber loss in a primate model of Parkinsonism. Neuro Report 3:265-268, 1992.

Schumacher J.M., Hantraye P., Brownell A-L., Riche D., Madras B.K., Davenport P.D., Maziere M-A., Elmaleh D.R., Brownell G.L., Isacson O.: A primate model of Huntington's disease: Functional neural transplantation and CT-guided stereotactic procedures. Cell Transplantation 1:313-322, 1992.

Melder R.J., Brownell A-L., Shoup T.M., Brownell G.L., Jain R.K.: Imaging of activated natural killer cells in mice by positron emission tomography: Preferential uptake in tumors. Cancer Res 53:5867-5871, 1993.

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BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Charles A. Burnham	Associate Physicist

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Northeastern University, Boston, MA	B.Sc.	1960	Electrical engin.
Northeastern University, Boston, MA	M.Sc.	1962	Electrical engin.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1960-1963	Engineer, Atomium Corporation, Billerica, MA
1963-1969	Assistant Applied Physicist, Physics Research Lab, MGH, Boston, MA
1969-1973	Associate Applied Physicist, (Medicine) MGH, Boston, MA
1971-1973	Associate in Medicine (Physics), Harvard Medical School, Boston, MA
1973-pres.	Associate in Radiology (Physics), Harvard Medical School, Boston, MA
1973-pres.	Associate Physicist (Radiology), MGH, Boston, MA

Publications:

Correia J.A., Burnham C.A., Chesler D.A., Elmaleh D.R., Alpert N.M., Brownell G.L.: Positron cameras in nuclear medicine. Journal Selected Papers in Physics, 209:189-199, 1980.

Burnham C.A., Bradshaw J., Kaufman D., Chesler D.A., Brownell G.L.: Application of a one dimensional scintillation camera in a positron tomograpbic ring detector. IEEE Meeting, San Francisco, Vol. NS-29, No. 1, Feb. 1982.

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Florida, 10/31-11/2, 1984.

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Yamada Y., Venegas G.J., Burnham C.A., Hales, C.A.: Assessment of local alveolar ventilation in intermittent positive pressure ventilation and high frequency ventilation with a PET scanner (Abstract) 1986 Annual meeting of American Society of Anesthesiologists, Vol. 133.

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Burnham C.A., Kaufman D., Chesler D.A., Stearns C.W. and Brownell G.L.: Cylindrical PET detector design. IEEE Trans. Nucl. Sci. NS-35 (1) 675-679, 1988.

Yamada Y., Burnham C.A., Hales C.A. and Venegas J.G.: Regional mapping of gas transport during high-frequency and conventional ventilation. J. Appl. Physiol., 66(3), 1989.

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Burnham C.A., Kaufman D.E., Chesler D.A., Stearns C.W., Correia J.A., Brownell G.L.: A low Z PET detector. IEEE Trans. Nucl. Sci., NS-37(2), 832-834, 1990.

Burnham CA., Elliott JT., Kaufmanm D., Chesler DA. and Brownell G.L.: Single Interation PET Detectors. IEEE, NSS Conference Record 2:1332-1336, 1990.

Burnham C.A., Kaufman D., Chesler D.A., Chen Y., Gregoire M.C., Brownell G.L.: MGH cylindrical PET detector characteristics. Proceedings of the IEEE Medical Imaging Conference, Santa Fe, NM, Nov. 1991 (Abstract).

Burnham C.A., Kaufman D.E., Chesler D.A., Gregoire M-C. and Brownell G.L.: MGH cylindrical PET operational characteristics. IEEE Nuclear Science Symposium, Orlando, FL., October 27-31, 1992 (Abstract).

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
David A. Chesler	Associate Physicist

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	B.Sc.		Electrical engineering
M.I.T.	M.Sc.		Electrical engineering
M.I.T.	Sc.D.	1955	Electrical engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1955-1957 Staff Engineer, Instrumentation Laboratory, MIT
1957-1960 Research Assistant, Research Laboratory for Electronics, MIT
1960 Instructor, Electrical Engineering, MIT, Cambridge, MA
1960-1970 Senior Engineering Specialist, General Telephone & Electronics Corp.
1970-1972 USPHS Fellowship, Massachusetts General Hospital, Boston, MA
1970-1973 Research Fellow in Medicine, Massachusetts General Hospital, Boston, MA
1973-1974 Reseach Fellow in Radiology, Massachusetts General Hospital, Boston, MA
1973-1975 Research Associate in Radiology, (Physics), Harvard Medical School Boston
1974-1975 Assistant Physicist, Radiology, Massachusetts General Hospital
1975-pres. Associate Physicist, Radiology, Massachusetts General Hospital
1975-pres. Principal Research Associate in Radiology (Physics), Harv. Med. Sch.

Publications:

Stearns C.W., Chesler D.A., Brownell G.L.: Three-dimensional image reconstruction in the fourier domain, IEEE NS-34, (1) pp. 374-378, 1987.

Stearns C.W., Burnham C.A., Chesler D.A. and Brownell G.L.: Simulation studies for cylindrical positron tomography. IEEE Trans. Nucl. Sci., NS-35 (1) 708-711, 1988.

Burnham C.A., Kaufman D., Chesler D.A., Stearns C.W. and Brownell G.L.: Cylindrical PET detector design. IEEE Trans. Nucl. Sci. NS-35 (1) 675-679, 1988.

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Chesler D.A. and Stearns C.W.: Calibration of detector sensitivity in positron cameras. IEEE Trans. Nucl. Sci., NS-37(2), 768-772, 1990.

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Chesler D.A., Gregoire M.C.: Frequency domain method for computing missing input data for a cylindrical PET camera. Proceedings of the IEEE Medical Imaging Conference,

Santa Fe, NM, Nov, 1991 (Abstract).

Burnham CA., Kaufman DE., Chesler D.A., Chen Y., Gregoire M.C., Brownell G.L.: MGH cylindrical PET detector characteristics. Proceedings of the IEEE Medical Imaging Conference, Santa Fe, NM, Nov. 1991 (Abstract).

Chesler D.A., Gregoire M-C.: Frequency domain method for computing missing input data for a cylindrical PET camera. Proceedings of the IEEE Medical Imaging Conference, Santa Fe, NM, Nov, 1991 (Abstract).

Chesler D.A. and Gregoire M-C.: Fast and accurate sensitivity calibration method for 3D cylindrical PET detector. The Society of Nuclear Medicine, 39th Annual Meeting, Los Angeles, CA., June 9-12, 1992, (Abstract).

Chesler D.A. and Gregoire M-C.: Calibration of detector sensitivities in a cylindrical PET camera. IEEE Nuclear Science Symposium, Orlando, FL., October 27-31, 1992, (Abstract).

Gregoire M-C. and Chesler D.A.: Comparison of two fast reconstruction methods for a cylindrical PET camera. IEEE Nuclear Science Symposium, Orlando, FL., October 27-31, 1992, (Abstract).

Burnham C.A., Kaufman D.E., Chesler D.A., Gregoire M-C. and Brownell G.L.: MGH cylindrical PET operational characteristics. IEEE Nuclear Science Symposium, Orlando, FL., October 27-31, 1992, (Abstract).

Kwong K.K., Chesler D.A., Zuo C.S., Boxerman J.L., Baker J.R., Chen Y.C., Stern C.E., Weisskoff R.H. Spin echo (T2, Tl) studies for functional MRI. Proceedings of the Soc. of Magn. Reson. in Med., New York, NY, page 172, 1993.

Carrere B.J., Christensen J.D., Boada F.E., Yu J.X., Reese T.G., Chesler D.A., Vevea J.M., Kosewski J.M., Mills C., Thulborn K. Absolute tissue sodium concentration maps of rat brain by $^{23}Na/^{1}H$ MR projection imaging. Proceedings of the Soc. of Magn. Reson. in Med., New York, NY, page 400, 1993.

Neuder M.S., Weisskoff R.M., Kwong K.K., Chesler D.A., Moore J.B., Rosen B.R. Echo planar imaging studies of blood-brain barrier permeability variations in vivo to Gd-DTPA with consideration given to the influence of T2 effects. Proceedings of the Soc. of Magn. Reson. in Med., New York, NY, page 683, 1993.

Kwong K.K., Chesler D.A., Boxerman J.L., Davis T.L., Weisskoff R.M., Rosen B.R. Strategies to reduce fMmacrovascular effects in fMRI. Proceedings of the Soc. of Magn. Reson. in Med., San Francisco, CA, page 650, 1994.

Kwong K.K., Chesler D.A., Weisskoff R.M., Rosen B.R. Perfusion MR imaging. Proceedings of the Soc. Magn. in Med., San Francisco, CA., page 1005, 1994.

McKinstry R.C., Weisskoff R.M., Chesler D.A. Rosen B.R. Ultrafast MRI of brain water mobility in stroke: A theoretical paradigm and an approach for statistical validation. Proceedings of the Soc. Magn. in Med., San Francisco, CA., page 1062, 1994.

BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME	POSITION TITLE
Anna-Liisa Brownell	Assistant Professor

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Helsinki, Finland	M.SC.	1969	Physics, Chemistry and Mathematics
University of Helsinki, Finland	Ph.D.	1974	Medical Physics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

1967 Research Associate, Academy of Finland
1969-1970 Associate in Physics, Faculty of Science, University of Helsinki, Finland
1970-1972 Associate in Physics, Faculty of Medicine, University of Helsinki, Finland
1972-1974 Research Associate, Academy of Finland
1975-1984 Senior Hospital Physicst, University Central Hospital of Helsinki, Finland
1979-pres. Docent in Applied Physics, Faculty of Science, University of Helsinki, Finland
1981-1983 Research Fellow, Harvard Medical School, Massachusetts General Hospital, Boston, MA
1984-1989 Chief Hospital Physicist, University Central Hospital of Helsinki, Finland
1986-1987 Visiting Scientist, Massachusetts Institute of Technology, Cambridge, MA
1987-pres. Lecturer, University of Technology, Helsinki, Finland
1987-1991 Research Fellow, Harvard Medical School, Massachusetts General Hospital, Boston, MA
1992-1994 Instructor in Physics, Harvard Medical School, Boston, MA
1992-1994 Assistant-in-Physics, Massachusetts General Hospital, Boston, MA
1994- Assistant Professor, Harvard Medical School, Boston, MA
1994- Assistant Physicist, Massachusetts General Hospital, Boston, MA

Selected publications (from 99; original articles (77), reviews/chapters (22)):

Launes, J., Nikkinen, P., Lindroth, L., Brownell, A.-L., Liewendahl, K., Iivanainen, M. Diagnosis of acute Herpes Simplex encephalitis by brain perfusion single photon emission computed tomography., The Lancet. May 1988, pp. 1188-1191, 1988 and The Yearbook of Neurology and Neurosurgery 10-11. Currier, R.D., DeJong, R.N., Crowell, R.N. (eds). Yearbook Medical Publishers, Inc. Chicago, 1990 and in: The Yearbook of Nuclear Medicine 15-7. Hoffer, P.B., Core, J.C., Gottschalk, A., Sostman, D., Zaret, B.L., Zubal, I.G. (eds). Year Book Medical Publishers, Inc. Chicago, 1990.

Launes, J., Nikkinen, P., Lindroth, L., Brownell, A.-L., Liewendahl, K. and Iivanainen, M. Brain perfusion defect size in SPECT predicts outcome in cerebral infarction., Nucl. Med. Comm. 10:891-900, 1989.

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Kallinowski, F., Brownell, A.-L., Vaupel, P., Brownell, G.L. Combined tissue oxygen tension measurement and positron emission tomography studies on glucose utilization in oncogene transformed cell line tumor xenografts in nude mice., Brit. J. Radiol. 64:350-359, 1991.

Brownell, A.-L., Kano, M., McKinstry, R., Moskowitz, M.A., Rosen, B., Brownell, G.L. PET and MR studies of experimental focal stroke., J. Comput. Assist. Tomog. 15(3):376-380, 1991.

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