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MICHAEL REESE MEDICAL CENTER
and
ILLINOIS INSTITUTE OF TECHNOLOGY

LABORATORIES OF RADIATION BIOLOGY AND BIOPHYSICS
Chicago, Illinois

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MASTER

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I. Introduction

This is the first general progress report on the research being carried out in the Biophysics Laboratory of the IIT Department of Physics and the Department of Medical Physics at Michael Reese Medical Center. This collaboration started in 1963, stimulated by the now classic pulse radiolysis experiments of E. J. Hart and J. W. Boag several years before which led to the definitive identification of the hydrated electron. At that time, the IIT group was studying the photochemical generation of hydrated electrons and the implications of this process for photobiology. The availability of a 35 Mev electron linear accelerator (LINAC) in the (then) Tumor Clinic of MRH led to plans for the initiation of a pulse radiolysis research program, which was assisted by a \$22,000 grant from NIH general research support funds. An effort was made in the early work to coordinate the pulse radiolysis investigation at MRH with flash photolysis and related photochemical studies at IIT, an approach that has been continued through the present. To date, 21 research associates from 6 countries have contributed to these programs since 1962 and the work has led to four Ph.D. and five M.S. theses. Generous support from the National Institute of Health, the National Cancer Institute, and the U.S. Energy Research and Development Administration totaling more than one million dollars has been a major factor in making this training available to these students and young Ph.D.'s.

This biophysics research makes a significant contribution to the overall academic program of the IIT Department of Physics with the participation of three full-time faculty members (L. I. Grossweiner,

J. F. Baugher, G. E. Cohn), two adjunct faculty members (J. Ovadia, A. G. Kepka), two research associates (A. G. Kaluskar, J. Lee), and four pre-doctoral students. The participating scientific staff from the MRH Department of Medical Physics are J. Ovadia, L. I. Grossweiner, A. G. Kepka, L. Patterson, J. L. Redpath and 3 research technicians.

This group collaborates also with L. Cohen, M.D. and M. Colman, M.D. of the MRH Department of Radiation Oncology and with C. M. King of the MRH Division of Cancer Research. We wish to acknowledge also the cooperation of the Chemistry Division of the Argonne National Laboratory (P. Fields, Director) in making available their unique experimental facilities.

L. I. Grossweiner

Chairman and Professor of Physics
Illinois Institute of Technology
and
Senior Consultant, Department of
Medical Physics, Michael Reese
Medical Center

J. Ovadia

Director, Department of Medical Physics
Michael Reese Medical Center
and
Adjunct Professor of Physics
Illinois Institute of Technology

II. Progress Reports

1. Computer-controlled Pulse Radiolysis

L. K. Patterson

A computer-controlled, pulse radiolysis unit for gathering data related to transient optical absorptions has been developed around the Medical Physics PDP-11/computer, a Biomation 8100 Transient Recorder, and the existing pulse radiolysis apparatus. The computer and associated hardware provide properly synchronized measurements of monitoring light intensity, pulse dose, and the transient changes in transmittance as a function of time. By making pre-programmed measurements of transient behavior as a function of time at various wavelengths, data are gathered which the computer can display as time-dependent spectra or which it may analyze for kinetics parameters. The processed data and descriptions of experimental conditions are stored on magnetic tape, providing a compact and convenient filing system. The data-gathering sequence and data treatment are not dissimilar to those described earlier: Patterson and Lilie, Int. J. Rad. Phys. Chem., 6, 129 (1974).

2. Fluorescence Lifetime Apparatus

A. Kaluskar and L. K. Patterson

Boxcar averaging is a process of controlled sampling and sample averaging. In this process, the amplitude of a specific point on a repetitive signal is measured over many cycles and the average value is computed. The sampling aperture is scanned across the signal in order to determine the functional form. The PAR Model 162 Boxcar

Averager is used in combination with the Model 163 Processor Module. This system synchronously samples the input signal with an aperture that can be fixed at a specific point on the repetitive input signal or slowly scanned across the signal so that the synchronous waveform is reproduced at the output.

A "nanosecond" light source for exciting fluorescence is obtained from a Photochemical Research Associates Model 510A gas-filled flash lamp. The lamp profile halfwidth is 3.5 nsec at an average intensity of 2×10^9 photons/flash. The repetition rate can be varied from 5,000 to 30,000 Hz. The fluorescence signals are detected with a IP28A photomultiplier in a divider circuit designed to give 10 mA quiescent current with 1 nanosec time response. Corning filters are used to select the excitation band and the fluorescence signal. The waveforms of the excitation pulse $[EX(t)]$ and the fluorescence signal $[EM(t)]$ are recorded with an x-y plotter. Deconvolution analyses are carried out with the PDP-11 digital computer and Fluorescence lifetimes (τ) are calculated with the formula

$$EM(t) = \int_{t'}^t EX(t') e^{-(t-t')/\tau} dt$$

which is converted to

$$EM(t) = \sum_{t'=1}^{t'} EX(t') e^{-(t-t')/\tau}$$

for computer programming. Values of τ as low as 1 nsec have been obtained and agree with literature results, where available.

3. Properties of Tryptophan Excited States in Micellar Solutions

A. Kaluskar and L. K. Patterson

A molecule whose radiation chemistry is established in water

may behave quite differently in a more complex biological environment. Using surfactant micelles, one may introduce into the aqueous system simple elements of structure which may mimic the hydrophobic and electrostatic interactions of more complex systems. However, before kinetic effects in micelles can be interpreted, the nature of the substrate-micelle interaction must be characterized. Certain substrate molecules exhibit excited states that are very sensitive to their microenvironment and the behavior of the fluorescent state provides a good method for such characterizations.

The three ionic states of tryptophan under acidic, neutral, and basic conditions are expected to interact differently with micelles carrying negative or positive charges. It has been found that at pH 2, the 350 nm fluorescence maximum is shifted to 337 nm in the presence of 0.02 M sodium lauryl sulfate (NaLS) which carries a negative surface charge, while no shift was found with positively-charged cetyltrimethylammonium chloride (CTACl). At pH 11 the behavior is reversed with a red shift to 361 nm in CTACl and no shift in NaLS. These results are consistent with the marked electrostatic interactions. Substitution of bromide for chloride as a counterion in CTACl results in very marked quenching of the tryptophan fluorescence, altering the lifetime from 5.4 nsec to 2.4 nsec at pH 11. Although these data indicate marked interactions with the micellar surface, it is not yet possible to determine whether they reflect a pure electrostatic effect or whether hydrophobic forces also come into play.

4. Laser Flash Photolysis of Aqueous Tryptophan

F. Dudley Bryant, R. Santus, and L. I. Grossweiner

Laser flash photolysis of aqueous tryptophan at 265 nm gener-

ates the neutral radical product of indole ring N-H bond photolysis ($\lambda_{\max}$ 510 nm, $1800 \text{ M}^{-1} \text{ cm}^{-1}$; $\lambda_{\max}$ 330 nm, $3100 \text{ M}^{-1} \text{ cm}^{-1}$), the triplet state ($\lambda_{\max}$ 460 nm), and the hydrated electron as initial products. The photoionization quantum yields for tryptophan, 1-methyltryptophan, tyrosine, and glycine-tryptophan peptides have been determined using ferrocyanide as the reference system. The electron and aromatic radicals decay by a pseudo-first order back reaction of about 1 μsec half-time, leading to residual yields of the separated products after several microseconds significantly smaller than the initial photoionization yield. These kinetics results are consistent with the formation of a loose complex between the hydrated electron and the radical in which recombination competes with separation into free products. A comparable first-order, electron decay stage was observed with tryptophan derivatives, tyrosine, I^- , and $\text{Fe}(\text{CN})_6^{4-}$.

5. The Oxidation of Tryptophan by Radical Anions

J. L. Redpath, R. Santus, J. Ovadia and L. I. Grossweiner

Although the radical anions $(\text{CNS})_2^-$ and Br_2^- have been shown to oxidize aqueous tryptophan (TRP) and TRP in proteins to give transient products with identical absorption spectra, the mechanism of this reaction and identity of the transient product have not been established. We have found that the absorption of the transient radiolysis products in neutral solution have band maxima at 330 nm and 510 nm, and closely resemble the spectrum obtained by ultraviolet flash photolysis of TRP where the hydrated electron is a co-product. The photolysis radical has already been identified with the neutral

species (TRP) by Santus and Grossweiner (1972) who also showed that the photooxidation of 1-methyltryptophan (1-MeTRP) in neutral solution gives a different transient with band maxima at 340 nm and 580 nm attributed to the cation radical. The photolysis of TRP and its oxidation by Cl_2^- in acidic solution also leads to this product.

The object of this study was to explore whether the TRP radical products produced by photooxidation are, in fact, the same as the radiolysis reaction products. Pulse radiolysis measurements were made on TRP and 1-MeTRP to differentiate between the neutral and cationic species. The reaction products with $(\text{CNS})_2^-$ and Br_2^- were compared with a laser photolysis study of the same compounds leading to the same spectra and extinction coefficients. It is concluded that the radical anion reaction products are indeed identical to those produced photochemically.

R. Santus and L. I. Grossweiner, Photochem. Photobiol., 15, 101 (1972).

6. Formation of N-Formylkynurenine from Reaction of O_2^- with Tryptophan

P. Walrant, R. Santus, J. L. Redpath and D. Lexa

N-Formylkynurenine (FK), the primary oxidation product in the metabolism of tryptophan (TRP) has recently been shown to be a photodynamic agent. The primary steps leading to FK formation are not fully understood, although O_2^- ions have been suggested as intermediates in the biological oxidation of TRP by the enzyme tryptophan pyrrolase leading to FK production. The objective of this study was to see if O_2^- ions, produced both radiolytically and electrochemically, contribute to FK formation from TRP. The results show that O_2^- is

the only oxygen species involved in FK formation, in contrast to a previous suggestion that reaction of (TRP) radicals with molecular oxygen leads to FK formation.

7. Flash Photolysis of Enzymes

L. I. Grossweiner, A. G. Kaluskar, and J. F. Baugher

Flash photolysis transient spectra were obtained for lysozyme, trypsin, papain, ribonuclease and subtilisin Carlsberg under uniform conditions and have been analyzed by resolving into components identified with the aromatic amino acid and cystyl residues. Comparisons of the enzyme flash spectra with mixtures of the chromophoric constituents led to transient product quantum yields. The results show the photoionization of aromatic residues constitutes a major initial photochemical reaction in the ultraviolet photolysis of proteins at $\lambda > 250$ nm. The ejected electrons were observed as e_{aq}^- and the disulfide bridge electron adduct, and also must be trapped at unidentified sites. The number of tryptophyl (or tyrosyl) residues photoionized is approximately equal to the number of exposed residues. The flash photolysis data can be related to inactivation by considering how photolysis of these "photolabile" residues can affect enzymic activity, based on the microstructure and available information about permanent alterations and residue specificities. This analysis indicates that hen lysozyme and papain are inactivated by photolysis of a Trp residue adjacent to the key catalytic Ser residue plus other pathways initiated by excitation Tyr and Cys, that the efficient photoionization of Tyr in RNase A is not an inactivating reaction, and that the single Trp residue in subtilisin Carlsberg is photosensitive.

8. Ultraviolet Laser Flash Photolysis Studies of Enzymes

J. F. Baugher and L. I. Grossweiner

A program for the ultraviolet laser flash photolysis on enzymes has been initiated. The quantum yields of electron photoejection at 265 nm have been measured for several enzymes: subtilisin Carlsberg (0.044), subtilisin Novo (0.024), lysozyme (0.013), and trypsin (0.025). The electron quantum yield in papain varies linearly with laser intensity. The ejected electrons decay via pseudo-first order kinetics attributed to intermolecular reactions with the enzyme and with exogeneous electron scavengers when present.

9. Ultraviolet Inactivation of Papain

J. F. Baugher and L. I. Grossweiner

Flash photolysis transient spectra ($\lambda > 250$ nm) of aqueous papain show that the initial products are the neutral tryptophan radical Trp (λ_{max} 510 nm), the tryptophan triplet state ^3Trp (λ_{max} 460 nm), the disulfide bridge electron adduct $-\text{S}^{\cdot}-\text{S}-$ (λ_{max} 420 nm) and the hydrated electron $e_{\text{aq}}^{\cdot}$. The $-\text{S}^{\cdot}-\text{S}-$ yield was not altered by nitrous oxide or air, indicating that the formation of this product does not involve electrons in the external medium. The original papain preparation is activated when irradiated under nitrogen. The action spectrum for this process supports previous work attributing the low initial activity to blocking of cysteinyl site 25 with a mixed disulfide. Flash lamp irradiation in nitrogen led to inactivation at low starting activities and inactivation at higher starting activities, while only inactivation was observed with air saturation. The results are consistent with photoionization

of an essential tryptophyl residue as the key inactivating step.

10. Photoinactivation of Subtilisin Carlsberg

E. Zickgraf and J. F. Baugher

Subtilisin Carlsberg is a serine protease of photochemical interest because it has only one tryptophyl residue and no disulfide bridges. Flash photolysis studies indicate that the single tryptophyl residue is photolabile, as well as eight of the thirteen tyrosyl residues. Photoinactivation measurements ($\lambda > 250$ nm) of this enzyme have shown that the quantum yield is enhanced by the presence of air, not observed when light of wavelengths greater than 280 nm was used. A possible inactivation mechanism is the internal attack of electrons ejected from tryptophan on an essential histidyl residue accompanied by the production of damaging $O_2^{\cdot -}$ generated by photoionization of tyrosyls.

11. Radiosensitization of Hen Lysozyme by Dye Binding

F. T. Tien, A. G. Kepka and L. I. Grossweiner

Earlier pulse radiolysis studies on lysozyme have demonstrated Trp 108 is the principal target of the $(CNS)_2^{\cdot -}$ radical. Photochemical results in this laboratory have shown that the eosin-lysozyme complex is more sensitive to attack by singlet oxygen and the only Trp residue destroyed is Trp 108. From fluorescence studies, we have deduced that eosin binds approximately $7 \text{ \AA}$ from Trp 108 in a hydrophobic box adjacent to the active site. Using the selective nature of the $(CNS)_2^{\cdot -}$ radical, additional information has been obtained on the ionizing radiation damage pathway mediated by the binding of eosin to lysozyme. Spectrophotometric methods were used

to measure the binding constants. Inactivation G-values were measured first in the presence of 0.1 M Cl^- which suppresses dye binding. The results indicate that free eosin competes for OH and $(\text{CNS})_2^-$ in accordance with simple competition kinetics. When complex formation was not suppressed, the eosin-lysozyme complex was 40% more sensitive to $(\text{CNS})_2^-$ attack and 70% more sensitive to inactivation by OH. A detailed kinetic analysis of the pulse radiolysis data was carried out using the PDP 11/45 computer. The results indicate that oxidation of the bound eosin leads to a Trp radical enzyme product. This work shows that eosin binding to lysozyme provides an additional reaction site near an essential residue which enhances the radiosensitivity of the native enzyme.

12. Radiation Inactivation of Bovine Carbonic Anhydrase

J. L. Redpath, R. Santus, L. I. Grossweiner and J. Ovadia

This investigation was carried out to evaluate the role of liganded metal ions in the radiosensitivity of an active metalloprotein. Measurements were made with native zinc carbonic anhydrase (Zn-BCA), the inactive apoenzyme (apo-BCA) and the active cobalt enzyme (Co-BCA). The inactivation results, as assayed by p-nitrophenyl acetate, showed that Zn^{2+} does not alter the sensitivity to oxidizing radicals at pH 7 ($\text{OH}^\cdot$, Br_2^- , $(\text{CNS})_2^-$) but does provide considerable protection against reducing radicals (e_{aq}^- , CO_2^-). This protection can be explained by the temporary reduction of the metal to the mono-cation followed by hydrolysis restoring the active enzyme form. Pulse radiolysis transient spectra of Zn-BCA showed that $(\text{CNS})_2^-$ generates the Trp radical at pH 7 and Tyr at pH 11.

Assays of the permanent residue destruction showed that both tryptophan and tyrosine are lost at pH 7 but no tryptophan is lost at pH 11, indicative of a shift in the site of oxidative attack when the tyrosyl residues are dissociated. Comparison of the inactivation data with the reactivity of $(\text{CNS})_2^-$ for various amino acids indicates that BCA contains essential tyrosyl residues, a hitherto unreported finding. It is well known that histidyl residues are essential in BCA. The higher sensitivity of apo-BCA to e_{aq}^- attack at pH 5, where histidyl residues are protonated, supports the biochemical evidence.

13. The Sensitivity of E. coliphage T₆ to Inactivation by Selective Inorganic Radicals

J. L. Redpath

The radiosensitivity of bacteriophage suspended in buffer has been attributed mainly to indirect effects of primary water radicals on the protein coat of these organisms. The use of selective inorganic radicals (e.g. $(\text{CNS})_2^-$, Br_2^- , Cl_2^- , I_2^- , CO_3^-) as probes of sensitive residues in enzymes has received much attention and were recently used to probe sensitive residues on the protein coat of T₇ phage. The present work was carried out to investigate the sensitivity of T₆ phage to the selective inorganic radicals $(\text{CNS})_2^-$ and Br_2^- and to compare the results with those previously obtained for T₇. It was found that T₆, like T₇, are more sensitive to inactivation by Br_2^- than $(\text{CNS})_2^-$, which has been interpreted as tyrosine and/or histidine residues being more crucial targets than tryptophan. It was also observed, however, that T₆ phage are

about 9 times more sensitive to inactivation by $(\text{CNS})_2^{\cdot -}$ than T_7 implying that tryptophan residues are more essential to the biological function of T_6 than T_7 .

14. Effect of Medium on Radiosensitivity of T_7 Phage

D. Becker, J. L. Redpath and L. I. Grossweiner

The inactivation of T_7 phage by 25 MeV electrons has been measured in the presence of radical scavenging solutes with the objectives of delineating the transition from dominant indirect action to dominant direct action and determining the role of secondary solute radicals. These studies have been carried out in both oxic and anoxic environments. Solutes investigated include glucose, sucrose, ribose, histidine, tyrosine, uracil, nicotinamide, isonicotinic acid, p-nitroacetophenone. Several solutes with the property of binding to DNA have also been studied (see report below). An attempt was made to explain the data obtained with these solutes in terms of a single lethal primary radical such as OH and neglecting secondary radicals, by applying the Hutchinson model for free radical inactivation of enzymes. This model has now been extended to include secondary radical reactions. Oxygen was found to have a variable role in modifying radiosensitivity in these systems, i.e., in some cases it acts as a sensitizer and in others as a protector. The results can be attributed to competitive scavenging of primary reducing radicals, secondary solute radicals and interactions with initial DNA and protein lesions. Of the solutes used, histidine and tyrosine were found to be the best protectors and the sugars the worst, probably attributable to toxic irradiation products.

15. Radiosensitization of T₇ Bacteriophage by Psoralens and Other DNA Interactive Agents

D. Becker, J. L. Redpath and L. I. Grossweiner

The psoralens are in vivo DNA photosensitizers when irradiated from 320 nm to about 380 nm. Active derivatives such as 8-methoxypsoralen (8-MOP) complex with DNA in the dark and form stable photoadducts upon irradiation. The DNA photosensitizing properties do not require oxygen, suggesting that psoralens might act similarly for ionizing radiation. The present work was carried out with T₇ phage as the test system, where the distinction between direct action and indirect action can be evaluated by introducing radical scavengers in the medium. Experiments to date indicate that 8-MOP, 5,8-dihydroxypsoralen and 4,5',8-trimethylpsoralen are all radiosensitizers of anoxic T₇ phage when suspended in a nutrient medium or in an excess of radical scavenger (e.g. histidine), but have no sensitizing effect on oxic phage under similar conditions. We have proposed that the anoxic sensitizing effects of these compounds are due to the promotion of cross-link type lesions, a process which is suppressed by oxygen. The antibiotic anti-tumor agent mitomycin C also selectively radiosensitizes anoxic phage when irradiated in the presence of nutrient medium or radical scavengers.

16. Mathematical Model of Bacteriophage Inactivation

D. Becker, J. L. Redpath and L. I. Grossweiner

A mathematical model has been derived for the inactivation of T₇ phage irradiated by electrons in the presence of chemical agents, taking into account diffusion of the water radiolysis and

secondary solute radicals. Data at various dose rates allowed identification of the fraction of radicals lost to unidentified impurity scavengers. The remaining diffusive radical and direct-hit processes fit the observed data in the form

$$\frac{1}{D_{37}} = \sum \epsilon_i \eta_i$$

where ϵ_i is the probability then an interaction leads to inactivation and the η_i are the number of interactions of the i 'th type per unit dose. The summation includes: attack by water radicals on the protein coat; attack by solute radicals on the protein coat; attack by water radicals on DNA; attack by solute radicals on DNA; direct effect on DNA. The data for amino acids and uracil fit this equation where the ϵ_i values vary with the solute but not with the solute concentration. For psoralen derivatives, the data indicate the DNA terms are functions of the sensitizer concentration. A formula was derived relating the G-value of inactivation to G-values for single-strand breaks, double-strand breaks, nucleotide damage and cross-links. This relation indicates that the sensitization is due to cross-links (or a related damage type excluding enhanced SSB's, DSB's or ND's) and that the efficiency of inactivation for cross-links is about unity.

17. Photodynamic Sensitization by 8-Methoxypsoralen Via the Singlet Oxygen Mechanism

W. Poppe and L. I. Grossweiner

There is ample evidence that photosensitization by furocoumarins does not require oxygen. It is not known how furocoumarins differ from the many synthetic dyes and natural pigments that act as photodynamic sensitizers via the type II (dye-oxygen) mechanism.

We have found that 8-methoxypsoralen (8-MOP) is a good photodynamic sensitizer in aqueous solution, and that singlet oxygen ($^1O_2^*$) generated by triplet energy transfer is the principal reactive intermediate in the inactivation of lysozyme and oxidation of aqueous iodide ion. The triplet state of 8-MOP was identified by flash photolysis in aqueous and glycerol solutions. The decay in glycerol can be analyzed into two, first-order states of 200 μ s and 35 ms lifetimes where the longer-lived species is attributed to a secondary product. Similar transient bands at 600, 480 and 360 nm were obtained in water. A quadrupled Nd-glass laser was employed to measure the triplet decay lifetimes of 1.8 μ s in deaerated solutions and 0.4 μ s under oxygen saturation. The decreased decay lifetime in oxygen corresponds to a quenching rate constant of approximately 1×10^9 l/mol-s. The ability of 8-MOP to act as a photodynamic sensitizer of lysozyme inactivation was shown. An enhanced rate of inactivation in D_2O solvent compared with H_2O is attributed to the corresponding increase in the $^1O_2^*$ decay lifetime from about 2 μ s to 20 μ s. The dependence of the inactivation rate on lysozyme concentration was analyzed by assuming that scavenging of $^1O_2^*$ competes with the solvent-induced decay. A series of runs with oxygen-saturated, 8-MOP solutions in D_2O led to $k_L = 1.3 \times 10^9$ l/mol-s, in satisfactory agreement with $k_L = 1.9 \times 10^9$ obtained for lysozyme sensitization by eosin. The ' D_2O test' was employed also to show that 8-MOP sensitizes the photooxidation of I^- to I_3^- , where previous work demonstrated that $^1O_2^*$ is the major oxidizing agent of I^- with eosin sensitization. The presence of poly(dA-dT) diminishes the sensitizing efficiency of 8-MOP by more

than a factor of 2 in D_2O , suggesting that 8-MOP binding to poly (dA-dT) inhibits the type II pathway. The present results suggest that additional studies should be made on the irradiation conditions that suppress 1O_2 formation in connection with clinical applications of furocoumarins, in view of the high potential for cell damage by this diffusive reactive intermediate.

18. Photodynamic and Photosensitized Inactivation of Yeast Cells

G. E. Cohn, Miss H. Y. Tseng, S. C. Weiss, and L. I. Grossweiner

Photodynamic action has been investigated in diploid yeast cells, a unicellular eukaryote. Eosin Y has been employed as the sensitizer for the irradiation of aqueous yeast suspensions with visible light ($\lambda > 400\text{nm}$). Survival measurements indicate that both eosin and molecular oxygen are required for substantial inactivation, although a small but measurable degree of dose-dependent killing occurs in the absence of oxygen. The ratio of the high-dose photosensitivity (D_0) values determined from the survival curves for oxygen and nitrogen saturation was approximately 1.8. Optical absorption measurements showed that less than 0.8% of the eosin initially present before irradiation was bound to or taken up by the cells. Survival measurements of cells washed after exposure to eosin reveal no significant amount of inactivation. These data indicate that the observed photodynamic inactivation is caused either by unbound, extracellular sensitizers or by sensitizers which can readily enter and leave the cell, with molecular oxygen playing an important role. No appreciable degree of dark recovery from eosin-sensitized photodynamic attack was observed.

Yeast cells have been irradiated also with UV-A ($\lambda > 310\text{nm}$) in the presence of 8-methoxypsoralen (8-MOP), which has been demonstrated to be an anoxic photosensitizer in other systems. Survival curves for irradiation in both oxygen and nitrogen-saturated aqueous cell suspensions have shown that 8-MOP is an extremely potent sensitizer of cell inactivation. At higher doses the exponentially-decreasing regions of the survival curve for nitrogen and oxygen-saturated samples were approximately parallel, but the shoulder observed at low doses was lengthened in oxygen. No evidence for post-irradiation repair was observed following dark liquid holding. Irradiation of cells which were washed following exposure to 8-MOP resulted in minimal killing, indicating that little if any 8-MOP was strongly bound to or taken up by the cells.

19. Spin Label Investigations of Photodynamic Action on Biological Membranes

G. E. Cohn, Miss H. Y. Tseng, S. Peplinski, C. Skupien, and L. I. Grossweiner

Specific alterations in the physical properties of natural and model membrane systems caused by photodynamic irradiation have been studied by means of the ESR spectroscopy of "spin label" molecular probes. Experiments have been performed on purified stearic acid to isolate the effects of photodynamic damage on a hydrocarbon matrix. The data indicate that the irradiation with visible light ($\lambda > 400\text{nm}$) of melted stearic acid containing small amounts of dissolved eosin Y disrupts the normal ordering of the matrix when the sample solidifies. Irradiation produces an increased hindrance to spin label motion and alters the temperature dependence

of label mobility. These effects are more pronounced in the presence of oxygen. ESR spectra of spin labeled yeast cells following photodynamic irradiation suggest a substantial disruption of the membrane structure, even though light scattering measurements do not indicate any significant degree of lysis.

20. Radiosensitization of Serratia Marcescens by Cetylpyridinium Chloride

J. L. Redpath and L. K. Patterson

It has been shown by pulse radiolysis that the surfactant, cetylpyridinium chloride (CPyCl), is capable of oxidizing such species as the isopropanol radical and thymine electron adduct by electron transfer. This electron affinic behavior indicates the potential of CPyCl as a radiosensitizer, and its surfactant characteristics suggest it as a possible probe for radiation damage associated with hydrophobic cellular regions. This surfactant has been shown, at concentrations as low as 1×10^{-6} M, to be an effective radiosensitizer of both oxic and anoxic suspensions of Serratia Marcescens in buffer. At concentrations of 5×10^{-6} M, CPyCl exhibited a dose modifying factor (DMF) of 3.2 in N_2 saturated solutions and 2.5 in O_2 saturated solutions. In parallel measurements, related compounds: ethylpyridinium bromide (EPyBr) and cetyltrimethylammonium chloride (CTACl) were examined as possible sensitizers of the bacteria. The surfactant CTACl contains no electron-affinic pyridinium moiety, but does have the hydrocarbon "tail" sixteen carbons in length; EPyBr contains the pyridinium moiety but has no hydrophobic hydrocarbon entity comparable to the cetyl group. Neither of these compounds enhances the radiosensitivity of the

bacteria at concentrations of 5×10^{-6} M. These findings are interpreted as indicating that the radiosensitizing effects of CPyCl arise from its electron-affinic head group which, through the hydrocarbon group, is bound in a hydrophobic region near a target for potential lethal damage. Such hydrophobic regions exist both in the lipid bilayer of cell membranes and in various macromolecules. The relative values of the DMF suggest that CPyCl may act, at least in part, on a target whose damage is normally fixed by oxygen. Cetylpyridinium chloride has previously been described as a radioprotective agent in reference to its ability to decrease ESR intensities in irradiated chondroitin sulfate systems. If these measurements reflect a scavenging of chondroitin sulfate radicals by CPyCl they are not at variance with our results, since we believe the radiosensitizing action of CPyCl may well be due to its rapid interaction with free radicals produced on cellular macromolecules. However, it is not yet possible to rule out any interference by CPyCl with slower biochemical steps subsequent to irradiation which may result in loss of reproductive capacity.

21. Irradiation-induced Adduct Formation of RNA with Carcinogenic Arylamine Derivatives

J. L. Redpath in collaboration with R. A. Cardona, R. M. Thissen and C. M. King, Division of Cancer Research, Department of Medicine, Michael Reese Medical Center

Many electron-affinic radiosensitizers are known to interact with free-radical induced damage to DNA by forming covalent adducts. Although such adduct formation is potentially lethal, it has also been correlated with cellular mutations and transformations. Many carcinogens which are electrophilic in nature are thought to act by forming adducts with cellular macromolecules. In view of our

interest in combination drug and radiation treatment of cancer, we thought it pertinent to investigate potential carcinogenic hazards of such treatments. The initial studies have been carried out using four known carcinogens which have received much attention in chemical activation studies: 2-acetylaminofluorene, 2-acetylaminobiphenyl and their corresponding N-hydroxy derivatives. We measured the radiation-induced binding of these carcinogenic arylamine derivatives to t-RNA and compared the nature and yield of binding to that obtained by chemical (enzymatic) activation of these compounds. The major precursor of adduct formation was shown to be a short-lived OH-induced RNA intermediate. Oxygen was found to suppress, but not completely inhibit adduct formation. These results are in general agreement with similar studies with electron affinic radiosensitizers. Work is now in progress to attempt to identify the nature of the radiation induced adducts. This is being pursued by studying radiation-induced binding to pure homopolymers. Results to date indicate no base specificity. Enzymatic degradation of the RNA-adducts is being used to try to locate sites of attachment of the carcinogen to the nucleic acid, i.e. base, sugar or phosphate. It is also hoped that radiation chemical studies can be applied to identify the nature of reactive intermediates involved in the chemical activation of these carcinogens.

22. Radiobiological Studies with Experimental Animals

J. L. Redpath in collaboration with L. Cohen, M.D., M. Colman, M.D., and R. David, M.S., Department of Radiation Oncology, Michael Reese Medical Center

These studies are broadly directed at optimization of clinical radiotherapy treatment through improvement of the therapeutic

ratio by:

1. Determination of specific radiobiological parameters for normal tissues and tumors in relation to optimization of radiotherapy treatment by means of selected fractionation regimes.
2. In vivo testing of chemical agents which modify radiation sensitivity. Such agents include anti-tumor drugs and hypoxic cell radiosensitizers.

To date experiments are underway studying the lethality due to the bone marrow and G-I syndromes in mice treated with whole body irradiation by a variety of radiation fractionation procedures. By determining several different fractionation regimes which yield similar radiation reactions, it is possible to compute from the single-hit multi-target radiation lethality model the following radiobiological parameters: mean cellular lethal dose, extrapolation number, the ratio of sublethal to irreparable events, the regeneration rate, and in some instances, the repopulation limit (cell cycles) and a field size or tumor volume factor.

Jigs have also been constructed to allow irradiation of mouse lungs for future studies of this normal tissue. Skin reaction studies of mouse feet have also been initiated. This system will constitute a simple yet quantitative method for evaluating chemical modifiers. C₃H mammary adenocarcinomas have been successfully transplanted into male recipients and the line is being maintained for future tumor studies involving radiation sensitizers.

III. Reporting of Research

Meetings

VII International Conference of Photochemistry, Jerusalem, August 29-September 4, 1973

1. "Photochemical Inactivation of Lysozyme", L. I. Grossweiner
2. "Photochemical Oxidation of Aqueous Iodide by Singlet Oxygen",
A. G. Kepka and L. I. Grossweiner

American Society for Photobiology, Vancouver, B.C., July 22-26, 1974

3. "Photodynamic Action in Hydrocarbon Matrices", G. E. Cohn and
L. I. Grossweiner.

5th International Congress of Radiation Research, Seattle, July 14-20, 1974.

4. "Radiolytic Cleavage of Thymine Dimer", L. I. Grossweiner,
J. A. Vigil, and R. Santus.
5. "Effect of Salt Concentration on the Reactions of the Radical
Anions $(CNS)_2$ and Br_2 with Several Enzymes", J. L. Redpath,
L. I. Grossweiner, and J. Ovadia.
6. "A Computer Controlled Pulse Radiolysis System", L. K. Patterson.
7. "Pulse Radiolysis Study of Carboxy- and Carbanoyl-Pyridinyl
Radicals", P. Neta and L. K. Patterson.

9th Annual Meeting of Biophysical Society, Philadelphia, Pa., February 18-21, 1975

8. "Motion of Impurity Molecules in Solid Unsaturated Lipids",
G. E. Cohn and L. I. Grossweiner.
9. "Effects of Surfactant-Substrate and Surfactant-Radical
Interactions on Radical Reactivity in Micellar Systems",
L. K. Patterson and S. J. Rzed.
10. "The Reaction of Radical Anions with the Lysozyme-Eosin Com-
plex", F. T. Tien, A. G. Kepka and L. I. Grossweiner.
11. "A Comparison of the Sensitivities of E. coliphage T_6 and T_7
to Inactivation by Selective Inorganic Radicals", J. L. Redpath.

12. "Irradiation of the Neck During Childhood: An Assessment of Factors which Influence the Development of Thyroid Tumors in Persons at Risk", M. Colman, L. R. Simpson, L. K. Patterson and J. Ovadia

American Society for Photobiology, Louisville, Ky.,
June 22-26, 1975.

13. "Laser Flash Photolysis of Aqueous Tryptophan", F. Dudley Bryant, R. Santus and L. I. Grossweiner.

E. J. Hart Conference on Aqueous Radiation Chemistry
and Solvated Electrons, Argonne National Laboratory,
July 7-9, 1975.

14. "The Role of the Hydrated Electron in the Photochemical Inactivation of Enzymes", L. I. Grossweiner.
15. "Studies of Hydrated Electron Interaction with the Micelle Potential Field in Mixed Surfactant Systems", L. K. Patterson.
16. "The Role of Metal Ions in the Radiation-Induced Inactivation of the Metalloprotein Bovine Carbonic Anhydrase", J. L. Redpath, R. Santus, J. Ovadia, and L. I. Grossweiner.

VIII Int. Conf. on Photochemistry, Edmonton, Canada,
August 7-12, 1975.

17. "Photochemical Inactivation of Enzymes", L. I. Grossweiner.

IAEA International Symposium on Biological Effects of
Low Level Radiation Pertinent to Protection of Man and
His Environment, Chicago, November 3-7, 1975.

18. "Thyroid Cancer Associated with Radiation Exposure-Dose-Effect Relationship", M. Colman, L. R. Simpson, L. K. Patterson and L. Cohen.

Journal Articles

1. "Photodynamic Inactivation of Lysozyme by Eosin", A. G. Kepka and L. I. Grossweiner; Photochem. Photobiol. 18, 49 (1973).
2. "Intramolecular Energy Transfer in the Lysozyme-Eosin Complex", J. F. Baugher, L. I. Grossweiner and C. Lewis; J. Chem. Soc., Faraday Transactions II, 70, 1389 (1974).
3. "Photochemical Inactivation of Trypsin", A. G. Kaluskar and L. I. Grossweiner; Photochem. Photobiol. 20, 329 (1974).
4. "Mathematical Analysis of Flash Photolysis and Pulse Radiolysis Data", L. I. Grossweiner; Advances in Radiation Research (Ed. Duplan & Chapiro) Gordon and Breach, London, 1973, pp.261-269.

5. "A Summary and Evaluation of Spin Labels used as Probes for Biological Membrane Structure", A. D. Keith, M. Sharnoff and G. E. Cohn; *Biochim. Biophys. Acta* 300, 379 (1973).
6. "ESR Analysis of the Nitroxide Spin Label TEMPONE in Single Crystals of Reduced TEMPONE Matrix", W. C. Snipes, G. E. Cohn and A. D. Keith; *Biophys. J.* 14, 20 (1974).
7. "Thymine Dimer Splitting by Ionizing Radiation", L. I. Grossweiner, A. G. Kepka, R. Santus, and J. A. Vigil; *Int. J. Radiat. Biol.* 25, 521 (1974).
8. "Radiosensitization of Lysozyme by Dye Binding", F. T. Tien, L. I. Grossweiner and A. G. Kepka; *Int. J. Radiat. Biol.* 26, 405 (1974).
9. "The Oxidation of Tryptophan by Radical Anions", J. L. Redpath, R. Santus, J. Ovadia, and L. I. Grossweiner; *Int. J. Radiat. Biol.* 27, 201 (1975).
10. "Radiosensitization of T₇ Bacteriophage by 8-Methoxypsoralen", D. Becker, L. I. Grossweiner, J. Ovadia, and J. L. Redpath; *Int. J. Radiat. Biol.* 28, 195 (1975).
11. "The Role of Metal Atoms in the Radiosensitivity of Metalloproteins; Model Experiments with Bovine Carbonic Anhydrase", J. L. Redpath, R. Santus, J. Ovadia, and L. I. Grossweiner; *Int. J. Radiat. Biol.* 28, 243 (1975).
12. "Photosensitizing Properties of N-Formylkynurenine", P. Walrant, R. Santus, and L. I. Grossweiner; *Photochem. Photobiol.* 22, 63 (1975).
13. "Ultraviolet and Photodynamic Inactivation of Lysozyme", L. I. Grossweiner; *Acad. Brasileira de Ciencias* 45, 45 (1975).
14. "Ultraviolet Inactivation of Papain", J. F. Baugher and L. I. Grossweiner; *Photochem. Photobiol.* 22, 163 (1975).
15. "Photodynamic Sensitization by 8-Methoxypsoralen via the Singlet Oxygen Mechanism", W. Poppe and L. I. Grossweiner; *Photochem. Photobiol.* 22, 217 (1975).
16. "Spin Label Translational Diffusion in Solid Tristearin", G. E. Cohn, A. D. Keith and W. C. Snipes; *Biophys. J.* 14, 178 (1975).
17. "Free Radicals", G. E. Cohn; Invited contribution to the 1976 McGraw-Hill Yearbook of Science and Technology (in press).
18. "Laser Flash Photolysis of Aqueous Tryptophan", F. Dudley Bryant, R. Santus, and L. I. Grossweiner; *J. Phys. Chem.*, 79, 2711 (1975).

19. "Flash Photolysis of Enzymes", L. I. Grossweiner, A. G. Kaluskar, and J. F. Baugher; *Int. J. Radiat. Biol.*, 28, 000 (1976).
20. "Photochemical Inactivation of Enzymes", L. I. Grossweiner, *Current Topics in Radiation Research Quarterly*, 11 (Ed. M. Ebert and A. Howard) North Holland Publishers, Amsterdam, pp. 141-200.
21. "Role des Ions O_2^- dans la Formation de la N-formylcynurenine a Partir du Tryptophane", P. Walrant, R. Santus, J. L. Redpath and D. Lexa; *C. R. Acad. Sci. Paris* 200, 1425-1428 (1975).
22. "The Sensitivity of E. coliphage T₆ to Inactivation by Selective Inorganic Radicals", J. L. Redpath; *Int. J. Radiat. Biol.*, 27, 493 (1975).
23. "Irradiation-induced Adduct Formation of RNA with Carcinogenic Arylamine Derivatives", R. A. Cardona, C. M. King and J. L. Redpath; *Cancer Res.* 35, 2007-2014 (1975).
24. "Radiosensitization of Serratia Marcescens by Cetylpyridinium Chloride: Evidence for Membrane Associated Events", J. L. Redpath and L. K. Patterson; *Radiology*, 118, 725 (1976).
25. "Derivation of Cell Population Kinetic Parameters from Radiobiological Data", L. Cohen and J. L. Redpath; *Radiat. Res.*, submitted.

IV. Seminars Given by Visiting Scientists

1/4/74	Dr. K. M. Bansal Hahn Meitner Institute Berlin	"Application of Polagraphic Techniques to Pulse Radio- lysis Studies"
5/22/74	Dr. Rolf Wideröe, Prof. Dr. Ing. e.h., Dr. med. h.c., Brown Boveri, Basel, Switzerland	"Radiobiology and Radio- therapy"
8/29/74	Dr. G. E. Adams Gray Laboratory, Mt. Vernon Hospital Northwood, Middx.	"New Anoxic Cell Radiosen- sitzers"
10/8/74	Dr. G. E. Adams	"Applications of Fast Response Techniques in Cellular Radiobiology"
2/7/75	Dr. G. Rosenbaum Max-Planck Institut Für Medizinische Forschung Heidelberg, Germany	"Application of Synchrotron Radiation to X-Ray Diffrac- tion in Biology"
5/20/75	H. A. S. van den Brenk, M.D. Director Dimbleby Research Labora- tory, St. Thomas Hospital, London, England	"Growth of Cancer Cells in Irradiated Tissues"
7/10/75	Dr. C. Greenstock Medical Biophysics Branch Atomic Energy of Canada Ltd., Whiteshell Nuclear Research Establishment Pinawa, Manitoba	"Mechanistic Studies of Radioprotection and Radio- sensitization"
7/16/75	Dr. A. J. Swallow Paterson Laboratories Christie Hospital and Holt Radium Inst. Manchester, M20 9BX	"Pulse Radiolysis Studies on the Reduction of Cytochrome-C by Hydrated Electrons"
7/16/75	Dr. M. Faraggi Atomic Energy Commission Nuclear Research Center- Neger, P.O.B. 9001 Beer-Sheva, Israel	"Pulse Radiolysis Studies of the Reduction of Peptides by Hydrated Electrons"
11/5/75	Prof. E. G. Niemann Institut für Strahlengotonik der GSF, Hannover, FRG	"Low Level Radiation Effects on Plants-Biochemical Aspects of Radiation Stimulation"

V. Research Support

1. To Illinois Institute of Technology

U. S. Energy Research and Development Association Contract
No. E(11-1)2217; (L. I. Grossweiner, Principal Investigator)

U. S. Public Health Service Grant No. GM-20117;
(L. I. Grossweiner, Principal Investigator)

2. To Michael Reese Medical Center

U. S. Public Health Service Grant No. CA-13307;
(J. Ovadia, Principal Investigator; L. I. Grossweiner,
Co-Principal Investigator)

Michael Reese Medical Center General Research Support Grant
No.'s 43133 and 43109; (J. L. Redpath and L. K. Patterson,
Co-Investigators)

VI. Report of Activities of Biomedical Computer Section of the Department of Medical Physics

I. Background

The Biomedical Computer Section of the Medical Physics Department has available a PDP-11/45 computer system (see hardware description below) and two full-time personnel whose primary responsibilities relate to the computer. The first phase of the hardware was ordered in February, 1974, and arrived in June, 1974. The system became operational in July, 1974.

The hardware was ordered as a joint venture between the Departments of Medical Physics and Radiation Oncology. Its original intended uses included the following:

1. Patient Radiation Dosimetry (Treatment Planning)
2. Patient Treatment Machine Monitoring
3. Tumor Registry
4. Pulse Radiolysis Research

II. Current Activities

Since the original purchase of the hardware, the planned uses for the computer have expanded considerably. Following is a list of current activities and their status.

A. Radiation Dosimetry and Treatment Planning System

This system has been operational for over a year. It is used routinely on a daily basis by physicists, technicians and physicians in the planning of patient treatments. Every patient starting treatment in the Radiation Oncology Department has at least part of his treatment calculated on the computer.

The PDP-11 treatment planning system supersedes and enhances a previous system used on a commercial time sharing network.

B. Patient Treatment Monitoring

This activity has at present been deferred to a future time. Recent improvements in film verification techniques and positioning aids have lessened the priority of treatment monitoring.

C. Tumor Registry and Radiation Oncology Patient Data Base

The conversion of the Tumor Registry has been deferred at the moment so that it may be incorporated into the Radiation Oncology Patient Data Base. Interest in Oncologic Research has made this a high priority activity. To date, a programming system has been developed to display a "form" on the CRT terminal which solicits information from a physician on a patient. The display program has extensive editing and error-checking facilities for operator convenience. The form itself is generated by the physician using a form generation program. The system is designed to be versatile, so that many different data acquisition applications can make use of the system. The system is designed to be flexible, leaving the data file storage structure up to the individual application.

D. Pulse Radiolysis Research

The pulse radiolysis accelerator control and data acquisition systems became operational in February, 1975. The computer is now used to control the operation of the 40 MeV electron accelerator in "research" mode for basic studies in radiation biology. The designer of this system is Dr. L. K. Patterson of the Medical Physics Department.

An important part of the system is the data display capability which allows a projection of acquired 3-dimensional data

from an arbitrary perspective.

Two physics graduate students from IIT doing their Ph.D. thesis work in the department have written and run programs for their research activities.

E. Operating System Enhancements

Because of the increased demand for the system over that originally planned and the addition of non-standard peripherals, a substantial amount of operating system level programming has been needed. Primary areas of concern have been:

1. System information functions to monitor system use and efficiency.
2. Device handler programs to interface peripherals not normally supported on this operating system.
3. File backup utilities, necessary to maintain file integrity in case of hardware failure.
4. Disassembler programs which produce assembly language source from binary code for the operating system. This source is not provided by the manufacturer except at prohibitive cost. It was necessary to obtain it for the first three activities above.
5. BASIC language processor.
6. An accounting system for future use of the computer by outside institutions.

F. Thyroid Project

A system of programs to acquire patient data for the Thyroid Project and provide error checking and correction were developed. This system was used for initial phases of the pro-

ject's data acquisition. The system was a precursor to the form generation and display programs described in (C) above.

G. Hematology

In recent months, Dr. R. Desser of the Hematology Department has made use of a survival table analysis and graphic display program developed on the PDP-11 for studies on various types of cancers and treatment modalities. He has expressed interest in establishing a comprehensive data base on the computer, possibly supported by research funds.

H. Pediatric Hematology

Dr. R. Chilcote of Pediatric Hematology has expressed interest in using the PDP-11 for oncologic research. There is a possibility here also of outside research fund support.

I. Surgical Pathology Registry

A feasibility and cost study has been made of the possibility of using the PDP-11 for an on-line surgical pathology registry. The Pathology Department is now studying the proposal.

J. BASIC Programming Course

In conjunction with Training and Development, Medical Physics has conducted a 10 week, 2 hr/wk course in computer programming using the BASIC language. The Medical Physics PDP-11 was used for the instruction and laboratory sessions. Mr. L. Simpson of the Medical Physics Department was instructor for the course, which was conducted in two sections of 12 students each.

The BASIC language processor was adapted from another operating system which we use. A quite extensive set of enhancements was added and another set is now planned.

K. Electron Scattering Research

Mr. G. Sandberg of the Medical Physics Department has used the PDP-11 to design a new scattering system for the 40 MeV linear accelerator. This new scattering system will enable a larger field to be used in the treatment of patients on the accelerator. The graphic display and machine control capabilities of the PDP-11 system were of major importance in this effort.

L. Fetal Monitoring Research

The Department of Obstetrics and Gynecology has recently purchased an on-line data acquisition and display system for the monitoring of various physiological parameters of mother and fetus during childbirth. Software development support is being provided by Medical Physics personnel, (Dr. L. K. Patterson and Mr. F. Penner). In addition, software is now being developed on the PDP-11 for transfer to the fetal monitoring system.

III. System Description

A. Hardware

PDP-11/45 with Floating Point Processor Option and Memory Management

RK05 Disk Drives (4) 2.5 megabytes each (intermediate size)

Magtape Drive - 9 track, 800 BPI

Storage Oscilloscope - Tektronix 611

Printer/Plotter (electrostatic) - Varian Statos 31

Terminal Interfaces (4 DL-11's + 2 DC-11's) + 6 terminals Laboratory Data Acquisition and Control - LPS + DR-11C's

B. Software Capabilities

RSX-11D is a real-time, multi-user operating system.

This means that it can handle a number of users simultaneously doing different things. Users are assigned a priority and the system responds in real-time on a priority basis, i.e., the highest priority task capable of being executed gets executed. It differs from true time-sharing in that tasks are not "swapped" in and out of main memory on a time-slice basis, although this mode of operation may be added in the near future for certain classes of users. In practical terms this means that a machine control application such as pulse radiolysis research dosimetry and record keeping.

IV. Personnel

Primary support, both software and hardware is provided by Mr. F. Borger and Mr. L. Simpson. This includes hardware maintenance, daily operations, system level program development and application development. A number of other people use the system to develop their own programs. See part II above.

V. Service

We do not have a maintenance contract on our system. The manufacturer's service organization is called only when the job cannot be handled by our people. During '74-75, total outside service came to \$830. To date this year, it has been \$172. During '74-75, the total spent on replacement parts was \$3,757. This includes both immediate replacements done by Medical Physics personnel and accumulation of commonly used parts for future repairs. The same figure to date for '75-76 is \$806. The total yearly cost of a service contract for the system is \$13,788.

VI. Other Areas of Involvement of Medical Physics Personnel
in Computers

A. Common Radioisotope Facility

One person, Mr. F. Penner, is employed as Common Radioisotope Facility physicist. A major part of his responsibility involves the support of a PDP-8/e computer system for use by research personnel from other departments.

B. Obstetrics and Gynecology

Support for the Hewlett Packard computer system being used in Obstetrics and Gynecology to develop a fetal monitoring system is being provided by Medical Physics personnel. See II-L above.