STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
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Answer Back: STANFRD
STNU A

702690

April 2, 1986

Dr. Edward Rubenstein
Medical Center TC-129
Stanford University

Dear ~~Dr. Rubenstein~~ Ed:

The angiography proposal, 456B, was submitted to SSRL in July of 1979. Two years later, January 1982, it was made a program proposal and extended for another two years by the PRP. In January 1984, it was extended again by the panel. This proposal has remained active beyond the January 1986 date because of the laboratory commitment of 20% time to this effort on Beam Line IV-2. This present commitment ends in September 1986.

At the last meeting of the Proposal Review Panel a specific recommendation was made that before this work continue, a new proposal be submitted for peer review and rating by the PRP. The next deadline for proposal submittal is September 1, 1986.

Since we will be passing an important milestone this spring, I believe that the PRP's recommendation should be followed and a new proposal submitted in September.

Yours sincerely,

Artie

A. Bienenstock
Director

cc: 456B File

REPOSITORY SSRL
COLLECTION Angiography Program
BOX No. File Cabinet
FOLDER Proposal 456B (1979-86)

0021623

SSRL END OF RUN SUMMARY FORM

Spokesperson: Hofstadter

Proposal #: 456
Experimental Station 4-2

The purpose of this questionnaire is to solicit information about the functioning of SSRL and to allow your input into the beam time you have received on your proposal. It is read by all the SSRL Group Leaders. Try and be legible! PLEASE TURN IT IN TO KATHERINE CANTWELL upon departure.

1. **Beam Time Received: Assigned Shifts** 32 **Scheduled Dates** 1/15 - 1/26

   Your estimate of received usable shifts 24

   Explanation:

2. **Samples Run: (Please list all):**

   Pig Heart Phantoms

3. **Did the research performed differ in any significant manner from the that proposed for this experiment?** ✓ **No** ____ **Yes (Please give details on back)**

4. **Was the experimental station ready for your run? Yes** ____ **No** ✓ **If no, give some details:** PB Shield wall was not removed at start of setup.

5. **Which software did you use: RT-11 EXAFS, RSX EXAFS, SPECTR, EXP, OWN, OTHER Did it fail to work as described in the documentation? If so, where?**

   RT-11

   Do you have suggested improvements/changes/clarifications to the software or documentation (feel free to attach extra sheets of paper)?

   No

6. **Would your run have been more successful if more help had been available from any of the SSRL staff? If so, which type of staff in particular?**

   No

Please turn over

0021624

7. **Please describe any particular problems you had and suggest how these might have been avoided:** The start up of the run was delayed by 3 days because a lead shield wall in hutch was not removed on Friday afternoon and we had to wait till Monday morning.

8. **Do you have any suggestions on ways to improve the functioning of SSRL?**

9. **Are there any aspects of the functioning of SSRL that you find particularly helpful?**

NO

10. **Do you have any suggestions for improving safety at SSRL?**

NO

11. **SSRL staff, SPEAR Operators and the DOE are extremely interested in experimental results obtained at SSRL. Please describe briefly results obtained (or attempted during this run). Significant results should be placed in context so that their importance can be readily understood.**

We successfully demonstrated that our new system using a dual detector and no rotating drums works well.

Name of Person Filling Out the Form: _____

0021625

EXPERIMENTAL RUN SUMM__ Spokesperson: Hofstac - Proposal #: 456

The purpose of this questionnaire is to solicit information about the functioning of SSRL and to allow your input into the beam time you have received on your proposal. It is read by all the SSRL Group Leaders. Try and be legible! **PLEASE TURN IT IN TO KATHERINE CANTWELL upon departure.**

1. Beam Time Received: Assigned Shifts 84 Scheduled Dates 4/21-5/26
Your estimate of received usable shifts_____ Experimental Station 4-2
Explanation:

2. Samples Run: (Please list all):

3. Did the research performed differ in any significant manner from the that proposed for this experiment? X No_____ Yes (Please give details on back of form).

4. Was the experimental station ready for your run? Yes X No_____
If no, give some details:

5. Would your run have been more successful if more help had been available from any of the SSRL staff? If so, which type of staff in particular?

No.

6. Please describe any particular problems you had and suggest how these might have been avoided:

None

7. Do you have any suggestions on ways to improve the functioning of SSRL?

You were great!

8. Are there any aspects of the functioning of SSRL that you find particularly helpful?

0021b2b Yes; we have had considerable help from staff.

9. Do you have any suggestions for improving safety at SSRL?

—

10. Did you obtain significant results during this run that should be reported to the DOE? (DOE program officers find this information useful in their efforts to obtain more funding for SSRL? If yes, please describe on back.

Has to await data analysis!

Name of Person Filling Out the Form: B. Hickman

0021627

CHANGE IN SPOKESPERSON

Proposal Number 456

From Hughes To Hofstadter

Method of Communication - conversation with Bienenstock
memo attached

Check off list:

Master List _____ (KC & CB)

Word 11 Proposal Labels _____ (KC)

Proposal List on Computer _____ (CB)

CUA File _____ (BP)

Mail List Changes (if any) _____ (SP)

cc: BP
SP

0021628

November 13, 1985

TO: K. Cantwell

FROM: A. Bienenstock A. Bienenstock

SUBJECT: R. Hofstadter

This is to inform you that, at the Users Meeting, Bob Hofstadter informed me that he would now be the person to contact for interactions between SSRL and the angiography group. This was subsequently confirmed by Ed Rubenstein.

Consequently, we should treat Professor Hofstadter as the spokesperson henceforth for Proposal 456.

0021629

S S R L M E M O R A N D U M

Date: February 26, 1985

TO: E. BARRIE HUGHES

FROM: JOHN CERINO

SUBJECT: ANGIOGRAPHY FAST SHUTTER

Dear Dr. Hughes:

A number of people have approached me to express concern about the safety of a component which you are using in your experiment. It is a mechanism which rotates two metal drums at, I am told, rather high speeds to select the alternate beams for an angiography exposure I refer to it as the FAST SHUTTER.

It is the policy at SSRL/SLAC to require a safety review of any apparatus which may be considered hazardous before its use here. In administering that policy I encourage people to submit any non-commercial equipment and equipment which has been modified from its "industry standard" configuration. Our intent is to assure the health and safety of all people at SSRL and to protect our property.

In as much as the above device is not commercially built, and especially since it incorporates rather massive objects turning at high speeds, I am hereby requesting that you submit the design and relevant engineering back-up data for review by a group of SSRL and SLAC staff members.

If you will notify me of a time when you will have such a presentation ready, I will set up a date. I realize that time is short between now and when you would hope to run here again, so I will make every effort to expedite the review.

Sincerely,

John A. Cerino
Operations Manager

cc:
A. BIENENSTOCK
G. BROWN
H. DESTAEBLER
H. WINICK
file

0021630

BIOLOGY SUB-PANEL RATINGS - JANUARY 1985

456Bp Hughes

The Biology panel is concerned that this program is going on without any apparent external review. Although it looks promising, we would hope that there is some mechanism for periodic external feedback and evaluation. Perhaps our PRT procedures should be applied here; perhaps some other mechanism is appropriate.

Not sent to Hughes

0021631

DATE: November 30, 1984

TO : Katherine Cantwell

FROM : E. Barrie Hughes EBH

SUBJECT: Extension of Proposal 456B

RECEIVED
DEC 05 1984
SSRL

Enclosed are four copies of a progress report on Program Proposal 456B. You needed this summary of our progress by December 1, 1984, as a requirement for the extension of this proposal.

EBH:gh

Shifts Used/Date		BeamLine	Running Conditions
24	3/84	4-2	DED
12	3/84	4-2	PAR
22	4/83	4-2	PAR
31	2/83	4-2	DED
20	12/82	4-3	PAR
10	11/82	4-2	PAR
13	3/82	4-3	DED
17	3/82	4-2	DED
19	1/82	4-3	DED
14	12/81	4-3	DED
15	6/81	4-3	DED
10	4/81	4-2	PAR
14	3/81	4-2	PAR
2	4/80	4-2	PAR

0021632

EXPERIMENT 456B

PROGRESS REPORT TO SSRL

NOVEMBER, 1984

INTRODUCTION

Experimental studies of dichromography with monoenergetic X-rays began in 1979 at SSRL. Developmental studies at SSRL since that time have focussed on inanimate phantoms, excised animal hearts and in vivo canine imaging. In vivo studies were first carried out in March 1982, at SSRL, and were continued in February 1983, and most recently in March 1984.

These studies are prompted by the need for a non-invasive diagnostic test for coronary artery disease in humans. No alternative test as yet has demonstrated an ability to provide images of sufficient quality to supplant the standard invasive procedure. To accommodate human subjects it is necessary to create a synchrotron X-ray beam of an appropriate width (at least 15 cm) and to adapt or modify the existing X-ray imaging system accordingly.

Preparations for pilot human subject studies and a subsequent human clinical evaluation at SSRL are now underway. A wiggler-illuminated beam has been expanded in horizontal aperture to 4.4 mr, a monochromator of matching width is being fabricated, and an examination room of the appropriate size is being prepared. In parallel, the imaging apparatus, originally developed for a 2 cm wide X-ray beam, is being modified and expanded to accommodate human subjects. Following the test and successful operation of this apparatus, starting in early 1985, a clinical evaluation with human subjects will begin at the earliest possible date (probably late 1985).

CURRENT ACTIVITIES

Recent activity has centered on the modification and expansion of the imaging system to accommodate human subjects. These modifications, the design of new components, and their status at this time are summarized below.

1. X-RAY BEAM

Engineering studies on the beam-widening operation were completed at SSRL and the changes called for were made in the summer of 1984. All the new high-vacuum equipment (including the beam pipe, larger valves and wider Be windows) were installed by June 1984, and the shielding modifications were completed by July 16.

2. X-RAY MONOCHROMATOR

Detailed design of the rapid-switching wide X-ray monochromator proceeded at SSRL, under the direction of Dr. G. S. Brown. A design review in December 1983, indicated that the required switching time (less than 1 ms) might be difficult to achieve without mechanical complexity.

0021633

Instead, an alternative design was conceived that avoided fast motions of the diffracting crystals to achieve energy switching. This latest design incorporates two curved crystals, each intercepting one half of the vertical beam profile, with independent adjustment in angle. This system will provide two focussed beams, with energies centered respectively above and below the iodine K-edge, but with a vertical separation at the patient position of 0.25 mm. Vertical focussing in this new monochromator will make maximal use of the available X-ray flux, permitting the acquisition of each image frame in the minimum possible time. The vertical separation between the two beams compensates for the vertical patient motion and assures registration between each related pair of line exposures. Rapid switching between the two beams will be accomplished by a rotating drum switcher that will admit either one or the other of the two beams with very high duty factor. Prototype testing of this monochromator concept will initially use flat diffracting crystals, and is planned for February 1985.

3. FAST BEAM-SWITCHER

A detailed design of a mechanism to achieve rapid switching between the two beams has been developed. The preferred beam-switching mechanism consists of two 12 inch diameter rotating steel drums, each of which has four lobes for alternately stopping and transmitting an incident X-ray beam. For the fastest anticipated scanning rate, corresponding to 2 ms per image line, these drums will rotate at 7200 RPM in synchronization with the 60 Hz line. This will be accomplished with an 1800 RPM synchronous motor, a system of toothed pulleys, and a double-sided toothed rubber belt. The system will also be capable of operating at four slower speeds, namely: 3600, 1800, 900 and 450 RPM. Two 512 line optical encoders will be used to allow the computer to determine the exact position of each drum at all times while they are rotating. Data-acquisition will be synchronized to the drum rotation, as was the case with the rotating slit system used in the preliminary studies. The drums will be dynamically balanced and will ride on ultra-high-precision ball bearings to minimize friction, vibration and noise. In addition, a noise-insulating wooden box will surround the drum system. Fabrication was begun early enough to assure completion by January 1985.

4. EXAMINATION ROOM

SSRL developed a design for a room capable of accommodating angiography studies in the wide X-ray beam and proceeded with the fabrication. This room is installed in the beam and available for use in February 1985. Patient occupation, however, is not anticipated until late 1985.

The room design, and a related operating procedure, have been developed to provide for the radiation safety of the patient and operating personnel, and to permit physician control of the imaging sequence and easy access to the patient at all times.

5. SIGNAL-PROCESSING ELECTRONICS

Minor circuit and connector modifications have been made to the signal-processing electronic modules, based upon experience with the 15 modules (60 channels) built earlier. The frequency of 5 MHz for the voltage-to-

frequency (V/F) converters was reaffirmed after review of the present linearity limitations on V/F circuits at 10 and 20 MHz.

6. DATA ACQUISITION SYSTEM

The design of an expanded control and data-acquisition system required for human subject studies has been specified. A high-performance data-acquisition computer has been received from First Computer Corp. The computer contains an LSI 11/73 CPU, 256 Kbytes of memory, a Fujitsu Eagle 470 Mbyte Winchester disk drive, and a Cipher 3200 BPI 75 IPS magnetic tape drive. Because the Fujitsu drive is so fast, it should be possible to write imaging data to disk either between images or even during image acquisition. Hence, only enough RAM memory will be necessary to buffer one image (512 Kbytes).

7. PATIENT POSITIONING APPARATUS

A detailed specification for the conceptual design of a patient-positioning and scanning apparatus was written based on the concept of patient examination in the sitting position (in a chair). Circulation of this specification to industry, followed by visits to clarify the requirements and to inspect conceptual designs, led to the selection of Engineering Dynamics Corp. of Lowell, Massachusetts, to fabricate the chair. This company has extensive experience in the manufacture of patient-moving equipment and is capable of meeting all FDA requirements.

Design studies of the patient-positioning and scanning apparatus began in September 1984, at Engineering Dynamics Corporation. Delivery is expected early in 1985.

8. Si(Li) DETECTOR DEVELOPMENT

A contract with the Lawrence Berkeley Laboratory for the fabrication of a Si(Li) detector 15 cm in active width was released in June 1983. A Si(Li) detector 15 cm in active width has been fabricated. This detector has 300 sensitive regions 0.4 mm in width and a center-to-center spacing between adjacent regions of 0.5 mm. The active height is 4 mm and the thickness 5 mm. A 7-inch long crystal of high-quality silicon was sliced lengthwise to provide four wafers of the correct detector dimensions. These wafers were then lapped, etched, and lithium-drifted for approximately six weeks. A contact mask was laid over each of the drifted wafers and a gold evaporation done to produce the 300 isolated contacts on one side of each detector.

The total leakage current for each detector was measured at room temperature and found to be in the range 18-30 μA. Preliminary measurement of the leakage current in a 20-pad section of one wafer indicated leakage currents of about 2-5 nA at room temperature. A method of making spring contacts for the wide detector was developed at the Lawrence Berkeley Laboratory. This method, shown in Figure 7, uses 300 spring-loaded fingers. A major advantage of this method is that detectors can be removed easily from the cryostat for surface cleaning or exchange. The fingers couple the detector channels to a circuit board. Two 15-cm long Mylar circuit strips (to reduce thermal loading), each with 150 separate lines, are soldered onto each side of this board. At the remote

end of the Mylar strips four 75-pin connectors are attached. These connectors mate with similar connectors on the inside of the cryostat. A circuit card then carries the signals through the vacuum wall of the cryostat to twelve 25-pin coaxial connectors.

The support structure and cooling attachment in the cryostat assure that no intolerable mechanical stress is applied to the crystal from ambient to operating temperature (-30° C). Cooling is provided by three thermoelectric coolers which are soldered to the water-cooled back plate of the cryostat.

9. IN VIVO IMAGING

In vivo canine studies were conducted most recently at SSRL in March 1984, at which time the hearts of seven anesthetized dogs were examined. The lateral projection (6 hearts) or right anterior oblique projection (1 heart) was used to avoid overlap between the left anterior descending (LAD) coronary artery and the chambers of the left heart.

The major branches of the LAD are clearly revealed in reference images obtained by power injection of the iodinated contrast agent (Renografin-76) at the aortic root using an R-wave trigger. Using this technique, closure of the aortic valve preceding the injection prevents the contrast agent from entering the left ventricle. The contrast agent was injected through a 5 French pigtail catheter into the right femoral artery, at a rate of 25 ml s^{-1} for 0.6 s. Ventilation of the animal was suspended during the image acquisition.

Non-invasive images were obtained by injection of the contrast agent at the junction of the superior vena cava and the right atrium. Power-injection through a 7 French catheter introduced into the right jugular vein was used, also with an R-wave trigger, at a rate of 12 ml s^{-1} for 1 s. Both the LAD and the much smaller right coronary artery are visible in these images. In the edge-enhanced versions of these images the ostia of both the left and right coronary arteries are visible.

A report on these studies was presented at the Meeting of the American Heart Association in Miami Beach, Florida in November 1985.

10. INSTRUMENTATION STUDIES

Instrumentation studies were also conducted with the X-ray beam in March-April 1984, to assess: 1) the sensitivity of soft tissue and bone artifacts to the energy separation between the high and low X-ray energies adjacent to the iodine K-edge, and 2) the lack of crosstalk, or otherwise, between adjacent channels in the Si(Li) detectors used in this work. Initial results of these studies were presented at the Conference on the Applications of Accelerators in Research and Industry at Denton, Texas in November 1985.

SUMMARY

The are no major changes in the program plan (schedule) submitted to the NIH in December 1983. In particular, the widening of the beam at SSRL is complete, and the construction of the examination room is well advanced.

Testing of the wide beam and new monochromator will begin as soon as SSRL resumes operations in 1985. *In vitro* testing of the expanded imaging system will begin immediately following the commissioning of the beam. The new Si(Li) detector and extra channels of signal-processing electronics will be available at that time, and the patient-positioning and scanning apparatus at a later time but well before needed for the pilot human subject studies.

0021637

August 17, 1984

To: Barrie Hughes

From: Katherine Cantwell KC

Subject: EXTENSION OF PROPOSAL 456

I have discussed the extension of Program Proposal 456 with Art Bienenstock. Since this proposal has been granted priority time at the Laboratory for the next two years a new proposal for formal review is not required. Instead, a two page detailed summary of the progress to date should be submitted. This summary should be received at SSRL by December 1, 1984.

This review will allow both the Director and the Proposal Review Panel to remain cognizant of the work being carried out under this proposal.

cc: C. Mitchell

0021638

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
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TWX: 910-373-1162
Answer Back: STANFRD
STNU A

July 3, 1984

E.B. Hughes
Hansen Labs
Stanford U.
ID Mail

At the January 1984 PRP meeting a decision was reached to limit program proposals to a single two year extension. Your program proposal 456 has already received one extension and will now terminate in January 1985. If you wish to continue research on the material covered by this proposal a new proposal should be submitted by the September 1, 1984 deadline. This new proposal will be rated in January at the PRP meeting.

Since there is no dedicated time available this fall proposals which die in January will be eligible for beam time in the January-February 1985 run. Beam time request forms for this period will be send out in September.

Please give me a call if you have any questions.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Assistant to the Director

0021639

EXPERIMENTAL RUN SUMMARY Spokesperson: HUGHE Proposal #: 456

The purpose of this questionnaire is to solicit information about the functioning of SSRL and to allow your input into the beam time you have received on your proposal. It is read by most of the SSRL staff. **PLEASE TURN IT IN TO KATHERINE CANTWELL upon departure.**

1. Beam Time Received: Assigned Shifts 13 Scheduled Dates 3-14/3-18
Your estimate of received usable shifts 13 Experimental Station 4-2
Explanation:

2. Samples Run: (Please list all):

S_r PHANTOM

3. Was the experimental station ready for your run? Yes X No
If no, give some details:

4. Would your run have been more successful if more help had been available from any of the SSRL staff? If so, which type of staff in particular?

5. Please describe any particular problems you had and suggest how these might have been avoided:

6. Do you have any suggestions on ways to improve the functioning of SSRL?

7. Are there any aspects of the functioning of SSRL that you find particularly helpful?

NO BARS OPERATION

8. Do you have any suggestions for improving safety at SSRL?

9. Please use the back of this sheet for any miscellaneous comments you would like to transmit....

Name of Person Filling Out the Form:

E B HUGHES

0021640

W.W. HANSEN LABORATORIES OF PHYSICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305-2184

RECEIVED
DEC 28 1983
S. S. R. L.

Edward L. Ginzton Laboratory
High Energy Physics Laboratory

Telephone (415) 497-

December 27, 1983

Claire L. Burke
Stanford Linear Accelerator Center
P.O. Box 4349, Bin 69
Stanford CA 94305

Dear Claire:

Enclosed are the materials necessary for our program proposal renewal.

1. Extension request form.
2. Bibliography
3. Recent activity report
4. Recent publications

Sincerely yours,

Barrie H.

E. Barrie Hughes

gh

Encls.

0021641

PROGRAM PROPOSAL EXTENSION REQUEST

Proposal Number 456B Spokesperson E.B. Hughes

I do not wish to extend this program_____
Reason:

For Extension:

1. List current collaborators if different from original proposal.

   E.B. Hughes, H.D. Zeman, L.C. Finman, R. Hofstadter, J.N. Otis, E. Rubenstein, D.C. Harrison, R.S. Kernoff, A.C. Thompson, G.S. Brown

2. Briefly describe where you are in the outlined work for this proposal.

   As indicated in the latest Activity Report and the attached publications, the program is now preparing as quickly as possible for human subject studies at SSRL. In vivo canine studies will continue in the immediate future, both to refine the experimental technique and to acquire realistic images for image processing studies.

3. Briefly describe the next step you plan to pursue.

   The human subject studies will begin as soon as the 12.3cm wide beam at 28 meters is available in beam line IV-2. This is expected in October, 1984. In vivo canine studies will continue in the 2cm IV-2 beam in the immediate future.

4. If no activity report (March 1983) is available attach a one page description of progress to date.

5. If activity report is attached is there any new information which you feel the panel should have (describe on separate sheet of paper).

   Funding for a clinical evaluation has been provided by the National Institues of Health.

6. List Publications resulting from work:

   See attached bibliography

**********For SSRL use**********

Shifts Used/Date Beam Line Running Conditions

see next page

0021642

****

PN 456

Shots Used	Date	Beam Line	Running Condition
22	4/83	4-2	Parasitic
31	2/83	4-2	Dedicated
20	12/82	4-3	Parasitic
10	11/82	4-2	Parasitic
13	3/82	4-3	Dedicated
17	3/82	4-2	Dedicated
19	2/82	4-3	Dedicated
14	12/81	4-3	Dedicated
15	2/81	4-3	Dedicated
10	4/81	4-2	Parasitic
14	3/81	4-2	Parasitic
2	4/80	4-2	

0021643

EVALUATION OF SYNCHROTRON X-RAYS FOR DIGITAL SUBTRACTION CORONARY ANGIOGRAPHY

E.B. Hughes, H. D. Zeman, L. C. Finman, R. Hofstadter
J. N. Otis and J. Rolfe
Hansen Laboratories of Physics and
Department of Physics, Stanford University

E. Rubenstein, D.C. Harrison, R.S. Kernoff
Department of Medicine, Stanford University School of Medicine

A.C. Thompson, Lawrence Berkeley Laboratory

G.S. Brown, Stanford Synchrotron Radiation Laboratory

The results of the most recent in vivo canine studies were summarized in the preceding report. These tests took place in the period February 7-21, 1983 in beam line IV-2. Relative to earlier in vivo studies, the imaging system was upgraded in three significant ways. First, a Si(Li) detector with improved spatial resolution was introduced. Second, a special rotating slit was constructed to define and to move the beam vertically at the speed of the animal during the acquisition of each related pair of line exposures, thereby assuring registration between each image pair. Third, all line scans were started at the same phase relative to the cardiac cycle to assure matching at the borders of adjacent vertical frames. (The narrow beam width, 2 cm, necessitates multiple injections at appropriate intervals to cover the desired field.

The image quality in February 1983, was found to be impaired by 60 Hz line-frequency electrical noise. This, in general, resulted in an unwanted modulation of the reconstructed image, and prompted the adoption of an operating procedure designed to minimze its effect. This procedure was successfully tested in the period April 1-13, 1983, under parasitic conditions.

After reduction of line-frequency signal noise by standard electronic techniques, a means of compensating exactly for the residual 60 Hz noise was developed based on synchronizing the operation of the rotating slit accurately to the line frequency. A controller was introduced for this purpose, by means of which the rotation speed of the DC servo-motor driving the rotating slit could be set either at the line frequency or at a multiple thereof. By synchronizing the data acquisition with the rotating slit, all the necessary measurements could then be taken at selected phases relative to the line. If the amplitude of the interfering noise itself is stable with time, it is reasonable to expect that at each phase the signal associated with the line-frequency noise will be constant. For example, if the rotating slit is operated at the line frequency, the exposure time for each high and low energy line image will be 4.17 ms and one measurement of each type will be made, at known phases (separated by 180 degrees), during each full rotation period of the slit. Corresponding pedestal measurements can be made, for each detector channel, at each of the two relevant phases with the X-ray beam intercepted by an independent solenoid-driven shutter, both before and after each vertical line scan. When these pedestal determinations are interpolated in time and subtracted from the scan data, the effects of pedestal drift and, in particular, line-frequency noise are very strongly suppressed.

The canine images acquired in February 1983, do not reflect the suppression of the line-frequency noise by the method of synchronizing the acquisition of the image data to specific phases relative to the line. The need for this synchronization only became fully evident after the introduction of the rotating slit and the Si(Li) detector with improved spatial resolution into the imaging system. In addition to the beneficial aspects of these additions, the system became more susceptible to a residual line-frequency noise signal because for each pixel in the image the true signal level is reduced. In contrast to the earlier reported canine studies, the true signal-to-line-frequency noise ratio was reduced by an overall factor of 16 for the more recent studies. The reduced pixel size contributed a factor of 4 to this reduction, and an average rotating slit transmission efficiency of 50% contributed another factor of 2. The extra factor of 2 is attributable to a temporary mode of data readout whereby the noise was integrated over twice the X-ray exposure time of 4.17 ms. The enhanced sensitivity to line-frequency noise prompted the introduction of phase synchronization into the data acquisition procedure. The effectiveness of this technique was subsequently demonstrated with phantom studies (in April 1983, under parasitic conditions), but an opportunity to repeat the canine studies has not yet occured.

To accommodate human subject studies an X-ray beam width of at least 15 cm is required. In the immediate future a wiggler-illuminated beam line at SSRL will be reconfigured to provide a beam 12.3 cm in width and it is expected that initial human subject studies will be conducted in this beam. Subsequently, a beam of width 15 cm can be provided by relocating the examination room downstream. These studies will also require a monochromator of matching width. The design presently preferred incorpoarates two curved crystals, each intercepting one half of the vertical beam profile, with independent adjustment in angle and longitudinal position. This system will provide two focussed beams, with energies respectively above and below the iodine K-edge, but with a vertical separation at the patient position of 0.25 mm. Vertical focussing in this new monochromator will make maximal use of the available X-ray flux, permitting the acquisition of each image frame in the minimum possible time. The vertical separation between the two beams compensates for the vertical patient motion and assures registration between each related pair of line exposures. Rapid switching between the two beams will be accomplished by a rotating blade shutter that will admit one or the other of the two beams with very high duty factor. Also required is the fabrication of a Si(Li) multichannel detector 15 cm in width, and an appropriate expansion of the data acquisition system. These changes to the imaging system are now in the design and fabrication stage, and will be ready for use at the time the wide beam is available.

0021644

BIBLIOGRAPHY

1. E. Rubenstein, E. B. Hughes, L. E. Campbell, R. Hofstadter, R. L. Kirk, T. J. Krolicki, J. P. Stone, S. Wilson, H. D. Zeman, W. R. Brody, A. Macovski and A. C. Thompson. Synchrotron Radiation and its Application to Digital Subtraction Angiography. SPIE Vol. 314, Digital Radiography, 42, 1981.

2. H. D. Zeman, E. B. Hughes, L. E. Campbell, R. Hofstadter, R. L. Kirk, T. J. Krolicki, J. Rolfe, J. P. Stone, S. Wilson, E. Rubenstein, A. C. Thompson and J. T. Walton. Implementation of Digital Subtraction Angiography with a Synchrotron X-Ray Beam. IEEE Trans. on Nucl. Sci., Vol. NS-29, No 1, 442, 1982.

3. A. C. Thompson, F. S. Goulding, H. A. Sommer, J. T. Walton, E. B. Hughes, J. Rolfe and H. D. Zeman. A Multielement Silicon Detector for X-ray Flux Measurements. IEEE Trans. on Nucl. Sci., Vol. NS-29, No 1, 793, 1982.

4. E. B. Hughes, H. D. Zeman, L. E. Campbell, R. Hofstadter, U. Meyer-Berkhout, J. N. Otis, J. Rolfe, J. P. Stone, S. Wilson, E. Rubenstein, D. C. Harrison, R. S. Kernoff, A. C. Thompson and G. S. Brown. K-Edge Digital Subtraction Angiography with Synchrotron X-rays. Proceedings of the International Workshop on Medical Applications of Synchrotron Radiation, Noordwijkerhout, the Netherlands, April 13-15, 1982 (to be published in Acta Radiologica).

5. E. B. Hughes, H. D. Zeman, L. E. Campbell, R. Hofstadter, U. Meyer-Berkhout, J. N. Otis, J. Rolfe, J. P. Stone, S. Wilson, E. Rubenstein, D. C. Harrison, R. S. Kernoff, A. C. Thompson and G. S. Brown. The Application of Synchrotron Radiation to Non-Invasive Angiography. Nuclear Instruments and Methods 208, 665, 1983.

6. E. Rubenstein. Medical Applications of Synchrotron Radiation. Presented at the Stanford Synchrotron Radiation Laboratory New Rings Workshop, July 28-29, 1983.

7. H. D. Zeman, E. B. Hughes, L. [redacted] R. Hofstadter, A. [redacted] J. N. Otis, J. Rolfe, E. Rubenstein, D. C. Harrison, R. S. Kernoff, A. C. Thompson, G. S. Brown. Evaluation of Synchrotron X-Rays for Transvenous Coronary Angiography. Presented at the Third National Conference on Synchrotron Radiation Instrumentation, Brookhaven National Laboratory, New York, September 12-14, 1983 (to be published in Nuclear Instruments and Methods).

8. E. Rubenstein. Medical Imaging with Synchrotron Radiation. Presented at the Third National Conference on Synchrotron Radiation Instrumentation, Brookhaven National Laboratory, New York, September 12-14, 1983 (to be published in Nuclear Instruments and Methods).

9. J. N. Otis, H. D. Zeman, E. B. Hughes, L. [redacted] R. Hofstadter, [redacted] J. Rolfe, E. Rubenstein, [redacted] A. C. Thompson, G. S. Brown. Evaluation of Synchrotron X-Rays for Digital Subtraction Angiography. Proceedings of the IEEE 1983 Nuclear Science Symposium, October 16-23, 1983, San Francisco, CA.

0021645

ADD

ADD

10. H. D. Zeman (SU), E. B. Hughes (SU), J. N. Otis (SU), J. Rolfe (SU) and A. C. Thompson (LBL). Rotating X-ray Collimating Slit for Line-Scan Dual-Energy Medical Imaging. Proceedings of the IEEE 1983 Nuclear Science Symposium, October 16-23, 1983, San Francisco, CA.

11. A.C. Thompson (LBL), [redacted], [redacted], E. B. Hughes (SU), [redacted] (SU), [redacted] (SU), and H.D. Zeman (SU). Computed Tomography Using Synchrotron Radiation. Presented at the Third National Conference on Synchrotron Radiation Instrumentation, Brookhaven National Laboratory, New York, September 12-14, 1983 (to be published in Nuclear Instruments and Methods).

A.C. Finman → Hansen LBL - S.U.
A. Linden → " "
J. Lacan →

0021646

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3860, Ext. 2[illegible]
TWX: 0[illegible]
Answer Back: STANFORD
STNUCA

January 17, 1984

Dr. E. B. Hughes
Hansen Labs
Stanford University
Stanford, CA 94305

Dear Barrie:

At the January, 1984 meeting of the PRP your Program Proposal No. 456 was extended until January, 1985. At that date you will be required to have a new proposal submitted for rating.

The PRP has decided that program proposals should only have one two year extension. This reflects their feeling that proposals that run too long often do not reflect the work described in the original proposal.

We look forward to having you continue your research at SSRL.

Sincerely,

Claire

Claire L. Burke
Proposal Administrator

0021647

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

November 1, 1983

Re: Proposal No. 456

Dear Spokesperson:

The termination date on your program proposal is 1/84. Program proposals may be extended on the basis of a report of activity. Please complete the enclosed program extension request form and attach a copy of your activity report to it along with any new information which you feel should be presented to the panel. If no activity report is available, please attach a one page description of progress on the proposal to date. This material should be sent to me by December 15th.

Thank you for giving this matter your attention.

With best regards,

Claire L. Burke
Proposal Administrator

0021648

RECEIVED
AUG 26 1982

WASHINGTON UNIVERSITY

ST. LOUIS, MISSOURI 63130

DEPARTMENT OF CHEMISTRY

July 19, 1982

Dr. Herman Winick
Deputy Director
Stanford Synchrotron Radiation Laboratory
P.O. Box 4349, Bin 69
Stanford, CA 94305

Dear Herman:

Thank you for the material on the angiography project. I was quite impressed with the approach and initial results when they were presented at the SPB Meeting May 27-28, 1982.

I took the liberty of dicussing this material with radiologists of the Washington University School of Medicine to ascertain if, in their view, there was clinical potential here. The response was that these initial results at SSRL were very exciting and that by all means further effort should be encouraged and supported. There are many reasons why radiologists would like to obtain images of the arteries from venous injection-primarily ease and safety to the patient. Digital subtraction techniques and dual energy subtraction are approaches being pursued avidly today to facilitate this approach. Digital subtraction techniques are being pursued here at Washington University and a group headed up by W.R. Brody of Stanford is pursuing the dual energy subtraction approach. Both these approaches are suffering from the motional artifacts not present in the angiography based on synchrotron radiation.

In other words, radiologists with competitive approaches to arterial imaging from venous injection are enthusiastic about the work being conducted by Rubenstein et al at SSRL. It would appear that the potential of the work is considerable and that it definitely should be continued.

Sincerely,

WDP

William D. Phillips
Professor of Chemistry
and Department Chairman

WDP/jm

cc: Dr. G.E. Pake
Dr. K.O. Hodgson

0021649

For 456 3 f6

College of Physicians & Surgeons of Columbia University | New York, N.Y. 10032

DEPARTMENT OF MEDICINE 630 West 168th Street

January 8, 1982

Dr. Charles Cantor
Department of Human Genetics
and Development

Dear Dr. Cantor:

The aim of this proposal, to be able to perform coronary angiograms, non-invasively by intravenous injection of iodinated contrast material is very worthwhile. The approach outlined here appears to be quite sound i.e. to use two monochromatic x-ray beams and to perform iodine k-edge digital subtraction angiography. The investigators have made good progress in their initial work. Unique features are the degree to which the x-ray beam is rendered monochromatic and the speed with which scanning with 2 beams can be performed. Problems of cardiac motion and in vivo imaging will require construction of a larger detector which is planned.

A negative feature of this work related to the fact that this technique could only be used at the very few facilities in the country with electron storage rings and wiggler magnets. Hence its impact on clinical medicine will be reduced. Also the approach of k-edge digital subtraction angiography with less monoenergetic beams is currently under development commerically by companies such as General Electric.

Sincerely,

PJC:rh

Paul J. Cannon, M.D.
Professor of Medicine

0021650

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

January 29, 1982

Dr. E.Barrie Hughes
W.W. Hansen Laboratories
of Physics
Stanford University
Stanford, CA 94305

Dear Dr. Hughes:

The SSRL Proposal Review Panel met on January 15th and 16th. Your requests concerning Proposal 456 were considered. The Biology Sub-Panel decided to convert the proposal to program status, upgrade the rating to 1.2 and to extend the termination date to 1/84.

Best wishes for continued success with your research.

Sincerely,

Claire L. Burke

Claire L. Burke
Proposal Administrator

0021651

December 28, 1981

To: E. B. Hughes

From: Katherine Cantwell KC

Subject: Priority Time on BL IV-3

I have examined the records of usage on experimental station IV-3 since it was commissioned in May 1981. Through December 1981 there have been 147 shifts assigned on this station . Your proposal has received 39 of these shifts or 26.5% I based the usage calculations on shifts assigned rather than received as the latter is a fairly subjective number.

We are extending your priority time agreement through December 1982 since the experimental station was commissioned in May rather than January as expected when the agreement between Drs. Bienenstock and Glaser was made in July 1980.

cc: 456B file

0021652

STANFORD SYNCHROTRON RADIATION LABORATORY

Opened May 1981

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

July 25, 1980

Robert J. Glaser, M. D.
President
Henry J. Kaiser Family Foundation
Two Palo Alto Square
Palo Alto, California 94305

Dear Doctor Glaser:

This letter is written in support of the dichromography research effort being proposed by Hughes, Rubenstein et al. for performance at the Stanford Radiation Radiation Laboratory (S.S.R.L.).

I have been in contact with the chairman of our Proposal Review Panel who has stated his beliefs that the quality of the proposed research warrants up to 25% of the scheduled S.S.R.L. experiment shifts from 1 January 1981 (the expected start date) through 31 July 1982 on one of our new experimental stations. In order for research to be performed on the station, however, funding for the fabrication of the required monochromator will have to be obtained.

In view of the above, I am happy to formally guarantee the Hughes/Rubenstein program up to 25% of the scheduled shifts on the appropriate experimental station over the eighteen-month period of 1-1-81 through 7-31-82 with the understanding that they will provide financial assistance for the procurement of equipment (primarily the monochromator) and manpower support during the installation of the beam line experiment station.

Sincerely,

A. Bienenstock

A. Bienenstock
Director

AB/j

cc: E. B. Hughes

0021653

Scheduled 4-3
on shifts

Barbee 11

Kortright 10

Liang 10

Shimomura 10

Warburton 19

On Actual Schedu

Barbee 20

Kortright 3 + 6 + 3 + 5 = 17

Shimomura 8 8

Moss 4/I 7 7

Warburton 11 + 4 15

Hughes 5 + 8 + 11 24 (15)

Bouldin-Steen = 11 11 (34)

Averill = 4 4

Ingalls = 11 11

Haderman = 7 + 8 15

132 Total shifts
15
147

26.5%

18%

0021654

November 30, 1981

TO: Biology Sub-Panel

FROM: Katherine Cantwell KC

Subject: Conversion of Proposal 456B to Program Status

I suggest that proposal 456B from E.B. Hughes be converted to a program proposal and given a two year extension. Work on this proposal has not proceeded terribly far due to its 1.5 rating and need for wiggler end station time. However, Dr. Hughes has a priority agreement for 25% time on the wiggler side station which has allowed him to do some work. This priority agreement ends this June. As I am sure you are aware this work has generated much excitement and the Hughes group is considering building their own beam line at SSRL.

Dr. Hughes has put together an extensive update on his work for your consideration.

0021655

PROPOSAL

to the

STANFORD SYNCHROTRON RADIATION LABORATORY

for a continued study of

IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

Co-Investigators: E.B. Hughes
E. Rubenstein
R. Hofstadter
D.C. Harrison
H.D. Zeman
(Stanford University)
A.C. Thompson
(Lawrence Berkeley Laboratory)

W.W. Hansen Laboratories of Physics
and
School of Medicine
Stanford University
Stanford, California 94305

November 1981

0021656

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ATTACHMENTS (4)

0021657

Proposal Number_____

SSRL PROPOSAL SUBMITTAL FORM

This Proposal is a new proposal ( ) or a replacement for for Proposal No. 456B .

This Proposal is for a single experiment (X) or a PROGRAM ( ).

CHECK MOST APPROPRIATE REVIEW PANEL: _____*X-RAY/MATERIALS & CHEMISTRY*____*VUV* X *X-RAY/BIOLOGY*

1. TITLE: *(10 words are less, type in capitals)*

CONTINUED STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

2. LIST OF COLLABORATORS *(Underline Spokesperson)*

Name	Full Address	Telephone Numbers Office	Home
E. Barrie Hughes	W.W. Hansen Laboratories of Physics	497-0135	368-2771
Edward Rubenstein	Stanford University Medical Center; Department of Medicine	497-7188	342-1888
Robert Hofstadter	Department of Physics	497-4235	326-6711
Donald C. Harrison	Stanford University Medical Center; Department of Cardiology	497-5935	968-5848
Herbert D. Zeman	W.W. Hansen Laboratories of Physics	497-0114	493-5788
Albert C. Thompson	Lawrence Berkeley Laboratory	486-6444	527-9922

3. EXPERIMENTAL STATIONS REQUIRED FOR EXPERIMENT *(If two stations are required list both under first choice. Note number of shifts required for each line in section 4.)*

First Choice: Alternates:

IV-2 (WIGGLER)

4. ESTIMATED DEDICATED BEAM TIME REQUIRED IN 8 HOUR SHIFTS: (3 GeV, 50 mA)

75

5. WILL IT BE POSSIBLE TO SCHEDULE THE EXPERIMENT FOR PARASITIC TIME? IF SO, WHAT WOULD BE THE THE MINIMUM BEAM ENERGY?

UP TO 50% OF THE EXPERIMENT, BUT NOT MORE, COULD BE ON PARASITIC TIME WITH A MINIMUM BEAM ENERGY OF 2.5 GeV.

6. For Experiments on Vacuum Beam Lines: Please list all samples you expect to insert into the vacuum system (and also lead time needed for preparation) and also any construction materials and components not generally considered to be UHV materials or components. Details must be given in proposal.

NONE

0021658

7. LIST ALL POTENTIAL HAZAR including all toxic, radioactive, r explosive materials, hazardous procedures and equipment. Furnish detailed safety procedures in the proposal. AGREEMENT TO BRING THESE MATERIALS TO SSRL MUST BE OBTAINED FROM J. CERINO, OPERATIONS MANAGER, AT LEAST TWO WEEKS PRIOR TO DATE OF THEIR ARRIVAL.

NONE

8. What equipment or materials do you expect to be provided by SSRL?

NONE

9. PLEASE GIVE A BRIEF ABSTRACT OF THE PROPOSAL:

ABSTRACT

The purpose of this proposal is to continue studies related to the implementation of digital subtraction (non-invasive) angiography with synchrotron X-ray beams at SSRL. Initial studies have been conducted under Proposal 456B and are fully reported in attachments I-IV to this proposal.

The intense X-radiation produced by wiggler magnets at SSRL is highly suited to iodine K-edge digital subtraction angiography. The monochromaticity and tunability provide maximum sensitivity to intra-arterial iodine and virtually eliminate image contrast due to non-vascular body structures. The sensitivity of the method to iodine offers the prospect of visualizing arteries by peripheral venous injection.

Confirmation of the principle of iodine dichromography has been provided by the work already done under Proposal 456B. The present proposal extends the earlier studies and concentrates on the problems of imaging moving structures, such as the coronary arteries, and of separating iodine images of the coronary arteries from residual iodine in the left ventricle. These questions will be addressed first with inanimate phantoms and excised animal hearts and then with animal subjects. It is expected that these studies will be preparatory to later studies on human subjects.

0021659

A. DESCRIPTION OF EXPERIMENT

The purpose of this proposal is to continue studies related to the implementation of digital subtraction angiography with synchrotron X-ray beams at SSRL. The intense synchrotron radiation produced by wiggler magnets at SSRL provides a source of X-rays highly suited to iodine K-edge digital subtraction angiography. The monochromaticity and tunability provide maximum sensitivity to intra-arterial iodine and virtually eliminate contrast due to soft tissue and bone. Visualization of arteries, in particular the coronary arteries, by peripheral venous injection is possible. If realized, the current need for arterial catheterization would be eliminated and both the risk and the cost of the diagnostic procedure greatly reduced.

Studies already accomplished at SSRL have considerably exceeded the scope of the limited tests outlined in Proposal 456B. Images have been obtained both of inanimate phantoms and of excised animal hearts, and a system design has been developed for the implementation of digital subtraction (non-invasive) angiography on human subjects. A prototype 30-channel Si(Li) X-ray detector has been developed and used to obtain digitally subtracted phantom and excised heart images; phantom and excised heart studies have been conducted to demonstrate the strong and simultaneous

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suppression of contrast due to soft tissue and bone and the exquisite sensitivity to iodine made possible with monoenergetic X-rays; and excised hearts have been imaged as a function of image pixel size and 0.5 mm x 0.5 mm shown to be desirable and sufficient for clinical work. These studies are fully described in attachments I-IV to this proposal.

Attachments I-IV are as follows:

I. NON-INVASIVE ANGIOGRAPHY USING SYNCHROTRON RADIATION.

E.B.Hughes, L.E.Campbell, R.Hofstadter, R.L.Kirk, T.J.Krolicki, J.P.Stone and H.D.Zeman. Hansen Laboratories of Physics and Department of Physics, Stanford University.

E.Rubenstein, Department of Medicine, Stanford University.

W.R.Brody and A.Macovski, Department of Radiology, Stanford University.

A.C.Thompson, Lawrence Berkeley Laboratory, University of California.

SSRL Activity Report 4/1/80 - 3/31/81, Proposal No. 456B, page VII-62, May 1981.

II. SYNCHROTRON RADIATION AND ITS APPLICATION TO

0021661

DIGITAL SUBTRACTION ANGIOGRAPHY.

E.Rubenstein, Department of Medicine, Stanford University.

E.B.Hughes, L.E.Campbell, R.Hofstadter, R.L.Kirk, T.J.Krolicki, J.P.Stone and H.D.Zeman. Hansen Laboratories of Physics and Department of Physics, Stanford University.

W.R.Brody and A.Macovski, Department of Radiology, Stanford University.

A.C.Thompson, Lawrence Berkeley Laboratory, University of California.

Proceedings of the SPIE Conference on Digital Radiography, September 14-16, 1981, Stanford University.

III. IMPLEMENTATION OF DIGITAL SUBTRACTION ANGIOGRAPHY WITH A SYNCHROTRON X-RAY BEAM.

H.D.Zeman, E.B.Hughes, L.E.Campbell, R.Hofstadter, R.L.Kirk, T.J. Krolicki, J.Rolfe, J.P.Stone and S.Wilson. Hansen L aboratories of Physics and Department of Physics.

E.Rubenstein, Department of Medicine, Stanford University.

A.C.Thompson and J.T.Walton, Lawrence Berkeley Laboratory, University of California.

Proceedings of the IEEE Nuclear Science Symposium,

0021662

October 21-23, 1981, San Francisco.

IV. A MULTI-ELEMENT SILICON DETECTOR FOR X-RAY FLUX MEASUREMENTS.

A.C.Thompson, F.S.Goulding, H.A.Sommer and J.T.Walton, Lawrence Berkeley Laboratory, University of California. E.B.Hughes, J.Rolfe and H.D.Zeman, Hansen Laboratories of Physics, Stanford University.

Proceedings of the IEEE Nuclear Science Symposium, October 21-23, 1981, San Francisco.

Beam access through 4/30/81 under proposal 456B is summarized in attachment I (SSRL Activity Report 4/1/80 - 3/31/81, VII-62). For convenience, these access times and related information through 4/31/81, together with one access since 4/31/81, are listed below.

a) I-5 non-wiggler beam, 11/26/80 - 11/27/80, 2 GeV, parasitic mode, 3 shifts.

b) I-5 non-wiggler beam, 12/5/80 - 12/6/80, 3 GeV, dedicated mode, 3 shifts.

c) IV-2 wiggler beam, 3/11/81 - 3/20/81, 1.8 GeV, parasitic mode, 24 shifts.

d) IV-2 wiggler beam, 4/7/81 - 4/14/81, 2.5-3.0 GeV, parasitic mode, 17 shifts.

e) IV-3 wiggler side-port beam, 6/3/81 - 6/6/81, 6/12/81 - 6/15/81, and 6/22/81 - 6/26/81, 3.0 GeV,

dedicated mode, 25 shifts.

Of accesses a)-d) in the above list, only d) was scheduled under operating conditions approximating those requested in proposal 456B. Access e) was obtained in partial recognition of a substantial financial contribution made by the 456B investigators to the commissioning of beam line IV-3.

The objective of the present proposal is to demonstrate, as soon as possible, the feasibility of in-vivo non-invasive arterial imaging in animals using synchrotron X-rays. This is preparatory to the subsequent step of demonstration tests in human subjects. Specifically the studies we propose are as follows:

a) continued development of the X-ray detector and signal-processing electronics to achieve quantum-limited signal-to-noise ratios.

b) studies with inanimate phantoms to explore the visibility of iodinated channels in the presence of extra-channel background concentrations of iodine.

c) studies with excised animal hearts with iodinated contrast agent simultaneously in both the coronary arteries and the left ventricle to demonstrate the existence of projections in which the coronaries may be observed without overlap by the left verticle and to

study the visibility of the coronaries when such overlap does occur.

d) studies with inanimate but cyclically-moving phantoms to demonstrate the ability of line-scanning to provide a sharply-focussed image despite simulated arterial motion.

e) the acquisition of in-vivo images in monkeys and dogs to demonstrate the image quality attainable by non-invasive angiography. This will be done first for arteries for which motion is not a major problem and then for the coronary arteries. (We estimate that the X-ray energy transmitted by the existing SSRL monochromator in beam line 1V-2 can be oscillated with a period of about 50 msec. To the extent that this is not sufficient, or cannot be easily decreased, the animal pulse rate can be reduced temporarily with drugs).

Accomplishment of the above objectives is essential to the start of studies with human subjects. Due to the significant anatomical and physiological differences between animal and human subjects, the minimum possible time, consistent with establishment of the technique, will be devoted to animal subjects. The apparatus necessary for studies with human subjects is already under construction. We request the highest possible rating for this proposal in

order that we may proceed with human subject studies with minimum delay and thereafter with the development of a beam line at SSRL dedicated to angiography.

B. EXPERIMENTAL EQUIPMENT

The experimental apparatus and control equipment will be supplied by the Hansen Laboratories of Physics at Stanford University and will be similar to that already used in Experiment 456B. This apparatus is being improved continually and its evolution since June 1979 is described in attachments I-IV. This evolution will continue as outlined in attachment IV. For example, the Si(Li) X-ray detector will in future be operated at -20 degrees C instead of at room temperture, the standard SSRL translation stages will be replaced by stages capable of faster and larger incremental movements, and new input analog and digital electronics will be used. In mid-1982 the prototype 30-channel Si(Li) detector with 1 mm postion resolution will be replaced with a 256-channel detector with 0.6 mm resolution.

The animal subjects will be provided by the School of Medicine at Stanford University, together with personnel thoroughly familiar with the care of such subjects.

0021666

C. EQUIPMENT DELIVERY SCHEDULE

The experimental equipment is presently available and in use in Experiment 456B.

D. PREVIOUS EXPERIENCE WITH TECHNIQUES AT FACILITY

Familiarity with the relevent techniques and the X-ray beam line has been established by the work carried out as Experiment 456B.

E. SAFETY CONCERNS

There are no hazardous materials associated with this study.

F. END STATION AND BEAM TIME REQUIRED

The preferred beam line and station for the proposed study is the rapidly-tunable wiggler-illuminated hard X-ray beam designated IV-2. Only in this beam, at electron energies 3 GeV or higher, is the intensity adequate for image acquisition in animal subjects for tissue thickness up to 20 cm. Also, only in this beam, or the equivalent VII-2, is adequate transverse space available for the positioning of large phantoms or animal subjects.

0021667

There are five separate questions of interest in this study; these are listed as items a)-e) in Section A. We estimate that the exploration of a) -c), associated with the development of a quantum-noise limited detection system, with the detectability of iodine in the presence of extra-channel iodine, and with the visibility of the coronaries in hearts with iodinated left ventricles, will each require approximately 10 shifts. Item d), the demonstration of the ability of the line-scanning method to image moving structures in sharp focus, will also require 10 shifts, and finally, item e), the acquisition of the first in-vivo images in animals, will require 20 shifts. The total time estimate is therefore 60 shifts, to which should be added a contingency of 15 shifts. The overall time estimate is therefore 75 shifts, which should be delivered in blocks of a minimum of 10 shifts. We regard these demonstrations as essential precursors to the subsequent efficient imaging of human subjects.

G. DATA ANALYSIS REQUIREMENTS

We intend to analyze the data from this study with a DEC LSI 11/03 minicomputer. Eventually we expect to transfer raw image data over a high-speed serial link, for analysis, to the SSRL VAX 11/780.

0021668

NON-INVASIVE ANGIOGRAPHY USING SYNCHROTRON RADIATION

E.B. Hughes, L.E. Campbell, R. Hofstadter, R.L. Kirk, T.J. Krolicki, J.P. Stone, H.D. Zeman
Hansen Laboratories of Physics and Department of Physics, Stanford University

E. Rubenstein, Department of Medicine, Stanford University

W.R. Brody and A. Macovski, Department of Radiology, Stanford University

A.C. Thompson, Lawrence Berkeley Laboratory

Angiography, the radiologic visualization of blood vessels and heart chambers containing contrast media, has become a powerful method of examining the structure of the heart and the coronary arteries and of diagnosing disorders involving the circulation of the heart, of the brain, and of other vascular beds. However, the techniques currently in widespread clinical use involve invasive procedures which carry significant risks of morbidity and mortality. These risks are far too high to permit the routine use of angiography to detect the presence of dangerous obstructing lesions in, for example, the coronary arteries of the many persons known to be at risk. Angiographic studies are limited therefore to symptomatic patients and are not conducted on asymptomatic patients even if they are at high risk because of hypercholesterolemia, hypertension, family history, etc. There is an urgent need to reduce the risk of these procedures.

The eventual purpose of the studies begun by proposal 456B is to bring into existence at Stanford a facility capable of conducting safe and non-invasive angiographic examinations on patients. Angiographic examinations of the coronary arteries will be emphasized. The acquisition of digital radiographs at X-ray energies slightly above and below the K absorption edge in iodine at 33.2 KeV and the subsequent differencing of these two images provides an exquisite sensitivity to intra-arterial iodine. This procedure promises the prospect of coronary arteriography with reduced concentration of iodinated compounds in the coronary arteries administered non-invasively by peripheral venous injection. This will eliminate the need for catheterization and substantially reduce the risk of the procedure.

Proposal 456B was submitted to SSRL in June 1979 and received its final rating in June 1980. This proposal called for the performance of certain basic tests on inanimate phantoms with minimum delay and with simple equipment already in hand. At the time this first proposal was submitted, solutions had been identified to some of the technical problems related to the realization of a diagnostic facility at Stanford, but not to all of them. Since that time studies of the outstanding questions continued, often in consultation with the SSRL staff, and practical solutions to all of the major problems have now been identified. These include the realization of a one-dimensional position-sensitive X-ray detector of satisfactory width and close to 100% efficiency, and the definition of a technique by means of which the motion of the heart muscle cannot degrade the image quality. For example, figure 1 shows a prototype silicon semiconductor detector fabricated to our specifications at the Lawrence Berkeley Laboratory. This detector is essentially one-dimensional (30 mm in width and 5 mm in height), its detection efficiency for 33 KeV X rays is close to 70%, it incorporates 30 independent contiguous sensitive regions each 0.9 mm in width with a center-to-center spacing of 1.0 mm, and it operates at room temperature.

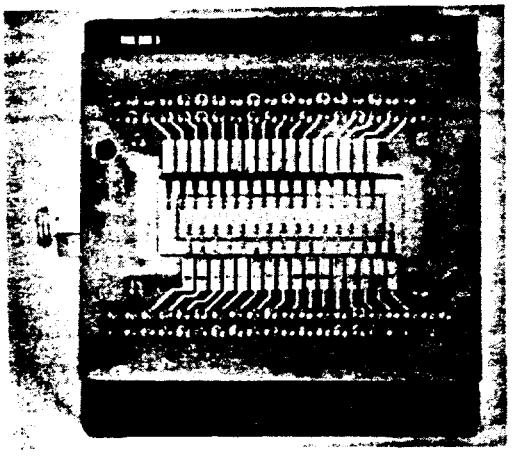

Figure 1. A prototype position-sensitive Si detector.

In the time made available to proposal 456B in this reporting period (through 4/14/81) the basic tests on inanimate phantoms with simple detection apparatus have progressed considerably. A start has also been made in the use of the prototype silicon detector for more efficient imaging, and in the preparation and use of animal hearts for more realistic imaging of the vessels and structures of eventual interest. Initial short opportunities to start work at SSRL occurred in the I-5 beam on 11/26/80 and on 12/5/80. Given the extremely low X-ray flux at 33.2 KeV and 2 GeV in the parasitic mode in a non-wiggler line, the first of these occasions was used to test the apparatus in the region of the K-edge in copper at 8.9 KeV. Clear difference signals were observed with the expected magnitudes for copper concentrations of 0.45, 0.9 and 1.8 mg cm^{-2} in inanimate phantoms. On the second occasion, at 3 GeV in the dedicated mode, the X-ray flux at 33.2 KeV as 400 times more intense and a useable beam at 33.2 KeV was obtained from the (440) plane in Si (~0.8 photons/pulse/mm^2). The contamination of 16.6 KeV X rays, from the (220) plane in Si, was reduced to about 50% with a 0.125 inch aluminum filter. Clear difference signals were observed with this beam for an iodine phantom concentration of 16 mg cm^{-2}.

The first access to beam line IV-2 for more than 24 hours occurred in the period 3/6/81 to 3/20/81 at 1.8 GeV in the parasitic mode. Despite the low flux at

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33.2 KeV, ~1 photon/pulse/mm^2 from the (220) plane of Si, good two-dimensional images of inanimate phantoms were obtained. One of these is reproduced in figure 2. The vertical iodinated channel, in a lucite block, is 1 cm in diameter at both ends and 1.5 mm in diameter in the central constricted region. The iodine concentration in the latter region is 5.5 mg cm^{-2}. Also in the field-of-view was a vertical wedge of lucite with an empty horizontal channel, also with a constriction. The images in figure 2 at the top left and right are of this composite phantom at X-ray energies just below and just above the iodine K-edge respectively. The lower images in figure 2 are, on the left, the difference between the two upper images, and on the right, the ratio of the two upper images. In both of the lower images, as expected, only the iodine content of the phantom is reproduced and image contrast due to the other structures is eliminated. These and other data obtained at this time were acquired by collimating the X-ray beam to a cross sectional size of 1 mm x 1 mm and scanning the phantoms, in raster fashion, in front of a single X-ray detector consisting of a CaF_2(Eu) scintillator and a 0.75" diameter EMI 9826A photomultiplier tube. Preliminary attempts were also made to image iodinated arteries in animal hearts (pig and calf) but this proved to be impractical since the time needed to acquire an image (several hours due to the low X-ray flux and the single X-ray detector) exceeded the durability of the iodine in the arteries for the heart preparation technique then used.

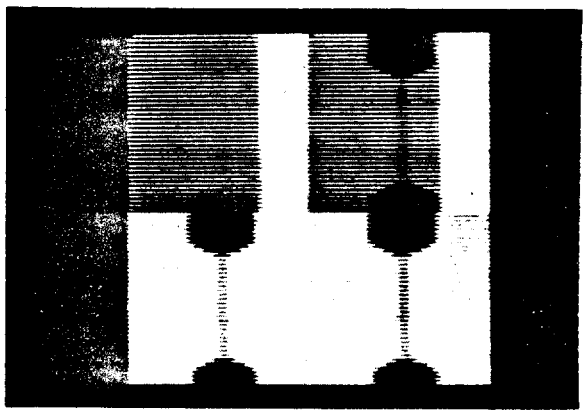

Figure 2 Raw and processed images of an iodinated channel in a complex phantom

The first, and to this date, the only access to beam line IV-2 under operating conditions approximating those requested in the proposal took place in the period 4/8/81 to 4/14/81. At this time, in parasitic mode*, the operating conditions were 2.5-3.0 GeV and about 25 mA, which correspond to a 33.2 KeV flux of ~320 photons/pulse/mm^2. For these tests the increased flux and the use of the prototype position-sensitive silicon X-ray detector (actually only 8 of the 80 1 mm wide channels were used due to limited availability, at that time, of electronics) combined to permit the acquisition of images with substantially reduced observing times (several minutes). Excellent images of a variety of iodinated inanimate phantoms were obtained and, in addition, due to a substantial improvement in heart preparation technique, a variety of animal heart images with iodinated coronary arteries were also obtained. The key to retention of iodine in the animal vessels was the use of a dental impression paste (CutterSil tm), in which the appropriate concentration of NaI powder was thoroughly mixed, and to which a curing compound was added immediately before insertion into the arterial system with a catheter and syringe. A typical set of images of calf heart coronary arteries is shown in figure 3. At the top are the separate images obtained above and below the iodine K-edge and at the bottom is their ratio. In the latter image all contrast due to non-iodinated heart structures is eliminated.

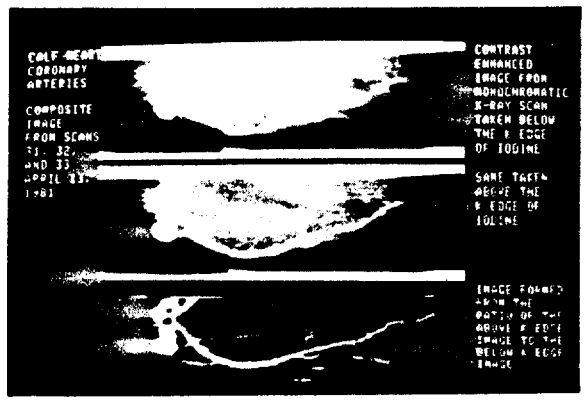

Figure 3 Raw and processed images of calf heart coronary arteries.

In future tests phantom images for the full range of parameters outlined in proposal 456B will be obtained. Also, following instrumentation of all 30 channels of the Si detector, animal heart images will be obtained for a wider range of iodine concentrations. Most importantly, animal hearts will be prepared with iodine concentrations typical of venous administration in the left ventricle as well as in the coronary arteries, and images will be obtained with some of the coronary arterial system projected against the filled ventricle. In this way the isolation of the coronary artery from the ventricular background by image analysis can be explored and developed. Also in preparation are realistic phantoms of animal hearts prepared from impressions taken from real hearts. These phantoms will permit arbitrary and adjustable iodine concentrations to be placed in coronary arteries and ventricular chambers and will eliminate, to some degree, the need for real hearts. Under discussion also is a phantom system that will permit tests to be made on beating hearts.

* Wiggler field 17 Kg.

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Synchrotron radiation and its application to digital subtraction angiography

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Abstract

The intense synchrotron radiation produced at electron storage rings provides a new source of X-rays highly suited to iodine K-edge digital subtraction angiography. The high intensity and small angular divergence permit the radiation to be monochromatized by Bragg diffraction and made available in beams of small vertical size, of arbitrary horizontal width, and of tunable energy. The use of such beams provides maximum sensitivity to intra-arterial iodine and virtually eliminates image contrast due to non-vascular body structures. The sensitivity of this method to iodine offers the prospect of visualizing arteries by peripheral venous injection.

Introduction

Digital subtraction angiography, based either upon images acquired at different times or at different X-ray energies, offers the prospect of imaging the small iodine thicknesses typical of intravenous arteriography. Both methods, as presently practised, encounter particular performance-limiting problems. Specifically, time-subtraction angiography is limited by patient motion between component images, and energy subtraction, when based upon the iodine K-edge and quasi-monoenergetic beams obtained by filtration, is limited by the available X-ray flux and by residual contrast due to superimposed soft tissue and bone. Both methods also face the need to suppress system noise to achieve a quantum-limited contrast sensitivity. In this paper we identify a new approach to K-edge subtraction angiography made possible by the properties of an X-ray source newly available to clinical radiology. This source is the synchrotron radiation produced at an appropriate electron storage ring.

Conventional X-ray sources provide a broad spectrum of X-ray energies. However, iodine preferentially absorbs at energies in the immediate vicinity of its K-absorption edge at 33.16 KeV. In addition, other body structures, such as soft tissue and bone are reproduced in the conventional image and subtract from the contrast due to the iodine itself. If the X-rays from a conventional source are filtered to select the energies specific to iodine and thereby enhance the iodine contrast, there is insufficient intensity in the beam to produce a generally useful image.

The properties of the X-rays that can be produced at electron storage rings by synchrotron emission substantially relieve both of the problems with energy subtraction identified above. First, the enormous intensity and inherent collimation permit the radiation to be Bragg-diffracted so that only a narrow band of energies remains. Second, because the selected energy of X-rays is subject to fine adjustment, by a small alteration of the Bragg angle in a crystal monochromator, digital radiographs may be acquired at X-ray energies slightly above and slightly below that of the iodine K-edge at 33.16 KeV and then logarithmically subtracted. This subtraction substantially eliminates all the image contrast due to non-vascular body structures and thereby achieves maximum contrast in the visualization of the intra-arterial iodine. The method is referred to as dichromography. If this sensitivity is realized, it offers the prospect of visualizing arteries by peripheral venous injection and, as explained below, without motion artifacts. This would achieve the goal of eliminating the need for arterial catheterization and thereby greatly reduce both the risk

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and the cost of the examination procedure.

Characteristics of Synchrotron X-ray Beams

The prospect of non-invasive K-edge digital subtraction angiography with monoenergetic X-ray beams is made possible by the development over the last ten years of the electron storage ring. The development of this device, in reality a form of particle accelerator, was motivated by the opportunity it creates to examine the fundamental structure of matter in a novel and penetrating way. Fortunately for other branches of science, the electron storage ring also created a new and enormously powerful source of electromagnetic radiation, including hard X-rays. This circumstance occurs because charged particles of low mass, such as electrons, readily and continuously lose energy in the form of electromagnetic radiation when accelerated, as in a storage-ring orbit. This radiation is called synchrotron radiation and, due to the extreme relativistic speed of the electrons, is strongly concentrated in its emission in the orbit plane. To maintain the electrons in a closed orbit with constant energy, this radiated energy must be replaced promptly by powerful radio-frequency oscillators. At equilibrium, the rate of production of synchrotron radiation by the orbiting electrons is equal to the amount of energy returned to them by the oscillator, and this is large. In effect, the electron storage ring serves as a device for the conversion of radio-frequency electromagnetic power into synchrotron radiation. This is an inconvenient but unavoidable fact of life for investigators of particle physics, who employ counter-rotating currents of electrons and positrons in identical orbits to generate electron-positron collisions, but it creates a novel source of ultra-violet radiation and X-rays for those interested in other areas of science. This is widely recognized today, and electron storage rings are now under design and construction world-wide solely for the synchrotron radiation they produce.

Despite the intensity of the synchrotron radiation emitted by electrons traversing simple dipole bending magnets, which are mandatory for storage ring operation, laboratories such as the Stanford Synchrotron Radiation Laboratory (SSRL) now rely upon special magnets, known as wiggler magnets, for the generation of their most powerful beams. [1,2] These magnets are irrelevant to the storage ring concept and are inserted into sections of the closed orbit where the electron curvature is usually zero. A wiggler magnet is designed with a periodic transverse magnetic field to enhance deliberately the emission of synchrotron radiation, but to transmit the electron beam with no net deflection. The synchrotron beam lines available at SSRL and those available for future development are indicated in Figure 1.

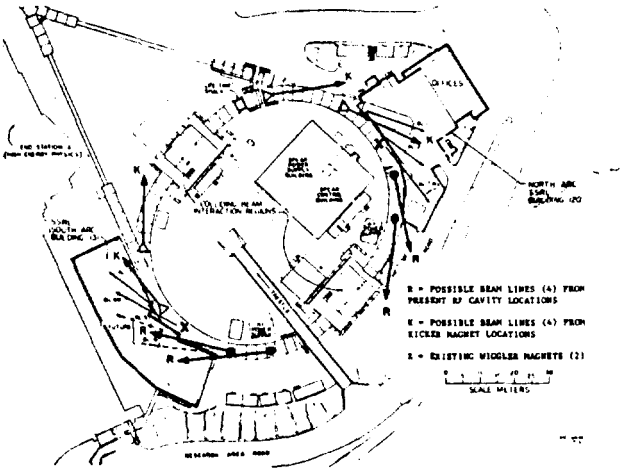

Figure 1. A schematic drawing of the storage ring and facilities at SSRL. Existing beam lines are 1, 2, 3, 4 and 7, all of which are subdivided into two or more lines. Beam lines 4 and 7 are wiggler-illuminated. Available for future development are the dipole-illuminated lines 5 and 6 and the eight wiggler-illuminated lines K and R.

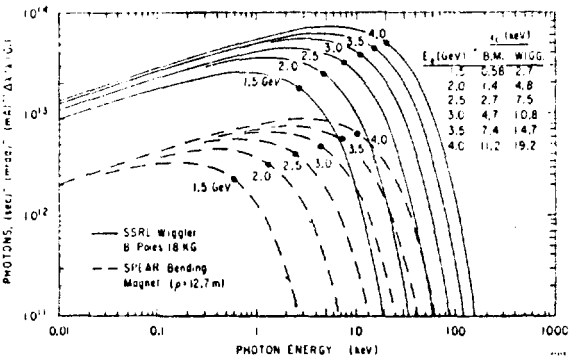

Figure 2. The synchrotron intensity distributions presently available at SSRL for both dipole and wiggler-illuminated lines. The curves are labeled with the stored electron energy in GeV at positions corresponding to the critical energy in KeV of the radiated spectra. Fifty percent of the radiated power occurs at energies higher than the critical energy.

The intensity of the synchrotron radiation presently available at SSRL is indicated in Figure 2 as a function of stored electron energy for both dipole and wiggler magnets. The intensities possible with new wiggler magnets presently under design are indicated in Figure 3 for an electron energy of 3 GeV. These future wigglers will be permanent magnets assembled from blocks of rare-earth cobalt magnetic materials (eg. $SmCo_5$) that make the

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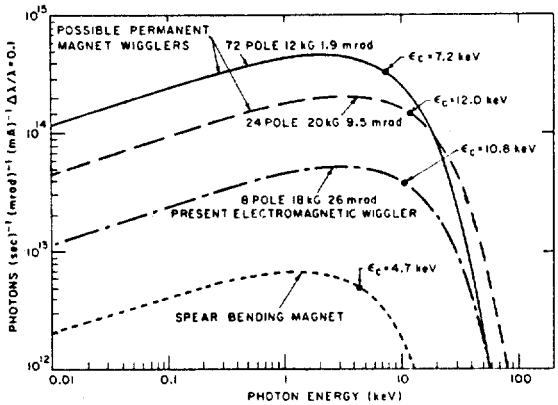

Figure 3. A comparison of the synchrotron intensity distributions available at SSRL for the existing dipole and wiggler magnets, and those expected for future permanent magnet wigglers with higher pole densities. All these wiggler magnets are 2 meters in length.

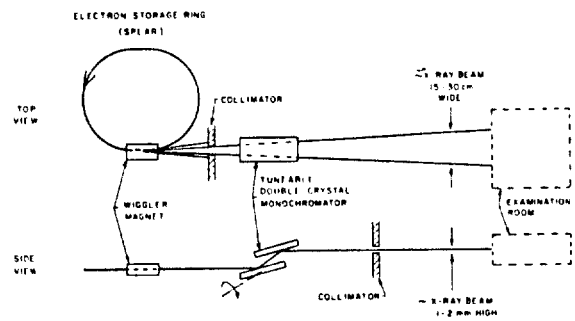

Figure 4. A schematic drawing of the method by which a tunable beam of X-rays may be produced at SSRL.

construction of magnets with many poles relatively simple and economical. Through choice of the field strength and the number of poles, the intensity, spectral distribution and angular width of the synchrotron radiation can be controlled. For example, the 72-pole wiggler in Figure 3 is intended to produce a narrow beam (1.9 mr) with a critical energy of 7 KeV, whereas the 24-pole wiggler is designed to produce the maximum flux at 33 KeV (for an electron energy of 3 GeV) with an angular width (9.5 mr) compatible with the requirements of clinical radiology.

The method by which a tunable beam of X-rays can be produced at SSRL for medical purposes is indicated in Figure 4. The radiation emitted by the electron beam during transit through a wiggler magnet is restricted first by a horizontal aperture and is then conducted through a vacuum or helium atmosphere to a double-crystal silicon X-ray monochromator. The first crystal in the monochromator is oriented at the appropriate angle to select, by Bragg diffraction, only a narrow band of X-ray energies. The second crystal, which is in accurate alignment parallel with the first, serves only to assure that the emergent X-ray beam exits from the monochromator in a direction parallel to the direction of the incident beam. After passage through a vertical aperture, the beam in delivered to the examination room. The bandwidth ΔE of the transmitted X-ray beam is given by the relation

$$\Delta E/E = \mathrm{Cot}(\theta_B) \cdot \Delta\theta_B$$

where E is the X-ray energy, θ_B is the Bragg angle and $\Delta\theta_B$ is the vertical angular width of the synchrotron beam. For the Si(220) plane, for example, the Bragg angle is 5.6 degrees. If the X-ray energy is 33.2 KeV and the vertical aperture 1 mm in height at a distance of 20 meters from the source (the wiggler magnet), then the bandwidth is 17 eV. To change the selected X-ray energy it is necessary only to rotate simultaneously both crystals in the monochromator by the same small angle. In particular, to change the X-ray energy by an amount equal to the bandwidth (17 eV), and thus to step from one side of the iodine K-edge to the other, the angle of rotation is only 2.4×10^{-3} degrees. This can be accomplished easily and rapidly, for example by the use of piezoelectrically-controlled adjustment devices.

Application to Digital Subtraction Angiography

The principle of dichromography was first mentioned by Jacobson in 1953[3] and in recent years has received most attention from Mistretta et al[4] and Macovski et al.[5] All developmental efforts however have employed standard X-ray generators and, in consequence, have suffered from the lack of truly monochromatic beams of adequate intensity. With the recent availability of intense, monochromatic and tunable X-ray beams, for example at SSRL, the opportunity now exists for the direct application of this technique. This is the objective of the studies reported here.

Attempts to implement the principle of dichromography have used heavy filtration (90-95%) of beams from standard X-ray generators to obtain quasi-monoenergetic beams of substantial linewidth (6-8 KeV) and limited intensity. In this way, a sensitivity to iodine thicknesses

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as small as 1 mg cm^{-2} has been demonstrated. The principal problem, due to the large linewidth and the resultant large separation (8 KeV) between the peak energies of the two quasi-monoenergetic beams, is the background difference signals due to variations in the soft tissue and bone thicknesses along possible trajectories through the specimen. If only two quasi-monoenergetic beams are used, the method is limited to essentially bone-free regions.[6] If three quasi-monoenergetic beams are used, this restriction is removed.[7] Each of the three quasi-monoenergetic beams, however, requires a different filter and at least one of them a different terminal voltage.

The ideal approach to iodine dichromography is to use two monoenergetic X-ray beams, both immediately adjacent to the K-absorption edge but one with energy above and one with energy below this edge. In this way the difference signals due to soft tissue and bone thickness variations are strongly suppressed. For a beam linewidth of 17 eV and a spacing of 17 eV between the two beam energies, the soft tissue and bone difference signal sensitivities are 1.8×10^{-2}%/gm cm^{-2} and 7.7×10^{-2}%/gm cm^{-2} respectively, whereas the iodine difference signal sensitivity is 3%/mg cm^{-2}.

At a convenient distance from the orbiting electrons, the wiggler-illuminated beam outlined in Figure 4 has a horizontal profile that approximates a line. If, for example, the angular width selected by the horizontal collimator is 7.5 mr (well within the 12 mr angular width of the radiation emitted by an existing 8-pole 18 Kgauss SSRL wiggler) and the operating distance is 20 meters, the X-ray beam will be 15 cm in width and, if uncollimated and unfocussed, only 0.3 cm (FWHM) in height. This beam may be collimated vertically to provide the desired vertical spatial resolution (0.5-1 mm), or it may be focussed in the vertical direction by reflection at grazing incidence from a curved X-ray mirror. After the beam, essentially one-dimensional, passes through the patient under examination, it is intercepted by a matching one-dimensional highly efficient X-ray detector. This detector is segmented along its length and provides a one-dimensional projected image of the planar segment of the patient intercepted by the beam. At each of these planar segments the image is recorded first at an X-ray energy just above the iodine K-edge and then, immediately following, at an energy just below the K-edge. A complete two-dimensional image of the body structure under examination is made by scanning the patient vertically relative to a stationary beam and detector and recording pairs of one-dimensional images at each adjacent vertical position.

In order, in particular, to visualize iodine within the coronary arteries, it is necessary to record each pair of one-dimensional images, i.e. above and below the K-edge, in a time short compared to the periodic motion of these structures. An appropriate time interval is approximately 15 msec or less. The total time to scan the heart is longer than the cardiac cycle, but this relatively long scanning time will not result in a blurred image. Each line exposure, due to the high X-ray intensity, will occupy only about 5 milliseconds. The X-ray energy is then switched, within a few (~5) msec, and the second exposure is made. Each pair of line exposures occurs within 15 msec, a period within which the coronary arteries are essentially stationary. Upon completion of each exposure pair, the patient is moved vertically by the required positional increment and the procedure repeated. The lack of blurring is governed by the line-pair exposure time and not by the total frame time. This is a direct analog of photographic cameras with focal plane shutters which are free of blurring despite relatively long exposure times of the scanning slit. The price paid for this effect is that all portions of the image do not represent the same time interval. A subtle distortion is generated due to motion, but this does not represent blurring. For example, a horizontally moving vessel, which would otherwise be blurred, is reproduced in good focus at a slight inclination since the top and bottom are scanned at different times. The rapid changes in X-ray energy required by this method of image acquisition pose no fundamental difficulty for synchrotron beams. This may be achieved by synchronously rotating, or oscillating, the crystals in the monochromator at the required frequency (67 Hz) by the small angular amount necessary to step the transmitted beam back and forth through the iodine K-edge.

A major attribute of the synchrotron X-ray beam is that it is capable of providing, after monochromatization, an X-ray intensity entirely adequate to record precise projected images even after transmission through thick body sections. Under standard operating conditions of the storage ring at SSRL (a circulating electron current of 100 mA at an energy of 3 GeV) the existing wiggler-illuminated X-ray beam, without vertical focussing, has an intensity of 6.2×10^9 photons/second/mm^2 of aperture at 20 meters from the storage ring. The bandwidth, at energies close to 33 KeV, is 17 eV, for the Si(220) plane. For comparison, a powerful modern X-ray generator of conventional design, dissipating 50 kilowatts of power, can provide 5.0×10^9 X-ray photons/second/mm^2 at 1 meter distance, but these photons are distributed over an energy range from 20-100 KeV. If this latter beam were to be monochromatized by the same method used with the synchrotron beam, its intensity would be reduced by a factor of approximately 2000.

Even after transmission through a soft tissue thickness of 20 cm the intensity of the existing SSRL synchrotron beam is 7.2×10^6 X-ray photons/second/mm^2, or 3.6×10^4 photons in

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the nominal time exposure of 5 msec required for coronary arteriography. The statistical noise contributed by this beam intensity to the X-ray image in a pixel size 0.5 mm x 0.5 mm is only 1.1% (for 100% X-ray detection efficiency), which, in principle, permits iodine thicknesses as small as 1.1gm cm^{-2} to be detected with a signal-to-noise ratio of 3.0. This is much smaller than the thickness typically used in current practice and is, in essence, the reason why non-invasive arteriography is possible with synchrotron X-ray beams.

If, in a dichromographic study, Renografin 76 (iodine concentration 370 mg ml^{-1}) is introduced by peripheral venous administration and undergoes dilution by a factor of 30, the iodine thickness in an artery 2 mm in diameter will be 2.5 mg cm^{-2}. Upon the logarithmic subtraction of two 5 msec digital images, for a tissue thickness of 20 cm and the X-ray intensity stated above, this iodine thickness will generate a signal-to-noise ratio of 7.5 for a pixel size of 0.5 mm x 0.5 mm. The patient exposure for this study will be 308 mR. The total time occupied in the acquisition of the image in a line-by-line scan with 0.5 mm vertical resolution over a 15 cm range will be 4.5 seconds. This is a good match to the time required for the iodine bolus to transit the coronary arteries.

The description of the imaging procedure given immediately above is based on the specific X-ray intensity provided at SSRL from an existing 8-pole 18 Kgauss wiggler with no vertical focussing. This beam was not designed with the needs of a future medical imaging facility in mind. In particular, the wiggler output is split horizontally into three parts, each of which is delivered to a separate user. None of these component beams is wide enough for medical purposes. The typical SSRL user does not require a wide beam, but instead wishes to concentrate the available radiation onto a target of relatively small width. A new beam, especially designed for clinical applications, will include a wiggler magnet designed to maximize the X-ray intensity within a horizontal aperture of 7.5 mr. In this way an increase in specific X-ray intensity by a factor of at least 5 relative to the existing beam can be achieved. Further increases, should they be necessary, can be obtained through the use of vertical focussing (for efficient use of all the radiation available) by raising the stored electron energy closer to the maximum value of 3.9 GeV at SSRL, by increasing the stored electron current, and through the use of a Si diffraction plane with a smaller Bragg angle than 5.6 degrees. By these means, should it be necessary, the line exposure time can be reduced correspondingly to well below 5 msec and the image-acquisition time to much less than 4.5 seconds.

In addition to the basic attributes of monochromaticity and high intensity, which collectively make true dichromography possible and permit snapshots to be taken of structures in motion, the one-dimensional character of the synchrotron X-ray beam is also well-suited to high-quality radiologic imaging. This latter property, in particular, substantially eliminates the scatter problem encountered in conventional radiology due to the use of two-dimensional, or area, X-ray beams. Another benefit of monochromaticity is that beam-hardening artifacts are also eliminated.

Initial Studies at the Stanford Synchrotron Radiation Laboratory

Experimental studies of dichromography with monoenergetic X-rays began in December 1979 at SSRL. An early phantom image is reproduced in Figure 5. The vertical iodinated channel, in a lucite block, is 1 cm in diameter at both ends and 1.5 mm in diameter in the central constricted region. The iodine thickness in the latter region is 5.5 mg cm^{-2}. Also in the field-of-view is a vertical wedge of lucite whose thickness, from top to bottom of the phantom, varies from 1.0 to 4.0 gm cm^{-2}. This wedge is penetrated horizontally by an empty channel, also with a constriction. The images in Figure 5 at the top left and right are of this composite phantom at X-ray energies conservatively chosen to be 200 eV below and 200 eV above the iodine K-edge respectively. The lower images in Figure 5 are, on the left, the ratio of the two upper images, and on the right, the difference between the two upper images. In both of the images, as expected, only the iodine content of the phantom is reproduced and image contrast due to the other structures is eliminated. These early data were acquired by collimating the X-ray beam to a cross-sectional size of 1 mm x 1 mm and scanning the phantom, in raster fashion, in front of a single X-ray detector consisting of a $CaF_2(Eu)$ scintillator and a 1.91 cm diameter EMI 9825A photomultiplier tube.

In subsequent tests at SSRL, images were acquired with considerably improved efficiency through the use of a one-dimensional position-sensitive X-ray detector with efficiency close to 70% at 33 KeV. A photograph of this prototype silicon semiconductor detector, fabricated to our specifications at the Lawrence Berkeley Laboratory, is shown in Figure 6. The sensitive area is 30 mm in width and 5 mm in height and incorporates 30 independent adjacent sensitive regions each 0.9 mm in width with a center-to-center spacing of 1.0 mm. The silicon thickness is 5 mm. It is expected that the fabrication and testing of this prototype detector will provide the experience necessary to produce similar detectors up to at least 15 cm in width and with finer spatial resolution (~0.5 mm).

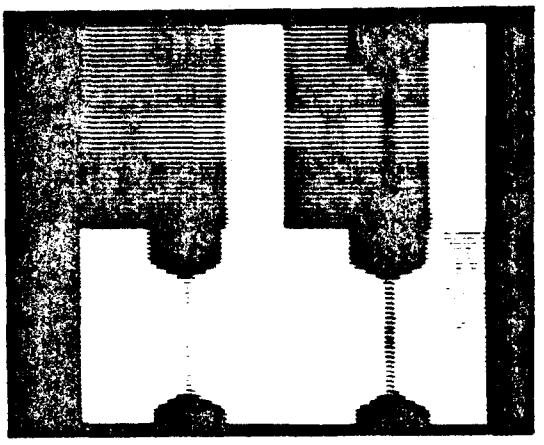


Figure 5. Component and processed images of an iodinated channel in a lucite phantom.

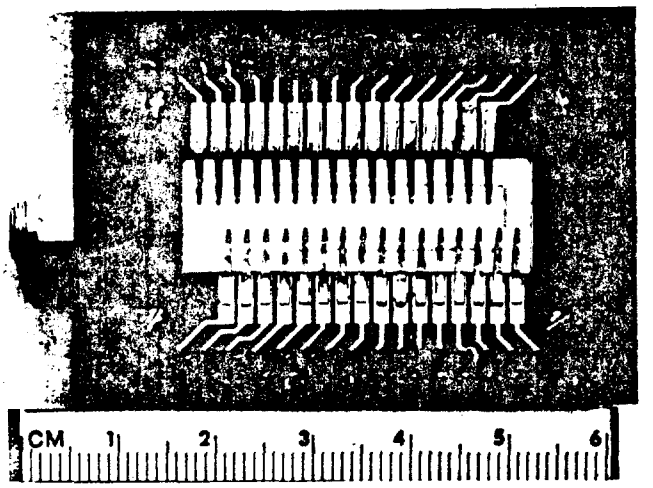
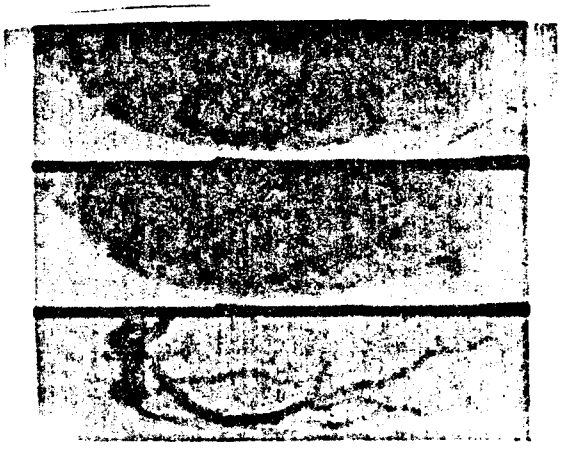


Figure 6. A prototype position-sensitive Si(Li) detector.

Figure 7 is an early example of an excised calf heart image obtained with the prototype silicon detector. The outputs of 8 channels of the detector were connected to 8 separate commercial instruments (5 Keithley 424 current amplifiers and 3 Keithley 616 digital electrometers). The voltage outputs of these instruments were read by a LeCroy model 2259A 12 channel CAMAC ADC. The heart was scanned in 5 adjacent vertical swaths each 48 mm in height. An object area 48 mm x 48 mm was scanned, with 1 mm x 1 mm resolution, first at an X-ray energy 20 eV above the iodine K-edge and then 20 eV below the edge. Three such 48 mm x 48 mm images of adjacent sections of the heart were combined to produce the overall image in Figure 7. Because of the poor match between the relatively low output impedence (50 K ohm) of the detector and the high input impedance (10^{14} ohm) of the Keithley electrometer, a considerable drift in the signal reaching the ADC's was noted. To correct for pedestal drift and possible drift in gain of each electronic channel, 3 mm lead absorbing strips were placed at the top and the bottom of each image and an unobstructed strip was left immediately above the lower lead strip. The incident X-ray flux was monitored throughout by an upstream ionization chamber whose output was digitized and recorded together with the x-ray image data.



The iodine was retained in the arteries of the calf heart used in Figure 7 by the use of a dental impression paste (CutterSil) in which the appropriate concentration of NaI powder was thoroughly mixed, and to which a curing compound was added immediately before injection, with a catheter and syringe, into the arterial system. At the top in Figure 7 are the separate (logarithmic) images obtained above and below the iodine K-edge and at the bottom is their difference. In the latter image all contrast due to non-iodinated heart structures is eliminated. The iodine concentration used for this study was 100 mg ml^{-1}.

Figure 7. Component and processed images of calf heart coronary arteries. The component images are both logarithmic images.

A more complete set of phantom images, designed to demonstrate the strong and simultaneous suppression of contrast due to soft tissue and bone made possible with monoenergetic X-rays, is displayed in Figure 8. At the left is indicated the structure of each phantom in this set. The three images in each row on the right are, respectively, those obtained for each phantom above the K-edge, below the K-edge, and from their logarithmic subtraction. For all four phantoms the resultant image, in the third row, is the same. Only contrast due to iodine remains. The iodine thickness for all these studies was 2.5 mg cm^{-2} in the 1.5 mm diameter constricted lucite channel. The lucite, or soft tissue, thickness variations, from left to right are 2.5, 2.5, 12.0 and 12.0 gm cm^{-2} and the range of bone thicknesses, where a bone is used, is 1.5 gm cm^{-2}. These images were acquired with 8 channels of improved electronics incorporating low-noise operational amplifiers well-matched to the output impedence of the detector. The electronic drift was thereby greatly reduced

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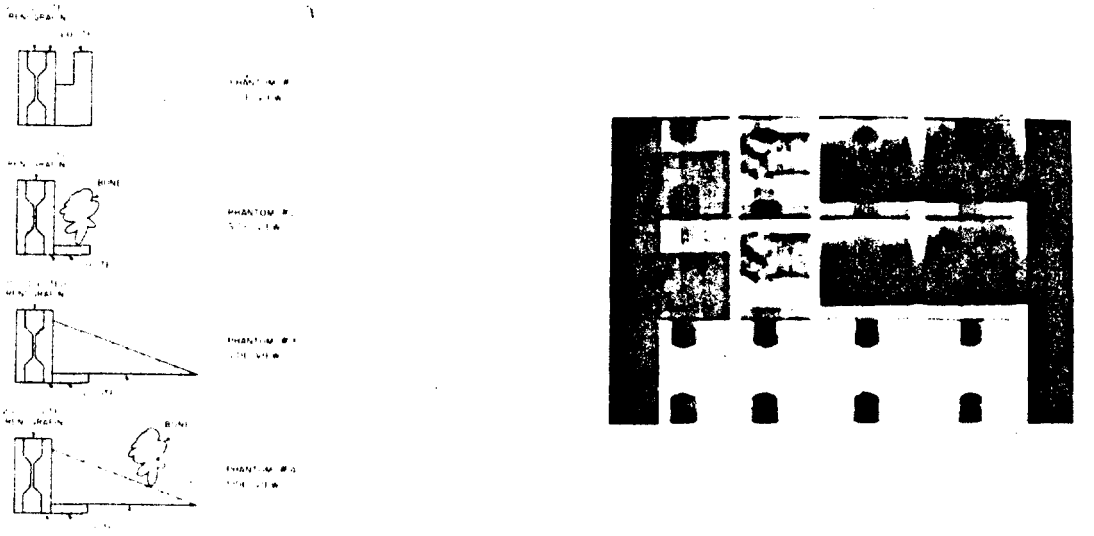

Figure 8. Component and processed images of an iodinated channel in a set of four complex phantoms. The structure of each phantom is indicated at the left and the corresponding images, ordered from left to right, are shown at the right.

and the unobstructed strip used with the Keithley electrometers no longer necessary. Also in these images, unlike Figures 6 and 7, each line exposure (8 channels wide) was made first 50 eV above and then 50 eV below K-edge before the object was moved to the next raster position. This procedure, although not essential for static objects, does suppress systematic image noise due to electronic drifts. For moving structures, such as the arterial system in a patient, and especially the coronary arteries, fast energy switching of this type will be mandatory.

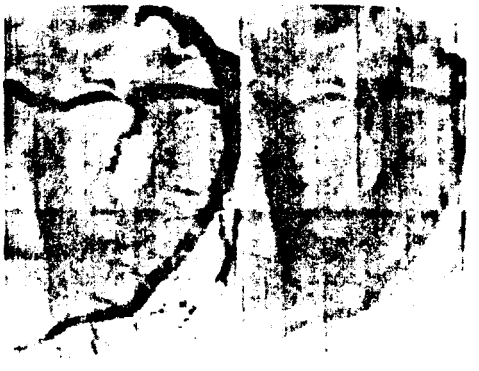

Figure 9. Component images of calf heart coronary arteries taken with 0.5 mm x 0.5 mm spatial resolution. At the left is the image taken above the K-edge and at the right is the image taken below the K-edge. Both images are logarithmic.

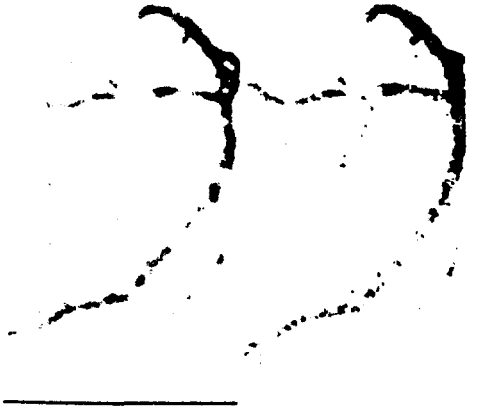

Figure 10. The logarithmically subtracted images corresponding to Figure 9 for resolutions of 0.5 mm x 0.5 mm (at the right) and 1 mm x 1 mm (at the left). In the middle of the horizontal vessel there is a region, about 1 cm in length, with unexpectedly low iodine thickness. Dissection of this region revealed an air bubble in the CutterSil-NaI paste. Other smaller bubbles are evident in the descending vessel and were also confirmed by dissection. These bubbles are easily preventable (see Figure 7), but their accidental occurrence here was useful from the standpoint of detecting disease-like arterial structure.

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Figures 9 and 10 show the arterial system of an excised calf heart. This heart was imaged for detector spatial resolutions of both 1 mm and 0.5 mm to help select the position resolution in a much wider future detector. A detector resolution of 0.5 mm was achieved by placing a mask, with 0.5 mm aperatures spaced by 1 mm and centered on the 0.9 mm wide contacts, in front of the present detector and by acquiring two interlaced component images for each scan. A matching vertical resolution of 0.5 mm was achieved by collimation. The images in Figure 9 are those taken 50 eV above and 50 eV below the K-edge with the masked detector, or 0.5 mm resolution. Figure 10 shows the difference images for 1 mm and 0.5 mm resolutions respectively. It is apparent that 1 mm is marginally acceptable for clinical evaluation and that a resolution close to 0.5 mm is preferable for clinical work. The iodine concentration used in this study is 67 mg ml^{-1}.

Summary

The studies and initial tests outlined above suggest that synchrotron X-ray beams can be applied successfully to digital subtraction angiography for the arterial iodine thicknesses typical of venous administration.

The advantages that synchrotron X-ray beams bring to arteriography are as follows: a) The intensity of the beams permits short exposure times and allows images to be recorded in sharp focus despite arterial motions. b) The monochromaticity of the beams maximizes the sensitivity to intra-arterial iodine and permits the use of peripheral venous injection. c) The monochromaticity of the two beams and their very small energy spacing strongly suppresses background signals due to tissue and bone thickness variations. d) The one-dimensional character of the beams substantially eliminates the scatter problem encountered in the use of conventional X-ray beams. e) The monochromaticity of the beams eliminates the beam-hardening artifacts encountered with conventional X-ray beams.

The synchrotron X-ray beam potentially allows the principal difficulties associated with time- and energy-subtraction angiography with conventional sources to be overcome. In particular, it offers a new approach to arteriography of the coronary arteries by non-invasive means.

Synchrotron X-ray beams are now widely used in other, non-clinical, areas of research. The rapidly developing technologies of electron storage rings and of emission-enhancement devices, such as the wiggler and undulator magnets [1,2], are making useful beams available at more existing centers and reducing the potential size and cost of future facilities designed expressly for medical work. The studies reported here will continue. An X-ray beam of adequate width will be developed and in-vivo tests on animals and selected patients will be made.

Acknowledgements

This work was supported, in part, by grants from the William Randolph Hearst Foundation and the Henry J. Kaiser Family Foundation. Invaluable support in detector fabrication and electronic engineering respectively was provided by J. Walton of the Lawrence Berkeley Laboratory and J. Rolfe of the Hansen Laboratories of Physics.

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IMPLEMENTATION OF DIGITAL SUBTRACTION ANGIOGRAPHY WITH A SYNCHROTRON X-RAY BEAM

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Abstract

The intense synchrotron radiation produced by wiggler magnets at electron storage rings provides a new source of x-rays highly suited to iodine K-edge digital subtraction angiography. The monochromaticity and tunability provide maximum sensitivity to intra-arterial iodine and virtually eliminate contrast due to soft tissue and bone. Visualization of arteries, in particular the coronary arteries, by peripheral venous injection is possible. A system design, based on tests already performed, is presented.

Introduction

Blood vessels absorb x-rays with efficiency comparable to surrounding soft tissue and cannot be seen in routine examinations. Iodine-containing compounds are therefore introduced into the arteries during x-ray examination to provide the needed contrast. Conventional x-ray sources provide a broad spectrum of energies. However, iodine preferentially absorbs only at energies immediately above the K-edge at 33.16KeV. In addition, owing to the broad range of x-ray energies, other body structures, such as bone and soft tissue, are reproduced in the image and reduce the contrast due to the iodine itself. In consequence, highly concentrated solutions of iodinated compounds are introduced, by catheter, directly into the orifice of the artery of interest. The risks of this invasive procedure are far too high to permit the use of angiography to detect the presence of dangerous obstructing lesions, especially in the coronary arteries, in the many persons known to be at risk.

Digital subtraction angiography conducted with intense, monochromatic and tunable synchrotron x-ray beams substantially overcomes the problems associated with the use of conventional x-ray sources and offers the prospect of visualizing arteries by peripheral venous injection. The method is referred to as dichromography. It involves the acquisition of digital radiographs at x-ray energies slightly above and slightly below that of the iodine K-edge and the subsequent logarithmic subtraction of these two images to achieve exquisite sensitivity to iodine alone. If realized, the need for arterial catheterization would be eliminated and both the risk and the cost of the diagnostic procedure greatly reduced.

The application of synchrotron x-ray beams to subtraction angiography has been summarized recently by Rubenstein et al,[1] who also describe initial studies at the Stanford Synchrotron Radiation Laboratory (SSRL). These studies are continuing, and in-vivo tests on animals and human subjects are planned. In this paper the properties of the electronic instrumentation developed from these tests is described, together with the projected organization of the data acquisition and analysis system. A brief description of the first test images is also presented.

Line-Scan K-Edge Imaging with a Multi-Channel Solid-State Detector

The tests already conducted have used existing synchrotron x-ray beams at SSRL, none of which was designed for medical imaging. In the future, the method by which an x-ray image may be obtained with a synchrotron beam is indicated in Figure 1.

LINE-SCAN K-EDGE IMAGING SYSTEM

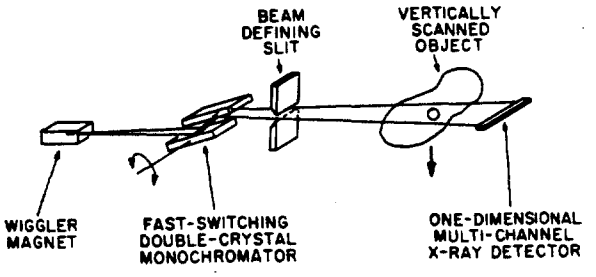

Fig. 1. Schematic diagram of the line-scan K-edge imaging system using synchrotron radiation.

At the patient examination area, the beam generated by a wiggler magnet can be 15cm or more in horizontal width and, if unfocused, typically 0.3cm FWHM in vertical width. After passing through a crystal monochromator and a vertical defining slit, the beam can have an energy bandwidth, if the Si(220) diffraction plane is used, of 17eV and a vertical width of 0.05cm. The x-ray beam, essentially one dimensional, passes through the patient and a projected image of a horizontal section is recorded by a one-dimensional multi-channel Si(Li) detector (see Fig. 2). The beam energy is adjusted in sequence to each side of the iodine K-edge and a pair of images taken for each section before the patient is moved by one vertical resolution element.

Figure 3 shows a block diagram of the electronic and computer system for use with the line-scan imaging apparatus. All operations in the production of an image will be controlled through a CAMAC crate by a DEC PDP11/34 data acquisition computer. Raw image data will be transferred over a high-speed serial link, for analysis, to a DEC VAX11/780. There the data will be processed into logarithmically subtracted and suitably enhanced images for display on a video monitor.

For images of human subjects, a detector with 256 elements, each 0.5mm wide and spaced 0.1mm apart, is

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planned. Hence, a 15cm x 15cm image, large enough to encompass a human heart, will require 256 x 256 pixels. This size image can be accomodated by the DeAnza ID-2000 display system.

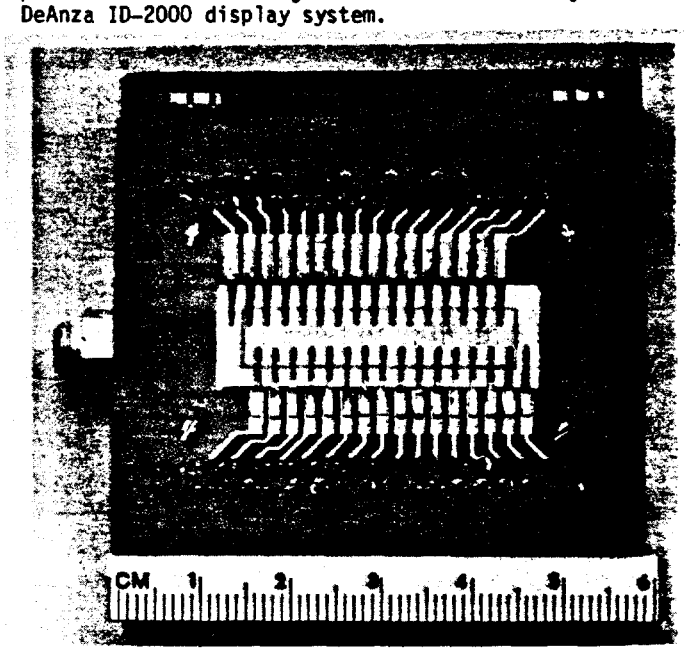

Fig. 2. Prototype 30-channel Si(Li) detector.

The existing prototype Si(Li) detector[2] has 30 elements, each 0.9mm wide and spaced 0.1mm apart. The detector is operated at positive high voltage and the separate pads are used as negative electrodes. A positive current therefore flows out of each pad into the input electronics. Because of surface conductivity, the separate detector pads are not totally isolated from each other. Each has a resistance of approximately 70KΩ to all the other pads and the guard electrode. This relatively low output resistance combined with an output current of only a few nanoamps (in diagnostic imaging), places severe demands on the performance of the analog section of the input electronics (see Fig. 4). The greatest demands are placed on the input operational amplifier. The OP-07 ultra-low offset voltage bipolar operational amplifier is well suited to this application. The pertinent specifications of the OP-07 are its input offset voltage drift of 0.3μV/°C, its input noise voltage of 0.4μV p-p (for a bandwidth of 30Hz) and its input noise current of 15pA over the same bandwidth. These specifications, when compared with the data in Table I, indicate that the noise produced by the OP-07 will be small compared with the photon statistical noise unless the input current falls below the 1nA range. In fact, no significant improvement in noise performance is possible, because the output noise level of the OP-07, when connected to the detector, is only 3db above the theoretical level expected from thermal noise in the 70KΩ resistance of the detector itself over the effective system bandwidth of 30Hz.

Figure 4 is a circuit diagram of the analog section of the planned input electronics. The input operational amplifier is used as a current-to-voltage converter. The input offset current used to cancel the leakage current of the detector is computer controlled by means of an eight-bit digital-to-analog converter (DAC). The effective feedback resistance of the first amplifier is increased by connecting a bridged-T network into the circuit by means of a reed relay, for a gain change of a factor of 4. A second relay connects a factor of 2 attenuator between the two operational amplifiers. The second amplifier has a gain of 2 or 32 depending upon the switching state of the third gain-adjusting relay. Three jumper connections can be used to change from positive to negative input current if a different type of detector is used. The output of the second amplifier goes to a 5MHz voltage-to-frequency converter which is used to integrate the detector current during the desired pixel exposure time. The output of the second amplifier is permanently biased at -1V for no input, so that the voltage-to-frequency converter always has a non-zero output frequency.

Table I.

Sensitivity and Resolution of Input Electronics

Full Scale Sensitivity (nA)	Resolution of Voltage/ Frequency Converter (pA/Count)	Photons in 0.5mm x 0.5mm Pixel in 5msec at Full-Scale Current	Equivalent Input Current for Statistical Counting Error (pA)
5000	200.0	1.4×10^7	1340
2500	100.0	7.0×10^6	940
1250	50.0	3.5×10^6	670
625	25.0	1.8×10^6	470
312	12.0	8.8×10^5	330
156	6.0	4.4×10^5	240
78	3.0	2.2×10^5	170
39	1.5	1.1×10^5	120

The combination of three independent gain adjustments gives eight overall gain values in binary steps from 1 to 128. Table I shows the full-scale current sensitivities of these eight gain settings. Also shown is the current resolution of the voltage-to-frequency converter for each gain setting, assuming a 5msec integration time and the photon statistical noise at full-scale for each setting. As can be seen, a considerably shorter integration time could be used before the resolution of the voltage-to-frequency converters would limit the accuracy of the image data.

The input electronics is housed in single-width NIM modules, with four channels in each module. Digital data for the DAC's and the gain-switching relays is transmitted from the CAMAC output register to the first module and from module to module over three daisy-chained lines (see Fig. 5). The serial-to-parallel conversion is performed by means of 16-bit latched shift registers. Two of these registers supply data to the four DAC's and the third supplies data to the 12 relays through high voltage power inverter chips. The clock signal is divided by 16 so that a new register is selected after 16 bits of data have been transmitted. After all three registers have been filled, the next module is selected and so on until all modules have data. The clear line must be raised high momentarily in order to prime the chain of modules for a data transfer. This scheme allows data to be transmitted over very few wires with relatively simple hardware and software. However, about 100msec may be needed to transfer data to 256 channels--a delay that is acceptable since adjustments in gain and offset should be required only occasionally.

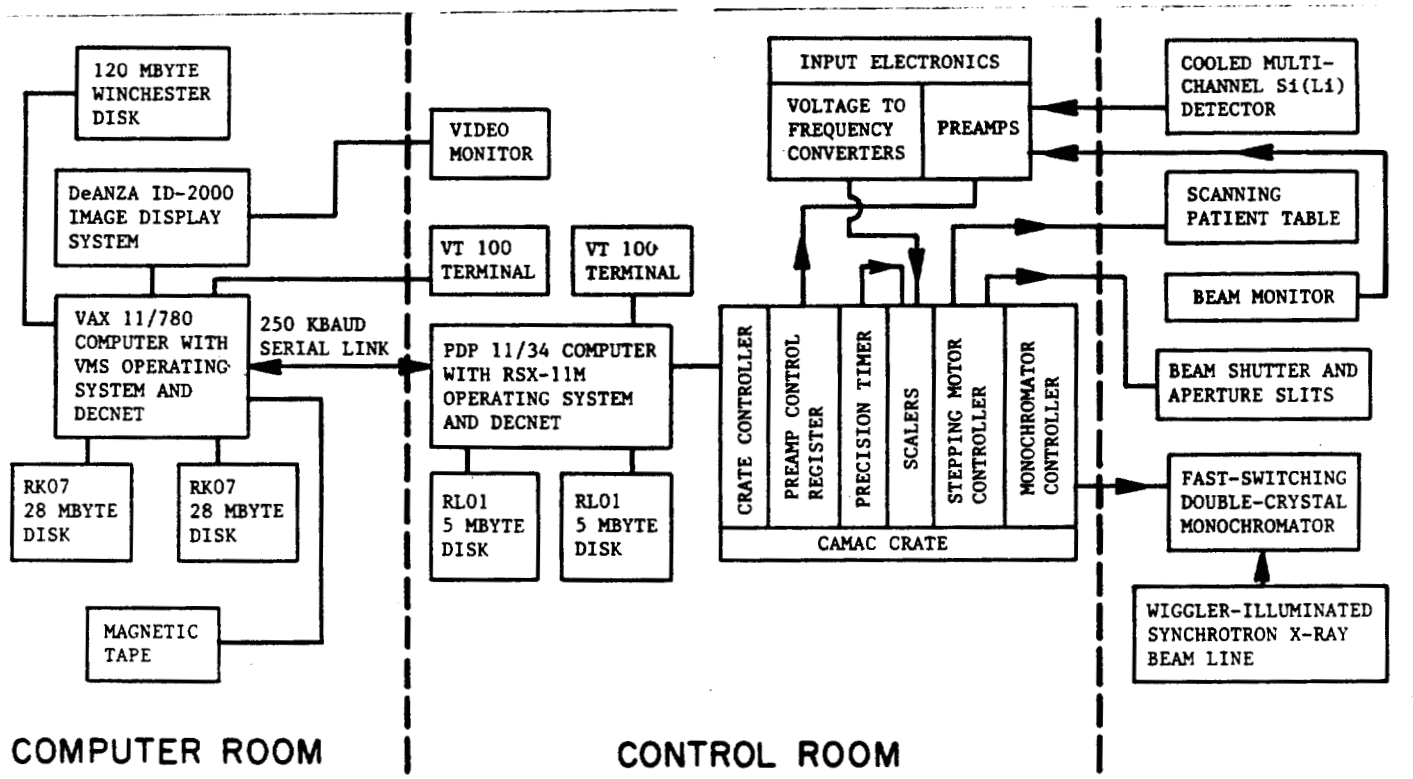

Fig. 3. System block diagram for K-edge digital subtraction angiography.

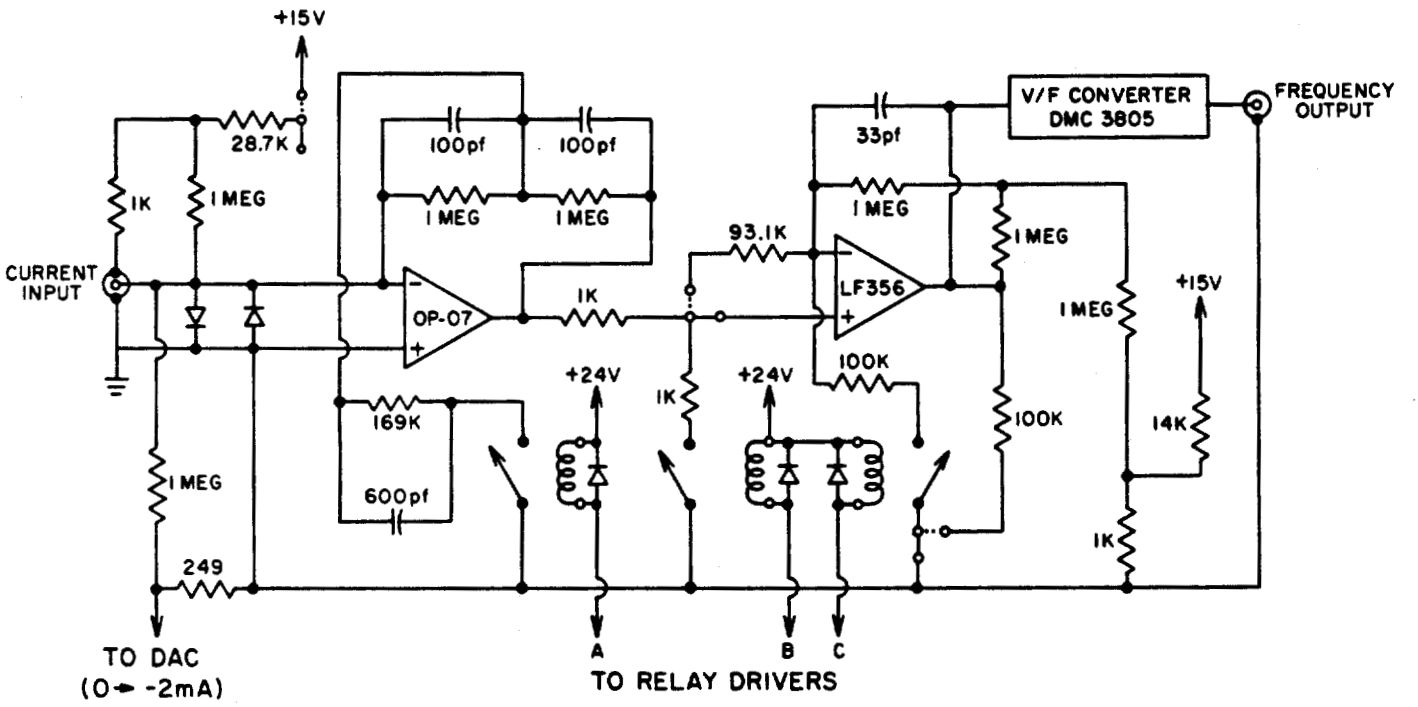

Fig. 4. Circuit diagram of the analog section of the input electronics.

The output of the voltage-to-frequency converters is counted in 32-channel, 24-bit CAMAC scalers. A precision timer gates the scalers on for 5msec, after which the data is latched into the scalers, read into the PDP11/34 computer memory, and then written onto the 5Mbyte disk. The monochromator energy setting will be switched between readings so that each line of the image is taken at two different energies within 15msec. This permits the logarithmic subtraction of the image lines to be performed without image artifacts due to vessel motion.

Initial Studies at the Stanford Synchrotron Radiation Laboratory

Initial line-scan K-edge images have been taken at SSRL with the prototype 30-channel Si(Li) detector.

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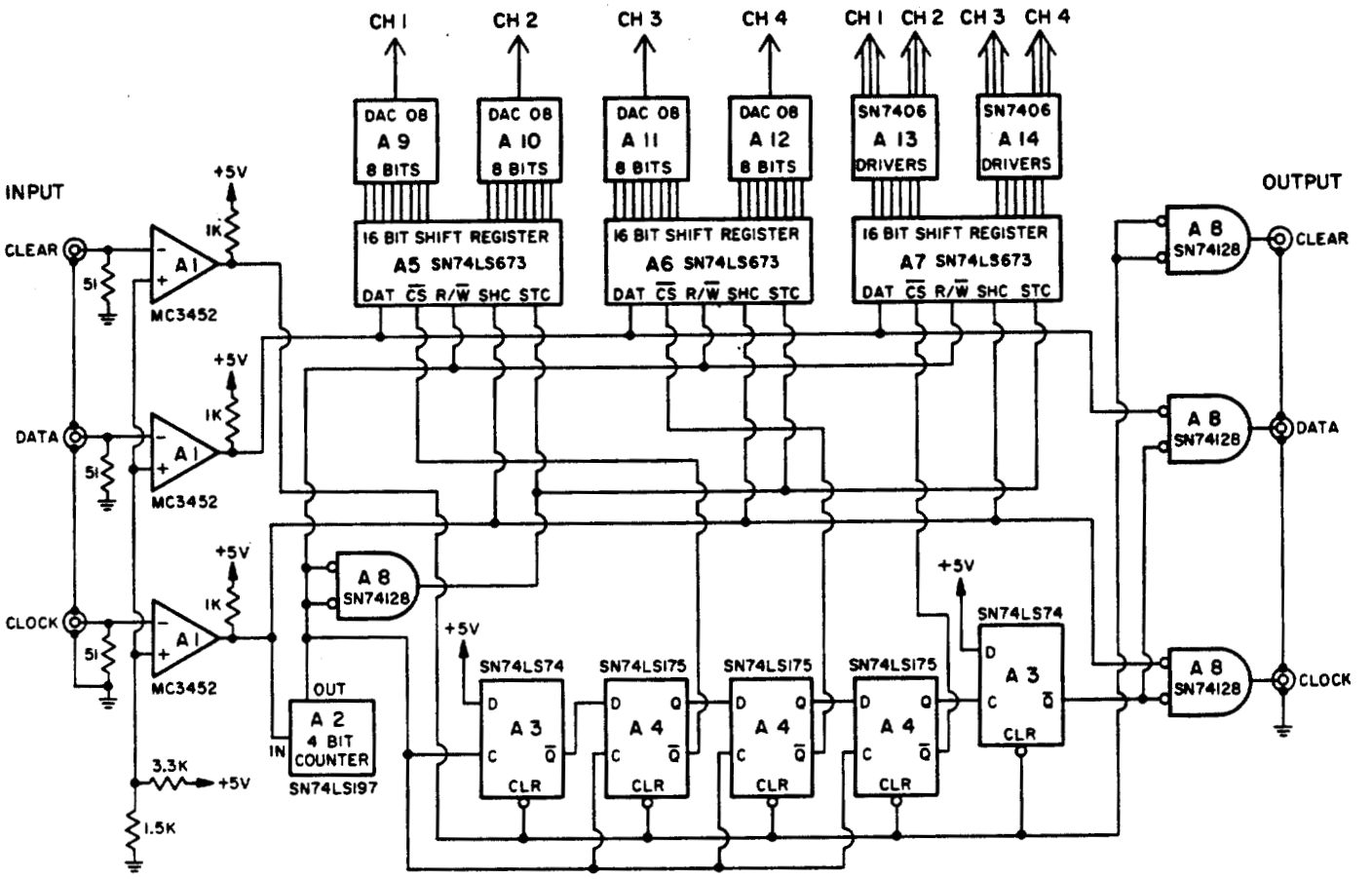

Fig. 5. Circuit diagram of the digital section of the input electronics.

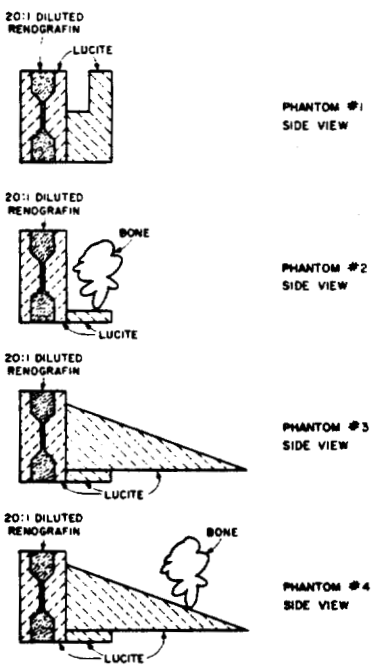

Fig. 6. Sketches showing the structures of the four phantoms used in the test images.

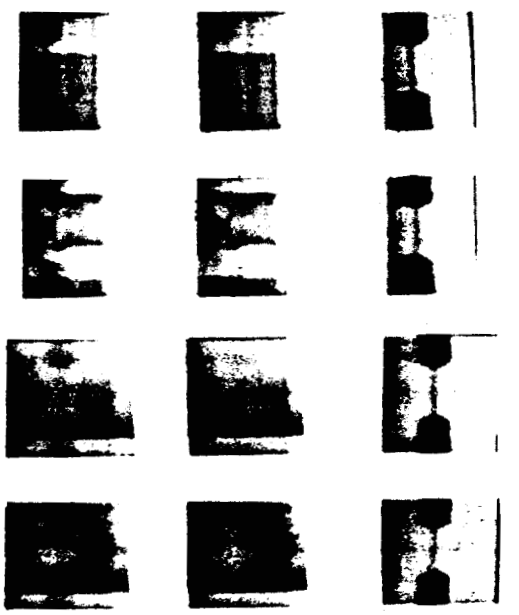

Fig. 7. Component and subtracted images of an iodinated channel in the set of four phantoms shown in Fig. 6.

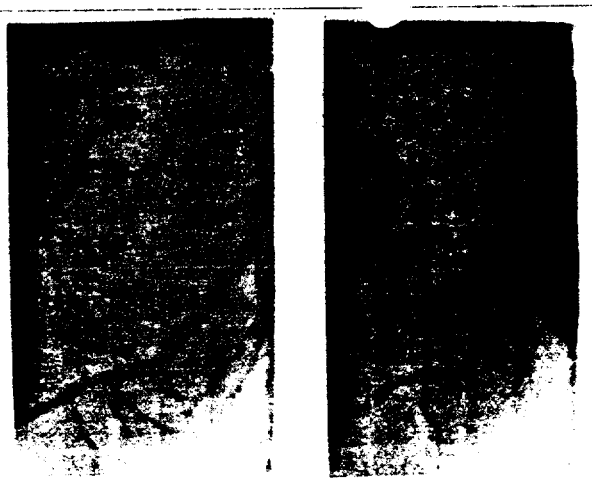

Fig. 8. Component images of calf heart coronary arteries taken wth 0.5mm x 0.5mm resolution. At the left is the image taken above the K-edge and at the right is the image taken below the K-edge.

Fig. 9. The logarithmically subtracted image corresponding to Fig. 8 for resolutions of 0.5mm x 0.5mm (at the right) and 1mm x 1mm (at the left).

An earlier, manually adjusted version of the input electronics shown in Figs. 4 and 5 was used. The detector was not cooled for these tests, and at low detector output current, the drift of the detector leakage current with temperature required frequent recalibration of the input electronics. Cooling to -20°C in future work is expected to eliminate this problem.

To remove the effects of drift from the first images, a strip of lead was placed at the top and bottom of each image field. Thus, for each vertical line and each detector channel, a measurement was made of the pedestal frequency at both top and bottom of the field. A straight line interpolation through these end points could be subtracted from the frequencies measured at intermediate points on this image column to yield corrected values.

Figure 6 is a drawing of four phantom objects constructed to demonstrate the ability of K-edge imaging to suppress structures not containing iodine. The central channel in each phantom contains iodine at a thickness (2.5mg cm^{-2}) typical of that expected in intravenous arteriography. The lucite wedge is 12cm thick, and simulates a large variation of tissue thickness. The bone is a human vertebral bone. Figure 7 is a photograph of digital images taken of these phantoms with the 1mm resolution of the prototype detector. In the first and second columns respectively are images taken above and below the iodine K-edge. The third column contains the logarithmic difference images. Only contrast due to iodine remains in the difference images.

Figure 8 is a photograph of images taken at 0.5mm x 0.5mm resolution above and below the K-edge of iodine of an excised calf heart. The coronary arteries were filled with a mixture of NaI powder and a silicon-based dental impression paste. This resolution was achieved by placing a mask with 0.5mm wide slits in front of the detector, by closing down the vertical slit to 0.5mm, and by taking two interlaced images separated 0.5mm from each other. Figure 9 shows the logarithmic difference image at 0.5mm x 0.5mm resolution on the right, and a separate image taken at 1mm x 1mm resolution without the mask on the left. The lower resolution image is marginally adequate, while the higher resolution image is quite acceptable for diagnostic work. Owing to inhomogeneities in the preparation of the NaI-silicon paste mixture, this picture accidentally afforded opportunities to see details in the imaged arteries. For example, the large lightened area in the artery in the middle of the picture was confirmed, upon dissection, to be an air bubble. Other smaller air bubbles are also visible.

Conclusion

The intensity, monochromaticity and tunability of synchrotron x-ray beams potentially overcomes the principal difficulties associated with digital subtraction angiography using conventional x-ray generators. In particular, it may be possible to perform coronary arteriography non-invasively. An x-ray detector technique and the associated electronic instrumentation have been developed. A data acquisition, control and analysis system has been designed to acquire images at high speed and to provide powerful image processing capabilities.

Acknowledgements

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A MULTI-ELEMENT SILICON DETECTOR FOR X-RAY FLUX MEASUREMENTS

LBL-12746

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Abstract

A 30-element Si(Li) detector has been fabricated to measure the one-dimensional flux profile of 33 KeV x-rays from a synchrotron radiation beam. The device, which is fabricated from a single 39mm x 15mm silicon wafer, is a linear array of 0.9mm x 7mm elements with a 1mm center-to-center spacing. It is 5mm thick and when operated at room temperature has an average leakage current of 10 nA/element. The x-ray flux in each element is determined by measuring the current with a high quality operational amplifier followed by a current digitizer.

This detector is being used to study the use of synchrotron radiation for non-invasive imaging of coronary arteries. The experiment uses the difference in the transmitted flux of a monochromatized x-ray beam above and below the iodine K-edge. Measurements have been made on plastic phantoms and on excised animal hearts with iodinated arteries. The images obtained indicate that a 256-element device with similar properties, but with 0.6mm element spacing, will make a very effective detector for high-speed medical imaging.

Introduction

Synchrotron radiation x-ray sources provide intense, tunable beams which make possible many exciting areas of research which are not possible with conventional x-ray sources. These x-ray beams place very demanding requirements on detector systems since they are very intense, highly collimated and have a pulsed time structure.

We have developed a 30-element Si(Li) detector for high-speed flux measurements with good spatial resolution and high efficiency. This detector is a prototype for a larger detector which will be used for digital subtraction angiography using synchrotron radiation.

Angiography, the radiologic visualization of blood vessels and the chambers of the heart containing contrast media, has become a powerful method of examining the internal condition of the cardiovascular system and of diagnosing disorders involving the circulation of the heart, the brain, and of other vascular beds. However, the techniques currently in widespread use involve invasive procedures that carry significant risks of morbidity and mortality. For example, the diagnostic procedure for coronary artery disease requires the insertion of a catheter into the ostia of each of these arteries in turn and the injection of concentrated solutions of iodine-containing compounds. The risks of this procedure are far too high to permit the routine use of angiography to detect the presence of dangerous obstructing lesions in the coronary arteries in the many persons known to be at risk. Angiographic studies are limited to symptomatic patients and are not conducted on asymptomatic patients even if they are at high risk because of hypercholesterolemia, hypertension, family history, etc. There is, therefore, an urgent need to reduce both the risk and cost of these procedures.

Conventional x-ray sources provide a broad spectrum of x-ray energies. However, iodine preferentially absorbs at energies in the immediate vicinity of its K-absorption edge at 33.16KeV. In addition, other body structures, such as soft tissue and bone are reproduced in the image and subtract from the contrast due to the iodine itself. If the x-rays from a conventional source are filtered to select the energies specific to iodine and thereby enhance the iodine contrast, there is insufficient intensity in the beam to produce a useful image. This is the reason, in essence, for the dangerous invasive procedure now in use.

The enormous intensity and inherent collimation of synchrotron radiation permit it to be energy monochromatized by Bragg diffraction to produce a fan beam of excellent energy resolution ($\Delta E/E \approx 10^{-4}$), high intensity and good collimation. Since the energy of the x-rays can be varied precisely and easily by a small rotation of a crystal monochromator, radiographs may be conveniently acquired at adjacent iodine-specific and iodine-nonspecific energies and then logarithmically subtracted. This subtraction substantially eliminates all the image contrast due to other body structures and thereby achieves maximum contrast in the visualization of the intra-arterial iodine. The method is referred to as dichromography.[1] Digital radiographs are acquired at x-ray energies slightly above and slightly below that of the K-edge in iodine at 33.16KeV. The iodine absorption cross section increases abruptly by a factor of six at this edge while the cross section of other elements remains relatively unchanged. The subsequent subtraction of these two images gives exquisite sensitivity to iodine alone. If this sensitivity is realized, it offers the prospect of arteriography and in particular, coronary arteriography by peripheral venous injection and therefore reduced concentration of iodinated compounds in the arteries. This would eliminate the need for catheterization and substantially reduce both the risk and the cost of the procedure.

Figure 1 shows how synchrotron radiation might be used with a multi-element Si(Li) detector to produce high resolution images of human arteries.

It is envisaged that in the final system the heart will be scanned using an x-ray beam which is 150mm wide and 0.6mm high. A line-scan procedure will be

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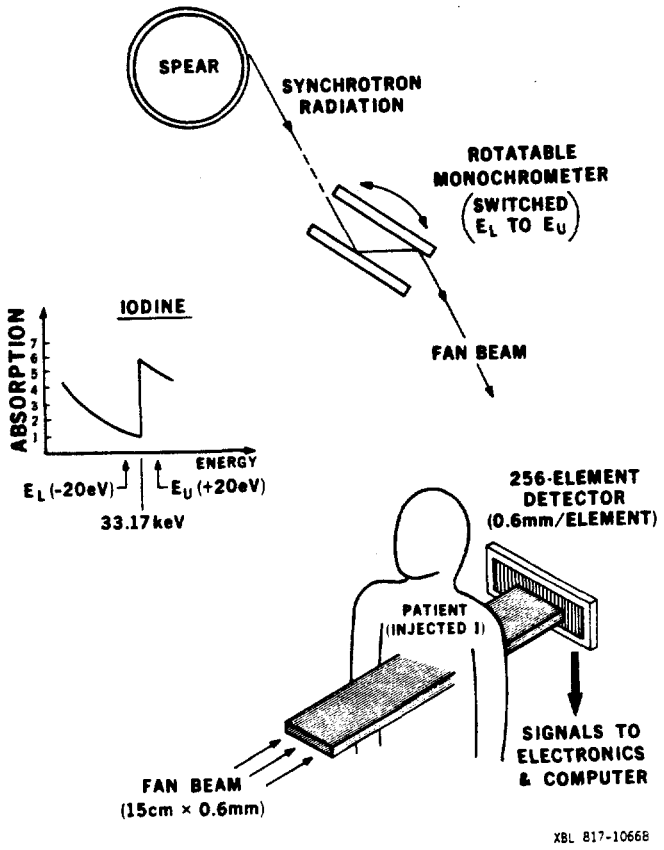

Fig. 1. Schematic layout of system for performing digital angiography using synchrotron radiation.

used in which the transmitted flux in each 0.6mm of the beam will be individually measured using a 256-element Si(Li) detector which will have an active volume 150mm long, 4mm high and 5mm thick and an element spacing of 0.6mm.

The imaging procedure will begin with the venous injection of about 40ml of Renografin 76*, an iodine containing compound commonly used in medical imaging. After about 12 seconds when the Renografin* has reached the coronary arteries the scan will start. The measurement interval will be 5ms following which the monochromator will be rotated 0.001° to the other energy for the second measurement. After each pair of measurements, the patient will be translated vertically by 0.6mm and the next pair of measurements performed. Since the iodine is rapidly dispersed throughout the body, the complete measurement must be accomplished within several seconds. We estimate that a complete scan of a 150mm x 150mm area can be completed within four seconds. The patient will receive a radiation dose of around 300mrad during the scan.

A silicon detector was chosen as the flux detector for this experiment for several reasons. A 5mm thick silicon detector has an efficiency of 70% at 33KeV and can be fabricated as a position-sensitive detector by replacing one of the contacts with a linear array of contacts connected to separate electronic readout channels. In a silicon solid-state detector, a photoelectric event produces one electron-hole pair for each 3.6eV of incident energy. A 33KeV photon therefore creates approximately 9,000 electron-hole pairs or a free charge 1.5×10^{-15}C. At this photon energy a flux of $10^7 sec^{-1}$ produces a current of 15nA. By measuring the current in each element the flux profile can be conveniently determined. Also inherent in the operation of such semiconductor detectors is the excellent linearity, stability and large dynamic range of the x-ray response. These properties are very useful in angiography where the flux per pixel can vary greatly because of tissue and bone variations but the flux difference must be measured to better than 0.5% if arteries are to be seen clearly. The charge transit time for a 5mm device is less than 1μsec so the response time is fast compared to the measurement time of several msec. This is important in angiography where the image must be acquired rapidly to reduce the effects of organ movement. An additional benefit of having all elements fabricated from the same silicon wafer is that the device gain of all elements is constant so the system can be calibrated accurately and conveniently.

Before embarking on the development of this large detector, we have been using the prototype detector in one of the wiggler x-ray beam lines at the Stanford Synchrotron Radiation Laboratory (SSRL) to study the feasibility of this concept.

Detector Characteristics and Fabrication

The prototype detector consists of a linear array of 30-elements which are 0.9mm x 7mm and have a center-to-center spacing of 1 mm. The geometry of the device and the electronics associated with each channel is shown in Fig. 2.

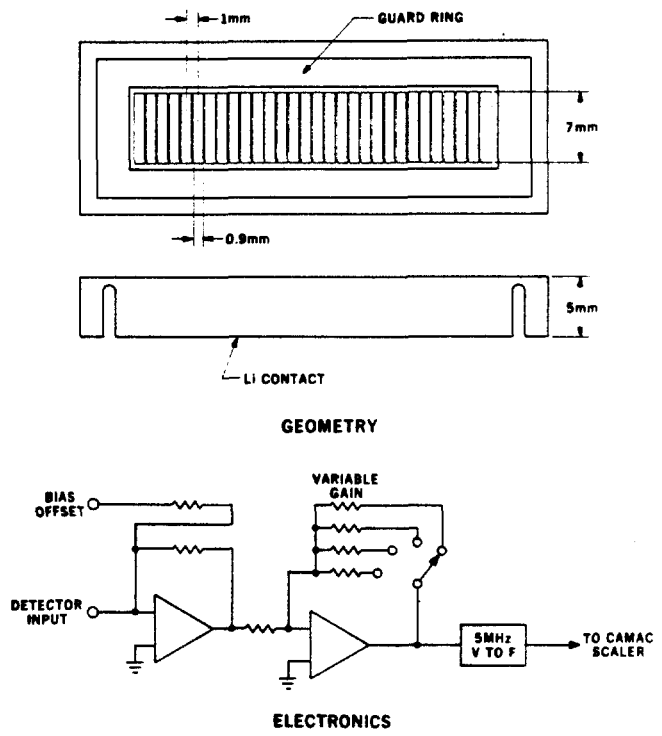

Fig. 2. Geometry of 30-element Si(Li) detector and the elecronics associated with each element.

The device was first fabricated as a 15mm x 39mm, 5mm thick Si(Li) grooved detector using standard procedures.[2] The rear contact of the detector is a common Li-diffused contact with a 4mm deep groove around the active area. Once the device had been tested as a single detector, the continuous gold

contact was removed and the strip geometry of 0.9mm x 7mm pads with 1mm center-to-center spacing surrounded by a guard ring[3] was made by evaporating gold through a metal mask. The thickness of the gold contact is about 0.03μm and that of the Li contact is about 125μm. The purpose of the guard ring is to absorb the surface leakage current and to provide a good electric field profile in the pad region. With this geometry, the total device leakage current at room temperature is 6.2μA at an operating voltage of 600 volts. The expected leakage current, I_D, of each element at room temperature due to thermal generation is given approximately by:[4]

$$I_D = q\, n_i\, V / 2\tau_p$$

where q is 1.6×10^{-19} coulombs; n_i, the intrinsic carrier concentration, is 1.6×10^{10} carriers/cm^3; V, the depletion volume, is 0.035cm^{-3}; and τ_p, the minority carrier lifetime, is 2×10^{-3}sec. Since the calculated element leakage current is 22nA and the average leakage current is 10nA, the leakage current is primarily thermally generated and not surface leakage. The thermally generated current can be expected to decrease by about a factor of two for every 10°C decrease of the device temperature. We are currently fabricating a thermoelectrically cooled cryostat for the device which will cool the detector to -20°C and should reduce the leakage current to less than 1nA/element.

The resistance in parallel from each element to its neighboring elements and the guard ring was found to be 70K ± 15K ohms. This resistance was determined by measuring the leakage current of one element at the operating voltage as a function of a small differential voltage applied to the surrounding elements and the guard ring.

Electrical contact is made to each element using an array of Be-Cu spring contacts mounted on a circuit card. Figure 3 shows the detector mounted on the circuit card. The signals are carried from the detector to the electronic readout modules outside the x-ray beam enclosure using two 20-conductor ribbon coaxial cables with mass-terminated connectors.

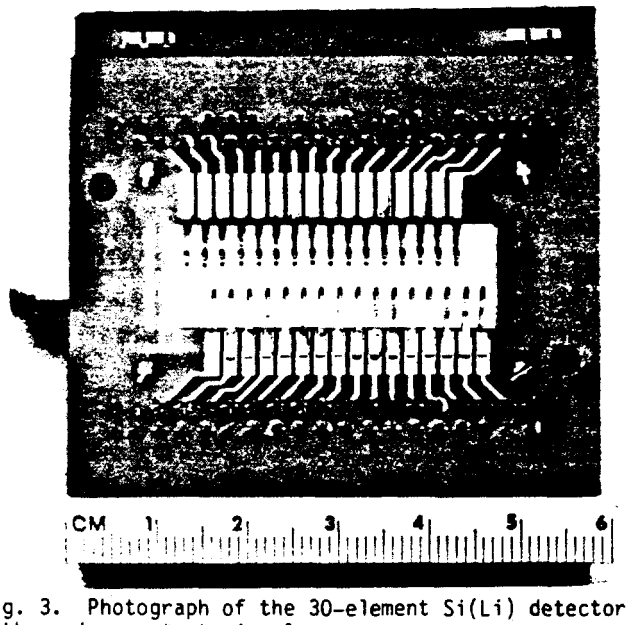

Fig. 3. Photograph of the 30-element Si(Li) detector with spring contacts in place.

The fabrication of the larger detector will be a challenging project. We currently plan to fabricate it from a single piece of silicon 170mm long, 12mm wide and 5mm thick. The device will have a similar groove and guard-ring structure as the initial detector. The element width, however, will be 0.5mm with a center-to-center spacing of 0.6mm. A photographic mask will be used to reduce the pad area and therefore minimize the leakage current and increase the inter-element resistance. Wire bonding to the detector elements may be used instead of spring contacts to improve the reliability of the 256 contacts.

Detector Electronics

The readout for this system requires the accurate measurement of the current flowing in each element. At SSRL a flux of 10^9 per second per mm^2 is available on the wiggler beam lines when the storage ring is operating in a dedicated mode at 3GeV and 60mA. Assuming that only 0.5% of the incident flux is transmitted through the patient, one estimates a photon flux of approximately 5×10^6sec^{-1} in each mm^2 and therefore a generated current of 7.5nA in each element of the prototype detector.

Since the detector inter-element resistance is relatively low (~70K ohms), it is important to use a high quality operational amplifier (OP-07) in the first stage of the electronics to keep the electronic noise and drift small. Provision is made in the electronics to change the gain and to bias off the detector leakage current from the data acquisition computer. A 5MHz voltage-to-frequency (V/f) converter is used to produce a digital output which is proportional to the input current. This digital output has excellent linearity, high resolution and a large dynamic range which complement the properties of the Si(Li) detector very well. Gating the V/f convertors with a common timing pulse of the desired period provides a measurement of the total flux in each element during the gating interval. The accuracy which can be achieved with this system with different fluxes has been presented elsewhere.[5] A typical clinical iodine concentration obtained with venous injection produces a flux difference of more than 2% and we estimate that an accuracy of better than 0.5% can be achieved in 5msec with the available flux from the the Stanford Synchrotron Radiation Laboratory (SSRL) wiggler beam line when SSRL is operating at 3GeV and 100mA.

The digital outputs from the individual elements are connected to separate CAMAC scalers which are gated with a common programmable CAMAC timer. The control of the sample position is done with stepping motors through the same CAMAC crate. The overall data acquisition and analysis system has been described elsewhere.[5]

Results

Initial studies with the prototype detector of the feasibility of synchrotron radiation for digital subtraction angiography were performed at SSRL in the spring of 1981. Detailed reports of the samples studied and the of images obtained in this experiment have been given elsewhere.[5,6,7] Very good initial images were obtained which indicate that this is a very promising technique. Only a summary of these results as they relate to the characteristics of the multi-element detector will be given here.

Cross-talk between detector elements can degrade the spatial resolution of the image. This cross-talk was measured by using a 0.5mm slit which was moved across the device in 0.05mm steps and then measuring the current in pairs of adjacent pads. As can be seen in Fig. 4, it is very low between elements which indicates that both the charge collection in the detector is well defined to the nearest pad and that the electronic feedthrough has been successfully minimized.

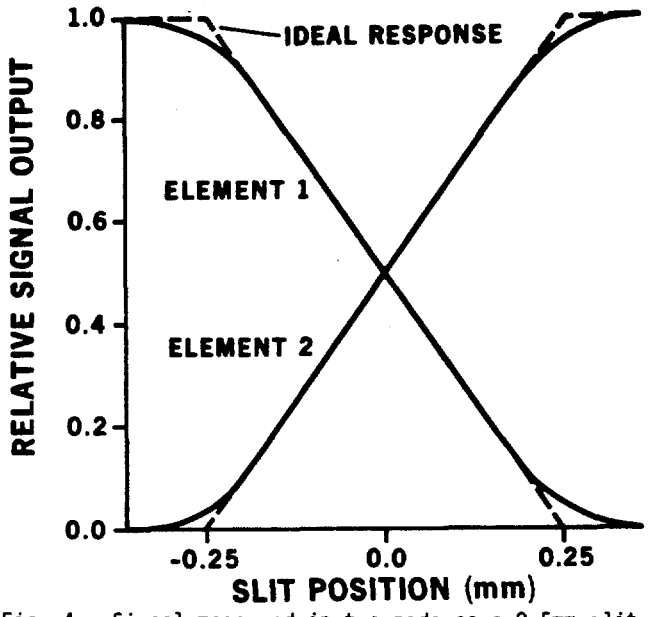

Fig. 4. Signal measured in two pads as a 0.5mm slit was scanned across the pads.

Images of both phantoms and excised animal hearts were obtained with this prototype detector. Due to limited availability at that stage of electronics, only eight adjacent channels of the detector were used to scan the heart in five adjacent vertical swaths each 48mm in height. A line-scan measurement (eight channels wide) was made, first 50eV above and then 50eV below the iodine K-edge before the object was moved vertically to the next raster position. An object area 48mm x 48mm was scanned, with 1mm x 1mm pixel size. The pedestals and gains of each electronic channel were monitored respectively by including 3mm lead absorbing strips at the top and bottom of each image and an unobstructed horizontal strip immediately above the lower lead strip. The total incident x-ray flux was monitored throughout by an upstream ionization chamber whose output was digitized and recorded with the Si(Li) detector data. This data was used to normalize each pixel to constant incident flux.

One of the set of phantom images, taken to demonstrate the strong, simultaneous suppression of contrast due to soft tissue and bone made possible with monoenergetic x-rays, is displayed in Fig. 5.

The figure shows that the energy resolution and dynamic range of the system are sufficient to eliminate the effects of bone and a variable amount of tissue in the difference image.

Figure 6 shows the arterial system of an excised calf heart obtained with two pixel sizes. Iodine was retained in the heart arteries by injecting into them a dental impression paste (CutterSil*) in which an appropriate concentration of NaI powder had been mixed. The heart was imaged for detector pixel sizes of both $1mm^2$ and $0.5mm^2$ to help select the width of the detector elements in the final detector. A pixel size of 0.5cm was achieved by placing a mask, with 0.5mm apertures spaced by 1mm and centered on the 0.9mm wide contacts, in front of the present detector and by acquiring two interlaced component images for each scan. The beam was also collimated to a matching 0.5mm height and the vertical motion after each line-scan was 0.5mm. Figure 6(a) and 6(b) show the difference images for $1mm^2$ and $0.5mm^2$ pixel size respectively. It is apparent that 1mm is marginally acceptable for clinical evaluation and that a resolution close to $0.5mm^2$ is preferable for clinical work. An element center-to-center spacing of 0.6mm has therefore been selected for the larger detector. With this spacing, a 15cm wide image can be obtained with 256 elements. This detector will give excellent image quality with a reasonable number of electronic readout channels.

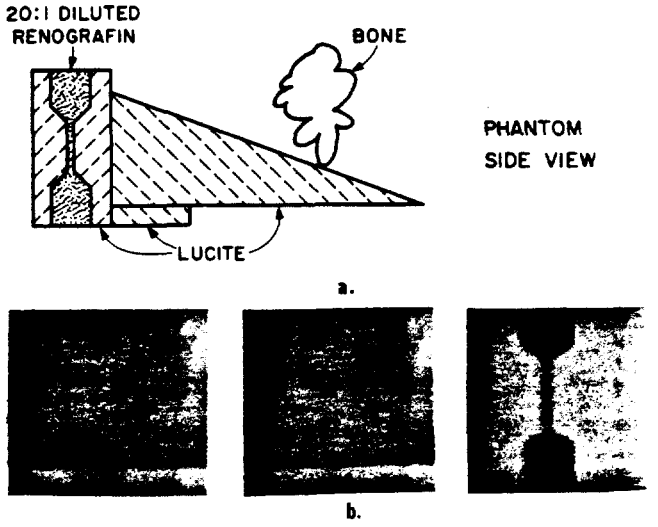

Fig. 5. Phantom image obtained with prototype system. 5(a) indicates the structure of the phantom. The row of images in 5(b) are, respectively, those obtained for the phantom above the K-edge, below the K-edge, and from their logarithmic subtraction. The iodine concentration was $2.5mg/cm^2$ in the 1.5mm diameter constricted lucite channel. The lucite wedge simulates a large tissue thickness variation and the bone is a human vertebral bone.

The images in Figure 6 inadvertently reveal arterial structure that is not really present. Towards the end of the circumflex artery (the major horizontal vessel), there appears a region about 1cm in length with lower than expected iodine concentration. Dissection of this region revealed an air bubble in the CutterSil*-NaI paste. Other smaller bubbles are evident in the left main descending artery. These air bubbles are easily preventable, but their occurrence accidentally in these images was useful from the standpoint of confirming that disease-like arterial structure could be seen with this system.

Summary

Multi-element Si(Li) detectors provide a method of making high precision x-ray flux measurements with good spatial resolution. These devices have excellent stablility, efficiency, linearity and dynamic range. Techniques are available to fabricate them with large areas and complex contact geometries. They are therefore very promising detectors for many experiments using the intense x-ray fluxes which are available at synchrotron radiation facilities.

The electronic readout of the current in each element using a high quality preamplifier and voltage-to-

frequency converter can provide an accurate flux measurement for many elements at reasonable cost.

Development of a 15cm wide wiggler x-ray beam line at a synchrotron radiation facility in combination with a 256-element Si(Li) detector may make possible the high-speed imaging of human arteries (especially the coronary arteries) non-invasively. With such a powerful instrument it may be possible to reduce the mortality of the present invasive procedure and to provide a diagnostic tool for the study and prevention of arterial disease.

Acknowledgements

The Hughes-Hofstader group at Stanford U. originated the project for non-invasive angiography using synchrotron radiation and proposed the use of a Si detector. The images were taken at SSRL with the assistance or advice of L.E. Campbell, R. Hofstader, R.L. Kirk, T.J. Krolicki, J.P. Stone and S. Wilson of the Hansen Laboratories at Stanford University and of E. Rubenstein, W.R. Brody and A. Macovski of the Stanford University School of Medicine.

This work was supported in part by the William Randolph Hearst Foundation, the Henry J. Kaiser Family Foundation, the U.S. Department of Energy under contract no. W-7405-ENG-48 and the N.S.F. (under contract DMR 77-27489 for the operation of SSRL).

*Reference to a company or product name does not imply approval or recommendation of the product by the University of California or D.O.E. to the exclusion of others that may be suitable.

References

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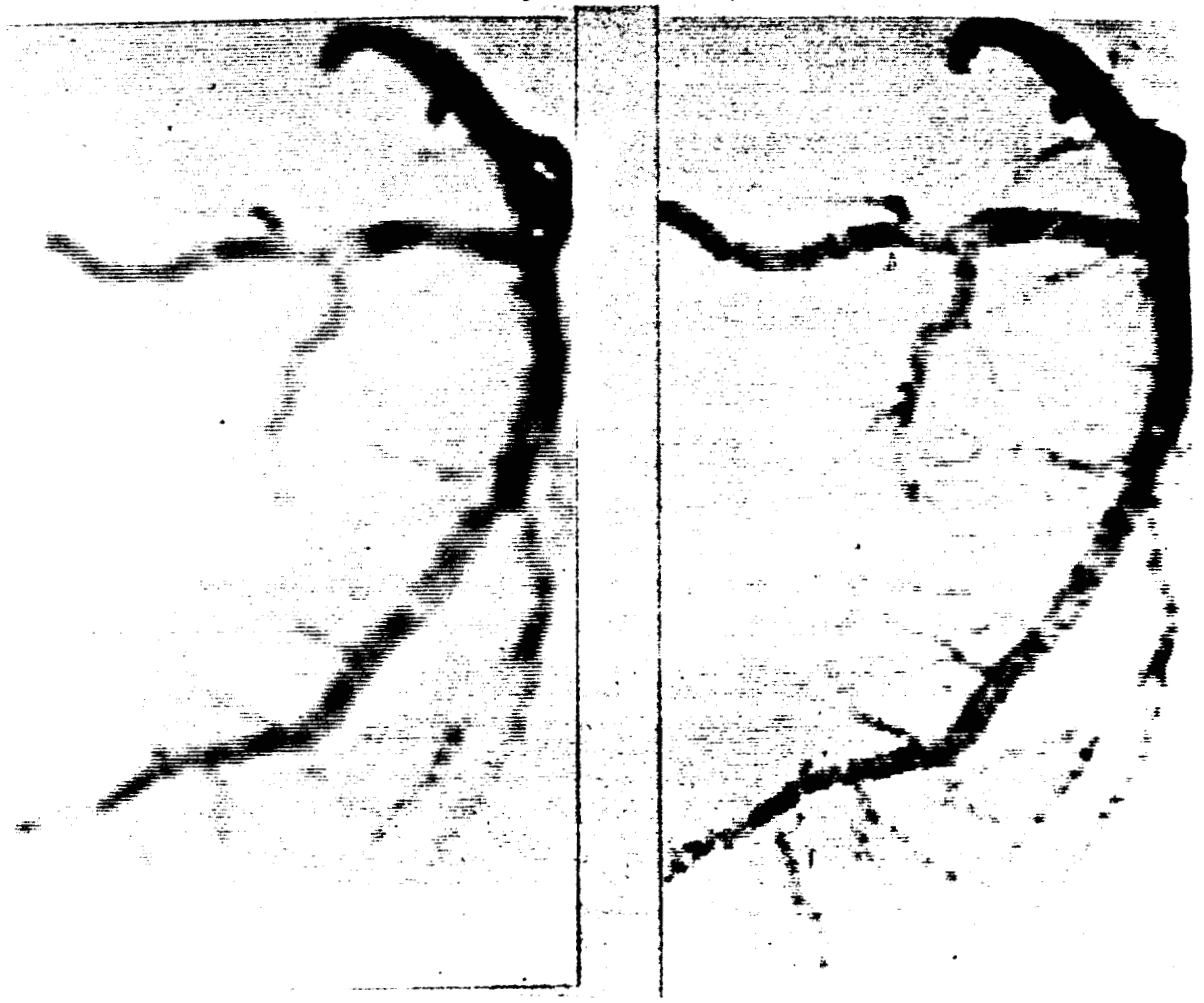
7. Thompson A C, Proceedings of the Second National Conference on Synchrotron Radiation Instrumentation, July 15-17, 1981, Cornell University to be published in Nucl. Instr. and Meth.



a. b.

Fig. 6. Difference calf heart images taken with (a) 1mm^2 pixel size, and (b) 0.5mm^2 pixel size.

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NON-INVASIVE ANGIOGRAPHY USING SYNCHROTRON RADIATION

E.B. Hughes, L.E. Campbell, R. Hofstadter, R.L. Kirk, T.J. Krolicki, J.P. Stone, H.D. Zeman
Hansen Laboratories of Physics and Department of Physics, Stanford University

E. Rubenstein, Department of Medicine, Stanford University

W.R. Brody and A. Macovski, Department of Radiology, Stanford University

A.C. Thompson, Lawrence Berkeley Laboratory

Angiography, the radiologic visualization of blood vessels and heart chambers containing contrast media, has become a powerful method of examining the structure of the heart and the coronary arteries and of diagnosing disorders involving the circulation of the heart, of the brain, and of other vascular beds. However, the techniques currently in widespread clinical use involve invasive procedures which carry significant risks of morbidity and mortality. These risks are far too high to permit the routine use of angiography to detect the presence of dangerous obstructing lesions in, for example, the coronary arteries of the many persons known to be at risk. Angiographic studies are limited therefore to symptomatic patients and are not conducted on asymptomatic patients even if they are at high risk because of hypercholesterolemia, hypertension, family history, etc. There is an urgent need to reduce the risk of these procedures.

The eventual purpose of the studies begun by proposal 456B is to bring into existence at Stanford a facility capable of conducting safe and non-invasive angiographic examinations on patients. Angiographic examinations of the coronary arteries will be emphasized. The acquisition of digital radiographs at X-ray energies slightly above and below the K absorption edge in iodine at 33.2 KeV and the subsequent differencing of these two images provides an exquisite sensitivity to intra-arterial iodine. This procedure promises the prospect of coronary arteriography with reduced concentration of iodinated compounds in the coronary arteries administered non-invasively by peripheral venous injection. This will eliminate the need for catheterization and substantially reduce the risk of the procedure.

Proposal 456B was submitted to SSRL in June 1979 and received its final rating in June 1980. This proposal called for the performance of certain basic tests on inanimate phantoms with minimum delay and with simple equipment already in hand. At the time this first proposal was submitted, solutions had been identified to some of the technical problems related to the realization of a diagnostic facility at Stanford, but not to all of them. Since that time studies of the outstanding questions continued, often in consultation with the SSRL staff, and practical solutions to all of the major problems have now been identified. These include the realization of a one-dimensional position-sensitive X-ray detector of satisfactory width and close to 100% efficiency, and the definition of a technique by means of which the motion of the heart muscle cannot degrade the image quality. For example, figure 1 shows a prototype silicon semiconductor detector fabricated to our specifications at the Lawrence Berkeley Laboratory. This detector is essentially one-dimensional (30 mm in width and 5 mm in height), its detection efficiency for 33 KeV X rays is close to 70%, it incorporates 30 independent contiguous sensitive regions each 0.9 mm in width with a center-to-center spacing of 1.0 mm, and it operates at room temperature.

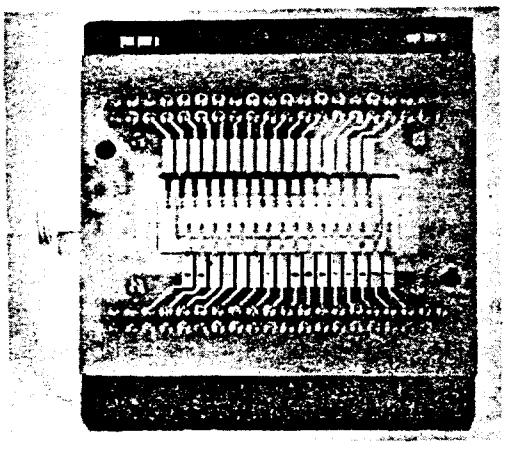

Figure 1. A prototype position-sensitive Si detector.

In the time made available to proposal 456B in this reporting period (through 4/14/81) the basic tests on inanimate phantoms with simple detection apparatus have progressed considerably. A start has also been made in the use of the prototype silicon detector for more efficient imaging, and in the preparation and use of animal hearts for more realistic imaging of the vessels and structures of eventual interest. Initial short opportunities to start work at SSRL occurred in the I-5 beam on 11/26/80 and on 12/5/80. Given the extremely low X-ray flux at 33.2 KeV and 2 GeV in the parasitic mode in a non-wiggler line, the first of these occasions was used to test the apparatus in the region of the K-edge in copper at 8.9 KeV. Clear difference signals were observed with the expected magnitudes for copper concentrations of 0.45, 0.9 and 1.8 mg cm^{-2} in inanimate phantoms. On the second occasion, at 3 GeV in the dedicated mode, the X-ray flux at 33.2 KeV as 400 times more intense and a useable beam at 33.2 KeV was obtained from the (440) plane in Si (~0.8 photons/pulse/mm^2). The contamination of 16.6 KeV X rays, from the (220) plane in Si, was reduced to about 50% with a 0.125 inch aluminum filter. Clear difference signals were observed with this beam for an iodine phantom concentration of 16 mg cm^{-2}.

The first access to beam line IV-2 for more than 24 hours occurred in the period 3/6/81 to 3/20/81 at 1.8 GeV in the parasitic mode. Despite the low flux at

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33.2 KeV, ~1 photon/pulse/mm^2 from the (220) plane of Si, good two-dimensional images of inanimate phantoms were obtained. One of these is reproduced in figure 2. The vertical iodinated channel, in a lucite block, is 1 cm in diameter at both ends and 1.5 mm in diameter in the central constricted region. The iodine concentration in the latter region is 5.5 mg cm^{-2}. Also in the field-of-view was a vertical wedge of lucite with an empty horizontal channel, also with a constriction. The images in figure 2 at the top left and right are of this composite phantom at X-ray energies just below and just above the iodine K-edge respectively. The lower images in figure 2 are, on the left, the difference between the two upper images, and on the right, the ratio of the two upper images. In both of the lower images, as expected, only the iodine content of the phantom is reproduced and image contrast due to the other structures is eliminated. These and other data obtained at this time were acquired by collimating the X-ray beam to a cross sectional size of 1 mm x 1 mm and scanning the phantoms, in raster fashion, in front of a single X-ray detector consisting of a CaF_2(Eu) scintillator and a 0.75" diameter EMI 9826A photomultiplier tube. Preliminary attempts were also made to image iodinated arteries in animal hearts (pig and calf) but this proved to be impractical since the time needed to acquire an image (several hours due to the low X-ray flux and the single X-ray detector) exceeded the durability of the iodine in the arteries for the heart preparation technique then used.

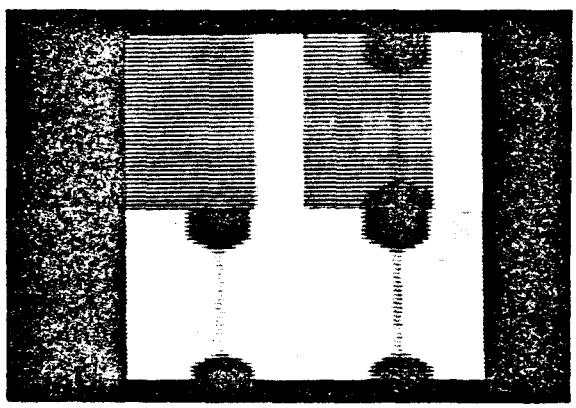

Figure 2 Raw and processed images of an iodinated channel in a complex phantom

The first, and to this date, the only access to beam line IV-2 under operating conditions approximating those requested in the proposal took place in the period 4/8/81 to 4/14/81. At this time, in parasitic mode*, the operating conditions were 2.5-3.0 GeV and about 25 mA, which correspond to a 33.2 KeV flux of ~320 photons/pulse/mm^2. For these tests the increased flux and the use of the prototype position-sensitive silicon X-ray detector (actually only 8 of the 80 1 mm wide channels were used due to limited availability, at that time, of electronics) combined to permit the acquisition of images with substantially reduced observing times (several minutes). Excellent images of a variety of iodinated inanimate phantoms were obtained and, in addition, due to a substantial improvement in heart preparation technique, a variety of animal heart images with iodinated coronary arteries were also obtained. The key to retention of iodine in the animal vessels was the use of a dental impression paste (CutterSil tm), in which the appropriate concentration of NaI powder was thoroughly mixed, and to which a curing compound was added immediately before insertion into the arterial system with a catheter and syringe. A typical set of images of calf heart coronary arteries is shown in figure 3. At the top are the separate images obtained above and below the iodine K-edge and at the bottom is their ratio. In the latter image all contrast due to non-iodinated heart structures is eliminated.

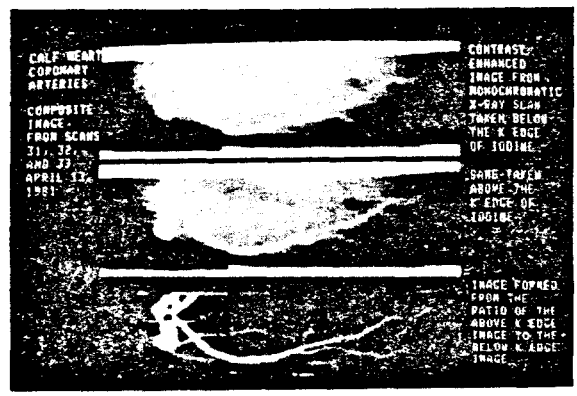

Figure 3 Raw and processed images of calf heart coronary arteries.

In future tests phantom images for the full range of parameters outlined in proposal 456B will be obtained. Also, following instrumentation of all 30 channels of the Si detector, animal heart images will be obtained for a wider range of iodine concentrations. Most importantly, animal hearts will be prepared with iodine concentrations typical of venous administration in the left ventricle as well as in the coronary arteries, and images will be obtained with some of the coronary arterial system projected against the filled ventricle. In this way the isolation of the coronary artery from the ventricular background by image analysis can be explored and developed. Also in preparation are realistic phantoms of animal hearts prepared from impressions taken from real hearts. These phantoms will permit arbitrary and adjustable iodine concentrations to be placed in coronary arteries and ventricular chambers and will eliminate, to some degree, the need for real hearts. Under discussion also is a phantom system that will permit tests to be made on beating hearts.

* Wiggler field 17 Kg.

DATE: August 13, 1981

TO : 456 File

FROM : K. Cantwell

SUBJECT: Telecon with Hughes

Hughes cannot submit new proposal by September 1. It is also not obvious that this is the correct course of action since he has only had one shot at this proposal which is essentially a program. We agreed I would take 456 to the panel in January with additional material he will provide in early December and ask for a two-year extension.

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STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
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TWX: 910-373-1162
Answer Back: STANFRD
STNU A

July 9, 1981

Dr. E. Barrie Hughes

Dear Spokesperson:

SSRL proposals are considered active for two years after their initial rating by the Proposal Review Panel. The purpose of this policy is to ensure that the entire group of active SSRL proposals is competitively rated and represents the most current issues and techniques in the various fields.

Your proposal 456B will be inactive as of January, 1982. If you wish to continue experimentation on this proposal after this date, a new proposal covering this work must be received at SSRL by September 1, 1981. This deadline is necessary to complete the refereeing process before the January, 1982 Proposal Review Panel Meeting. A call for proposals letter will be sent out in approximately two weeks time. This letter will have all the specifics for submitting new proposals. A current copy of the proposal guidelines is available by calling SSRL.

If you have any questions about your particular proposal do not hesitate to contact me.

Sincerely,

Claire L. Burke

Claire L. Burke
Proposal Administrator

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STNU A

June 18, 1980

Dr. E. Barry Hughes
HEPL
Stanford University

Dear Spokesperson:

The Proposal Review Panel considered your appeal for proposal 456B at their June 7th meeting. The results are shown below. If you have any questions please do not hesitate to call me.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

Action: 1.5 rating made permanent.

Rebuttal of referee's critique appears to be quite convincing.

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April 23, 1980

Dr. J. R. Cameron
Department of Radiology
University of Wisconsin
Medical School
Madison WI 53706

Dear Dr. Cameron:

On March 22, 1980 we sent you an addendum to Proposal 456B from Dr. Barry Hughes for your comments. I am sure you have a very busy schedule but we are very anxious for your response in order to have the necessary information to resolve this situation.

Thank you again for the time you have put into reviewing this proposal.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

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Answer Back: STANFRD
STNU A

March 22, 1980

Dr. J. R. Cameron
Dept of Radiology
University of Wisconsin
Medical School
Madison WI 53706

Dear Dr. Cameron:

Thank you for your considered review of SSRL Proposal 456B from Dr. Barrie Hughes et al. I am sending you Dr. Hughes' response to your review. I would very much appreciate it if you could read this addendum and return a second report to us.

Again, thank you for the time and thought you have put into this proposal.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

Encl: Addendum II
Cameron Review
Referee Form

0021695

ADDENDUM II TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

Co-Investigators: E. Barrie Hughes
Edward Rubenstein
Robert Hofstadter
William R. Brody
Albert Macovski

W. W. Hansen Laboratories of Physics
and
School of Medicine
Stanford University
Stanford, California 94305

0021696

March 1980

The preparation of this document was prompted by our receipt of the expert review requested by the SSRL Program Review Panel in January 1980. We will give our response to each of the items raised, but we wish first to remark that the scope of this latest review seems to go considerably beyond that of the six earlier reviews conducted in the period July - August 1979. The proposal under review was written, upon the advice of the Directorate of SSRL, not for the immediate purpose of securing sufficient beam time and facilities to take coronary arteriograms in patients, but only to conduct the first stages of such a program. This is specifically stated on page 5 of our Proposal, as is our intention to employ only inanimate phantoms at this time. The limited scope of our first proposal seems to have been well-understood by the earlier reviewers, four of whom gave us their unqualified endorsement. We are not at all surprised that the recent expert reviewer did not find a complete technical discussion of exactly how we intend to acquire coronary images in patients at SSRL. We regarded these details as appropriate for future proposals. At the time we wrote our current Proposal we had identified solutions to some of the technical problems related to the realization of a diagnostic clinic for coronary angiography at SSRL, but not to all of them. Since that time we have continued to study these problems, often in consultation with the SSRL staff, and at the present time we feel that we have practical solutions to all of the major problems. Not surprisingly, our project has been in a dynamic state of development for the past nine months, and we expect to communicate the results of these efforts to the Program Review Panel at the appropriate time in the context of new proposals. We did not feel it wise to delay the execution of the specific fundamental tests called for in our first proposal until our total development effort was conceptually complete and we hope therefore that the Program Review Panel, and the Directorate of SSRL, will continue to review our first proposal with these thoughts in mind, or instruct us otherwise.

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Clearly, we agree with the opinion of the expert reviewer that coronary arteriography cannot be done using the quasi-monoenergetic x-ray beams provided by standard x-ray sources. This is explicitly stated on page 7 of the Addendum to our Proposal that we submitted to SSRL on August 30, 1979.

Contrary to the claim of the expert reviewer, the instrumentation that we propose to use to obtain our initial one-dimentional radiographs is fully described on page 5 of our Proposal. It is also described on page 1 of the report we submitted to SSRL on December 20, 1979 describing the results of our first informal tests at SSRL, which were obtained with exactly this instrumentation. Obviously, for the reasons spelled out in the introductory paragraph of this document, we did not include a specific description of the instrumentation that we will need in due course to accumulate digital images rapidly in patients without the need for horizontal scanning.

We do agree with the claim of the expert reviewer that in order to visualize iodine within the coronary arteries it will be necessary to record each pair of digital images, i.e., above and below the K-edge, in a time short compared to the periodic motion of these structures. His estimate of about 30 msec for this time is quite correct. This is precisely why coronary arteriography cannot be done using quasi-monoenergetic sources derived from standard x-ray sources, which are insufficiently intense. We fully recognize this specific problem and have discussed it several times with the SSRL staff. It poses no fundamental practical difficulty, but its solution is also totally irrelevant to the realization of the objectives of our current proposal, all of which involve phantoms that are inanimate and static. Our eventual solution is to rotate, or to oscillate, the crystal monochromator at the requisite frequency ($\sim$ 30 Hz) by the small angular amount ($\sim 0.001^{\circ}$) necessary to step the transmitted beam back and forth through the iodine K-edge.

Another fundamental misconception held by the expert reviewer is that he expected we would eventually scan line-by-line through the complete coronary field of interest entirely at one x-ray energy before switching the energy and repeating the scan. He is correct in pointing out the severe limitations of this method. However, we have never had any intention of operating in this manner. We intend, at the proper time, to propose the use of an efficient linear array of detection elements encompassing the full width of the field of interest. This is the natural detector configuration for use at SSRL and, in addition, eliminates the familiar scatter background of standard radiology. In conjunction with Dr. George Brown of SSRL, we have conceived a method by which the horizontally planar x-ray beam may be scanned vertically through

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the field of interest (in contrast to moving the patient vertically through the horizontal x-ray beam). We intend, however, to use a scanning time longer than the cardiac cycle, but it must be emphasized that this relatively long scanning time will not result in a blurred image. Each line exposure, due to the high x-ray intensity, will occupy only a few milliseconds. The x-ray energy is then switched, within about 30 msec, and the second exposure is made. Each pair of line exposures occurs within 30 msec, a period within which the heart is essentially stationary. Upon completion of each exposure pair, the beam (or the patient) is moved vertically by the required spatial element and the procedure repeated. The lack of blurring is governed by the line-pair exposure time and not by the total frame time. This is a direct analog of photographic cameras with focal plane shutters which are free of blurring despite relatively long exposure times of the scanning slit. The price paid for this effect is that all portions of the image do not represent the same time interval. A subtle distortion is generated due to motion (the cardiac cycle), but this does not represent blurring. For example, a horizontally moving vessel, which would otherwise be blurred, is reproduced in good focus at a slight inclination since the top and bottom are scanned at different times.

The photographs reproduced below in Figs. 1 and 2 provide a convincing illustration of the viability of the focal plane shutter effect in coronary arteriography. These photographs were taken in the laboratories of Drs. Brody and Macovski, who are also co-authors of SSRL Proposal 456B. Fig. 1 shows an arteriogram of a dog heart which required five seconds to record despite the fact that the heart was beating at a rate of 120 beats per minute. The intra-arterial iodine, which clearly reveals the coronary arteries, was introduced invasively by means of a catheter, which is also visible. This picture was recorded with an instrument normally used for imaging by computerized tomography. It employs a fan-shaped x-ray beam detector. The image is accumulated one plane at a time, and the axial position of the dog is incremented between successive exposures. The coronary arteries are clearly defined, despite the motion introduced by the many cardiac cycles ($\sim$ 10) involved.

The same principle is also illustrated by the series of photographs in Fig. 2. The first frame (a) is a standard coronary arteriogram obtained in projection with a normal exposure time ($\sim$ 0.01 sec). The subject is again a dog and the iodine is again introduced invasively. The second frame (b) represents an integration over four seconds, with the resultant severe blurring

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and almost total loss of arterial detail. The third frame (c) is also taken over the same four seconds, where a line scan has been simulated by a vertically scanned horizontal slit. As is shown, the original detail is restored despite the motion. The streak artifacts are due to the non-uniform motion of the manually scanned slit.

The misunderstanding by the expert reviewer of our x-ray detection efficiency is 1% is hard to anticipate but easy to correct. Any x-ray detector that we have proposed, or will propose, for use at SSRL will have an efficiency of essentially 100%. The current proposal calls for the use of a bismuth germanate (BGO) crystal 3 mm in thickness, which corresponds to approximately 38 x-ray mean free paths at 30 KeV. Although the precise thickness of our BGO crystal is specified on page 1 of our Informal Test Report to SSRL, it is true that it is not explicitly stated in our Proposal. Our excuse for this omission must be our awareness of the excellent stopping power of BGO for 30 KeV x-rays and our implicit assumption that just the stated use of BGO would, by itself, clearly signal an excellent detector efficiency to the thoughtful reader. In fact, a BGO crystal thin enough ($\sim$ 0.01 mm) to have low detection efficiency ($<$ 10%) for 30 KeV x-rays would be about 30 times thinner than the minimum thickness ($\sim$ 0.25 mm) presently available.

Our mention of a 1% detection efficiency on page 5 of our Proposal occurs before we arrive at a description of our intended apparatus and arose only to illustrate how quickly data of excellent statistical quality can be acquired at SSRL due to the outstanding intensity of the x-ray beam. Never did it occur to us, or to our knowledge to anyone else, that this remark could be interpreted as a justification of the use by us of such an inefficient detector. Clearly this is impossible in radiology because of the consequent radiation dose.

We agree with the expert reviewer's remark that if the time occupied by a complete set of line scans at one energy followed by a second complete set of line scans at a second energy should collectively occupy more than about 30 msec, that a temporal subtraction methodology, using standard x-ray tubes, will produce cardiac images of comparable quality. Having said this however, we can repeat that we do not intend to acquire our cardiac images in this way. Images acquired by either of the two methods just outlined will be hopelessly blurred due to cardiac motion and be useless from the standpoint of visualizing the coronaries.

0021700

We also agree with the second academic point raised by the expert reviewer that, in the absence of motion (obviously impossible in coronary arteriography), the iodine sensitivity provided by time subtraction exceeds that provided by K-edge subtraction. This occurs because the small reduction in iodine contrast due to the subtraction of the image taken below the K-edge is avoided. Clearly, the situations of vital clinical interest in which patient motion can be so totally suspended as to realize this small benefit must be few in number, and are obviously totally disconnected to our area of interest where motion is ever-present and unavoidable.

We believe we have adequately explained in the introductory paragraph to this statement the reason why the expert reviewer finds our current Proposal to be incomplete. In summary, he is judging the full program of development from the perspective of an initial proposed investigation with limited objectives. It should be clear from the contents of this document that we could now write a much more convincing justification of our eventual goal than can be gleaned from our current Proposal. At the proper time we will write such a proposal. First, however, we wish to demonstrate our ability to isolate subtle amounts of iodine with the x-rays available at SSRL before we address, in proposals, such problems as motion and image field.

We have adequately responded in our first Proposal Addendum to the criticism that our non-invasive study can presently be made available at only storage ring laboratories. We wish to emphasize, as we also did in our earlier Addendum, our belief that a successful demonstration of our ideas at SSRL would result in the stimulation of a considerable technical effort to develop a compact source of monochromatic x-rays expressly for medical purposes. We indicated that the most likely way in which this could be done was by the combination of an argon-ion UV laser and a small ($\sim$ 25 MeV) betatron. Such a development would of course be of tremendous value to many scientists in other fields, who would thereby also be liberated from the storage ring laboratories.

We do not accept the view that the possible restriction of our intended procedure to laboratories such as SSRL is a sufficient reason to deny our proposal a high priority at this very early stage. We have listed in our Proposal Addendum of August 30, 1979 the specific diagnostic and research opportunities that can be realized for the first time at SSRL, and independent

0021701

statements attesting to the medical value of our projected procedure have been provided to SSRL by Drs. N. E. Shumway and J. W. Hanbery of the Departments of Cardiovascular Surgery and Surgery (Division of Neurosurgery) respectively at Stanford. We have pointed to one possible means by which compact sources of monochromatic x-rays for medicine may be developed and we believe that a successful demonstration of K-edge dichromography where it is now possible, namely at SSRL, is the best possible way to encourage the eventual development of such independent sources. As always in science it is impossible to predict exactly how medicine at large may benefit from the development effort we now envisage at SSRL, but we do believe that the potential rewards are so inviting that the present opportunity should not be missed.

We hope that this communication, together with the existing documents, reviews and recommendations relating to Proposal 456B, will persuade the Program Review Panel and the Directorate at SSRL to maintain, or to upgrade, their original rating of our Proposal and to defer consideration of later phases of our investigation to the proper time. We also wish to point out that we have discussed our current proposal and our future ideas on several occasions with members of the SSRL staff and we suggest that this resource be used for expert technical interpretation if there are residual unclear aspects of our Proposal.

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Fig. 1

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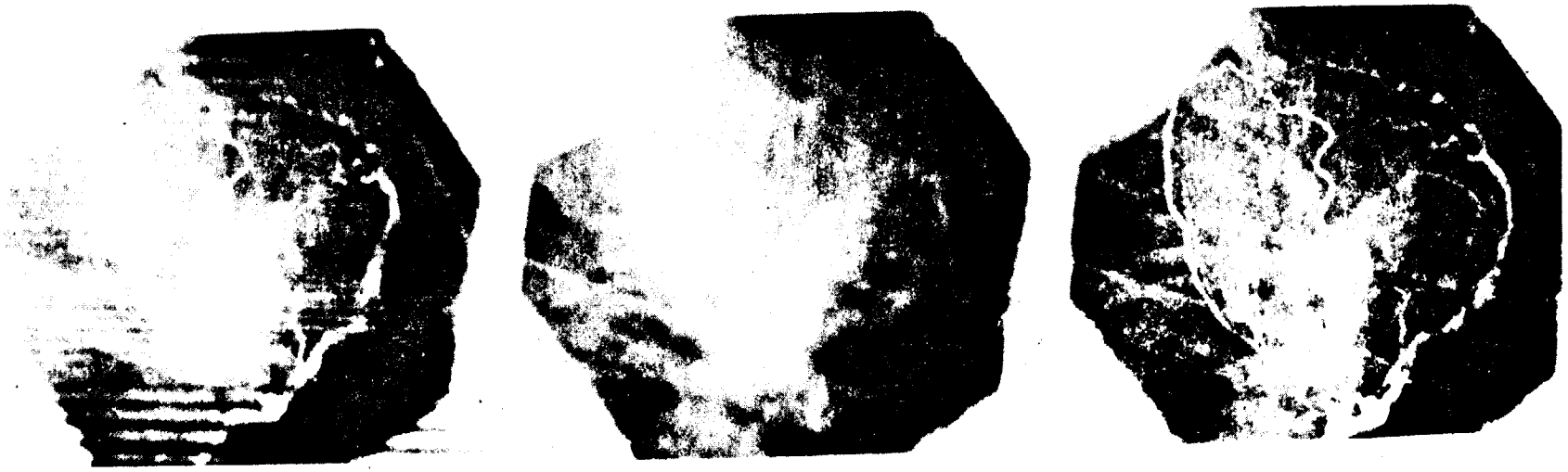

(a) (b) (c)

Fig. 2

0021704

SSRL PROPOSAL REVIEW

Investigators: Dr. E. Barrie Hughes et al

Proposal Number: 456B

Title: "Iodine Dichromography With Monochromatic X-ray Beams for Angiography

Referred to: Dr. J.R. Cameron
Dept. of ~~Nuclear Medicine~~ Radiology
University of Wisconsin
Medical School
Madison, Wisconsin 53706

RECEIVED
JAN 31 1980
S. S. R. L.

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

Contrary to some of the other reviews you have received, the use of K-edge subtraction techniques using quasimonoenergetic filtered x-ray beams is not feasible for coronary angiography. Study of grosser structures such as the left ventricle is feasible. However, beam intensities using standard x-ray beams are not high enough to deliver exposure sufficient to see the coronaries in an energy subtractive mode.

The largest weakness of the proposal has to do with the complete omission of a description of the imaging procedure to be used. In particular, it is not stated what the time separation of the two energy exposures to a particular picture element will be. Is it possible to switch the energy in times short compared to coronary artery motion? If it is intended to generate two complete sequential scans rather than switching energies in a scan line by scan line basis, then the temporal separation of the two complete scans must be no more than 30 m secs. If it is intended to dwell for 1 m sec on each line, then in 30 m secs one can only get a 30 line image which would be too crude to see coronaries.

The technique will work if it can be demonstrated that beam energies can be switched in times on the order of 15 m secs so that two energy exposures of the same scan line can be done in rapid succession. If this is done, sufficient intensity would be available.

The principal investigators mention of a 1% detection efficiency does not instill one with confidence in his knowledge of present x-ray detectors which

(continued)

John Cameron
Signature of Referee

0021705

PLEASE CHECK

Overall Desirability
( ) Excellent
( ) Very Good
( ) Good
(x) Fair
( ) Poor

Experimenter Competency
( ) Excellent
( ) Very Good
( ) Good
( ) Fair
(x) Poor - Rad. Imaging
(x) Unknown - Physics

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administrator,
SSRL, SLAC Bin 69
P. O. Box 4349
Stanford, CA 94305

Are there technical questions to be answered? (x) yes ( ) no
If yes, are they (x) Essential before approval?
( ) Desirable before approval? Comment on back
Are there safety concerns to be answered? ( ) yes (x) no
If yes, please describe on back.

Referee's Report
"Iodine Dichromography With Monochromatic X-ray Beams
for Aniography"
(continued)

are well over an order of magnitude better than this - which obviously works to his advantage.

If it is intended to take complete scans at one energy and then another at another energy, the scans must be completed in 15 m secs or so. If scan times become much longer than this then the motion problems will become such that temporal subtraction techniques will do a better job (these can be completed with conventional x-ray tubes which have sufficient intensity in this case since heavy filtration is not needed). It is also true that in the absence of motion of background anatomy - not including the heart, that iodine sensitivity provided by time subtraction is greater than that provided by K-edge subtraction (assuming the beam above the K-edge is as specified in the proposal).

The proposal is not without scientific merit, but it is not complete enough to judge properly. Assuming that what has been written represents the principal investigation present state of planning, I would have to reject it at this time. However, I do believe a reasonable proposal is possible.

I am pessimistic that the results of the experiment will have any impact on public health because of the obvious difficulty in the dissemination of synchrotron radiation. Therefore it is unlikely that I would ever assign it a high priority for beam time.

John Cameron

0021706

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

January 31, 1980

Dr. Barrie Hughes
HEPL
Stanford University

Dear Barrie:

Enclosed please find the referee report on your proposal 456B which was solicited at the request of the biology sub-panel of the Proposal Review Panel. As you can see it raises some detailed criticisms of your proposal. I have read this review to a member of the biology sub-panel over the telephone and he felt it was a significant review and requested that it be passed on to you for your considered response. When I receive your response I will mail the review and response to the entire biology sub-panel. In the meantime your rating of 1.5 will stay in effect.

Sincerely,

Katherine

Katherine Cantwell
Proposal Administrator

0021707

Bio master book

SSRL PROPOSAL REVIEW

Investigators: Dr. E. Barrie Hughes et al

Proposal Number: 456B

Title: "Iodine Dichromography With Monochromatic X-ray Beams for Angiograph

Referred to: Dr. J.R. Cameron
Dept. of ~~Nuclear Medicine~~ Radiology
University of Wisconsin
Medical School
Madison, Wisconsin 53706

RECEIVED
JAN 31 1980
S. S. R. L.

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The principal investigators mention of a 1% detection efficiency does not instill one with confidence in his knowledge of present x-ray detectors which

(continued)

John Cameron
Signature of Referee

PLEASE CHECK

Overall Desirability
( ) *Excellent*
( ) *Very Good*
( ) *Good*
(x) *Fair*
( ) *Poor*

Experimenter Competency
( ) *Excellent*
( ) *Very Good*
( ) *Good*
( ) *Fair*
(x) *Poor* - Rad. Imaging
(x) Unknown - Physics

To be fair to the experiment return within ten days to:
Katherine Cantwell, Proposal Administrator,
SSRL, SLAC Bin 69
P. O. Box 4349
Stanford, CA 94305

Are there technical questions to be answered? (x) *yes* ( ) *no*
If yes, are they (x) *Essential before approval?*
( ) *Desirable before approval? Comment on back*
Are there safety concerns to be answered? ( ) *yes* (x) *no*
If yes, please describe on back.

00210108

Referee's Report
"Iodine Dichromography With Monochromatic X-ray Beams
for Aniography"
(continued)

are well over an order of magnitude better than this - which obviously works to his advantage.

If it is intended to take complete scans at one energy and then another at another energy, the scans must be completed in 15 m secs or so. If scan times become much longer than this then the motion problems will become such that temporal subtraction techniques will do a better job (these can be completed with conventional x-ray tubes which have sufficient intensity in this case since heavy filtration is not needed). It is also true that in the absence of motion of background anatomy - not including the heart, that iodine sensitivity provided by time subtraction is greater than that provided by K-edge subtraction (assuming the beam above the K-edge is as specified in the proposal).

The proposal is not without scientific merit, but it is not complete enough to judge properly. Assuming that what has been written represents the principal investigation present state of planning, I would have to reject it at this time. However, I do believe a reasonable proposal is possible.

I am pessimistic that the results of the experiment will have any impact on public health because of the obvious difficulty in the dissemination of synchrotron radiation. Therefore it is unlikely that I would ever assign it a high priority for beam time.

John Cameron

0021709

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

Dr E Barrie Hughes
Hansen Laboratories
Stanford University
456B

January 9, 1980

Dear Spokesperson:

The SSRL Proposal Review Panel held its biannual meeting at SSRL January 4-5, 1980. Eighty-five new proposals were rated. Your proposal number 456B was reviewed. To aid you in interpreting your rating we would like to provide a little background information.

The PRP rates proposals between 1.0 (highest) and 5.0 (lowest). Continuing the pattern of the last years this new group of proposals was better, on the average, than its predecessors. We attempted, however, to maintain the absolute quality scale used during the PRP meetings of 1979 so that ratings at different meetings could be used consistently to schedule proposals. The average rating for all three sub-panels was 2.1.

This year, for the first time, we solicited proposals for programs rather than single experiments. Eleven were received. In many cases, the sub-panels found that there was no single unifying intellectual theme presented in the programs and consequently broke them into their component parts for rating purposes.

To further clarify what the ratings mean in practical terms we have made some projections based on the requests for beam time received this spring. On all the x-ray lines except the wiggler and EXAFS I we expect to be able to accommodate all requests. These two lines have requests for approximately twice as many shifts as time available. Thus, we do not expect to get beyond the 2.0's in scheduling on these two lines. On the VUV lines, proposals rated 3.0 or better are likely to be scheduled.

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Attached you will find a description of the appeals process. Appeals are due by February 15, 1980 to allow time for their disposition to have some effect on spring beam time assignments.

Sincerely,

Arthur Bienenstock
Director

Katherine Cantwell
Proposal Administrator

Your proposal was rated by: ( ) materials (x) biology ( ) VUV sub-panel

January 1980 rating: 1.5 provisional

Comments by the PRP: Well-reasoned proposal, but it is essential to obtain an additional opinion from another expert in this field. If he is negative, the proposal will be downgraded substantially.

0021711

Dec r 20, 1979

RECEIVED
DEC 28 1979
S. S. R. L.

INFORMAL TEST RESULTS (SSRL PROPOSAL 456B)

Introduction

This note contains a brief report on the activities of the 456B collaboration in the 1-5 beam at SSRL within the past month. The principal purpose of this activity was to gain some familiarity with SSRL (i.e., the instrumentation associated with a representative hard X-ray beam line) and with the properties of our own apparatus. Following our letter of November 6 to Dr. Bienenstock (attached), we were invited by the SSRL Operations Manager, John Cerino, to use the 1-5 beam initially from 0800 November 26 to 0800 November 27 and later from 1600 December 5 to 0800 December 6. On the first of these occasions SPEAR was operating in the parasitic mode at 2 GeV and on the second occasion in the dedicated mode at 3 GeV. In the following paragraphs we indicate briefly what we accomplished in the above time. These accomplishments were dictated primarily by what was feasible in the 1-5 beam at these times and do not coincide exactly with the specific objectives in our first stage proposal to SSRL (#456B). In large measure their present function is to demonstrate our competency to work efficiently at SSRL.

Run #1. Parasitic Mode

Faced with the impossibly low X-ray flux at 33.2 KeV (at the iodine K-edge), we decided to test our apparatus in the region of the K-edge in copper at 8.9 KeV. In anticipation of this possibility we prepared a 1/8" thick lucite target in which were cut three cells 1/16" thick × 0.6" wide. In these cells we placed solutions of $CuSO_4$ at concentrations corresponding to 0.45, 0.9 and 1.8 mg cm^{-2} of Cu respectively. Our X-ray detector consisted of a bismuth germanate crystal, 3 mm in thickness and 5 mm × 5 mm in cross

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section, coupled to a 3/4" diameter photomultiplier tube. Stainless steel collimators of adjustable width in both the horizontal and vertical directions were placed upstream of the crystal, and the photomultiplier tube output charge was integrated electronically, under computer control, for an arbirary number of SPEAR orbits. The X-ray intensity over the full horizontal aperture (~ 5 mm) of our BGO crystal detector was ~10/SPEAR pulse for these measurements.

Following a calibration of the 1-5 monochromator by an EXAFS measurement on a Cu foil, we obtained the results shown in the attached Figures 1 - 3 as each target cell was incrementally moved in turn through the X-ray beam at X-ray-energies centered just above and just below the K-edge in copper. The observed profiles differ, as expected, only when the beam intercepts a Cu solution. The difference signal is also indicated in each of these figures. The sloping edges of the difference signal are attributable to the horizontal slit width, which for all of these measurements was set at 5 mm. The absolute magnitude of the difference signals agrees with those expected. For example, at the smallest Cu concentration of 0.45 mg cm^{-2}, the observed difference signal was ~ 17% (relative to the X-ray intensity below the K-edge), whereas the expected signal was ~ 13%. Similarly, at the highest Cu concentration the observed and expected signals were 50% and 43% respectively.

Run #2. Dedicated Mode

In this second run the SPEAR energy was 3 GeV and the initial stored current ~ 80 mA. This provided an X-ray flux at 9 KeV about 400 times more intense than that available to us earlier. This enabled us to conduct a rapid check of our apparatus by repeating certain measurements on the Cu cells. We realized that, in principle, a useful flux of X-rays was now

0021713

available at 33.2 KeV, but initially thought that this was inaccessible to us due to a limitation on the physical length of the Si crystal monochromator in the 1-5 beam. However, after consultation with Dr. George Brown of SSRL, we decided to search for the 33.2 KeV beam reflected from the (440) plane in Si, which should pass through the crystal along the same trajectory as a 16.6 KeV beam reflected from the standard (220) plane. A useable beam at 33.2 KeV should then be accessible by tuning the monochromator to 16.6 KeV and preferentially filtering out the 16.6 KeV component.

The approach outlined above enabled us to obtain the iodine K-edge shown in Figure 4. This edge was observed with a 3/16" aluminum filter, and the expected X-ray intensity at 33.2 KeV was ~ 5/SPEAR orbit. The "iodine foil" used to obtain the EXAFS display of the I-edge was a dilute solution of the iodine contrast agent Renografin that is commonly used in clinical medicine.

Following the set-up of the 33.2 KeV beam, scans were conducted through an iodinated target cell. For these measurements the target cells used earlier for the Cu measurements were now occupied with diluted solutions of Renografin. Figure 5 shows the first scan across such a cell for an iodine concentration of 0.014 gm cm^{-2}. In this measurement the clinical contrast agent was diluted by a factor of 26.

Figure 6 shows a second scan across an iodine cell, in front of which was placed a column of $CaSO_4$. In this simple simulation of bone, the Ca concentration was 0.28 gm cm^{-2}. There is evidence in this data of an abrupt change in the response of our electronic integrator (during the scan below the K-edge), which causes the shoulders in the difference signal to be of unequal height. This is of course a temporary problem and easily remedied. Despite this technical inconvenience, it is evident that the image of the

bone, clearly seen in the two separate scans is greatly reduced in the difference signal. It is not fully removed in the difference signal because of a residual admixture of 16.6 KeV X-rays in the 33.2 KeV beam. The admixture of 16.6 KeV X-rays is expected to be about 50%. Given a pure 33.2 KeV beam, no residual bone image would be seen.

There are two other experimental observations that reveal the approximately equal admixture of 16.6 KeV and 33.2 KeV X-rays in the beam we employed. These are 1) the absolute iodine difference signal is about 50% smaller than expected, and 2) the difference signal is not zero when the beam does not intercept the iodine cell. The reason for the latter observation is the presence of the 3/16" aluminum filter in the beam and the differential change in the attenuation coefficient in aluminum between the two monochromator settings for the 16.6 KeV component. (A correction has been made for this latter effect in constructing the difference signals in Figs. 5 and 6.)

Summary

The results we have obtained informally to this date are by no means comprehensive, and do not address the detailed questions we have listed in our proposal. The effort expended has given us valuable practical experience at SSRL, and allowed us to assess the properties of our own apparatus. It has also provided SSRL with an opportunity to assess our competency. There is now good reason to expect that our proposed investigation can be conducted efficiently when we have access to the necessary intense and pure beam that we require.

E B H

E. B. Hughes
Spokesman (456B)

0021715

11/27/79

Fig 1

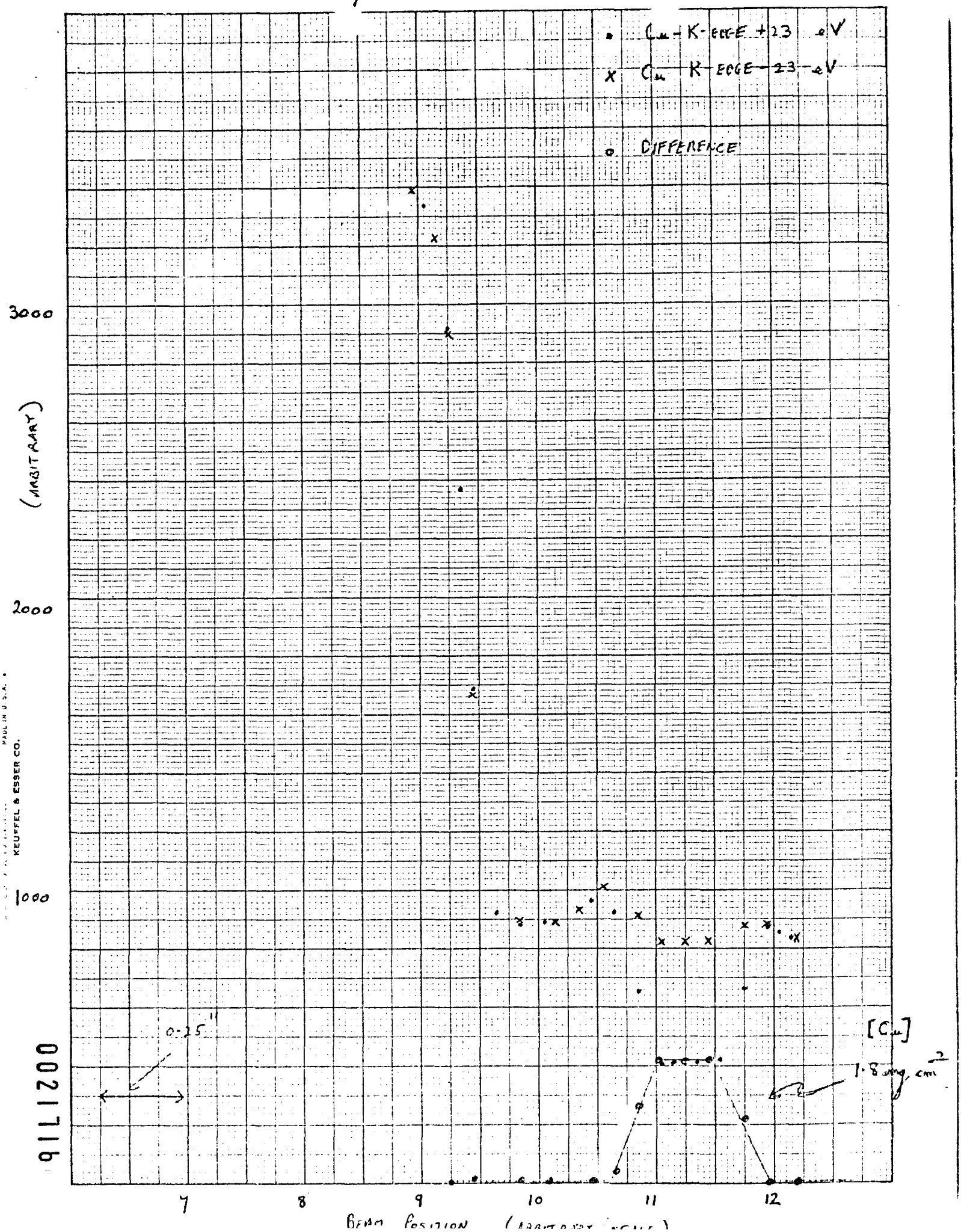

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Fig 2

11/27/79

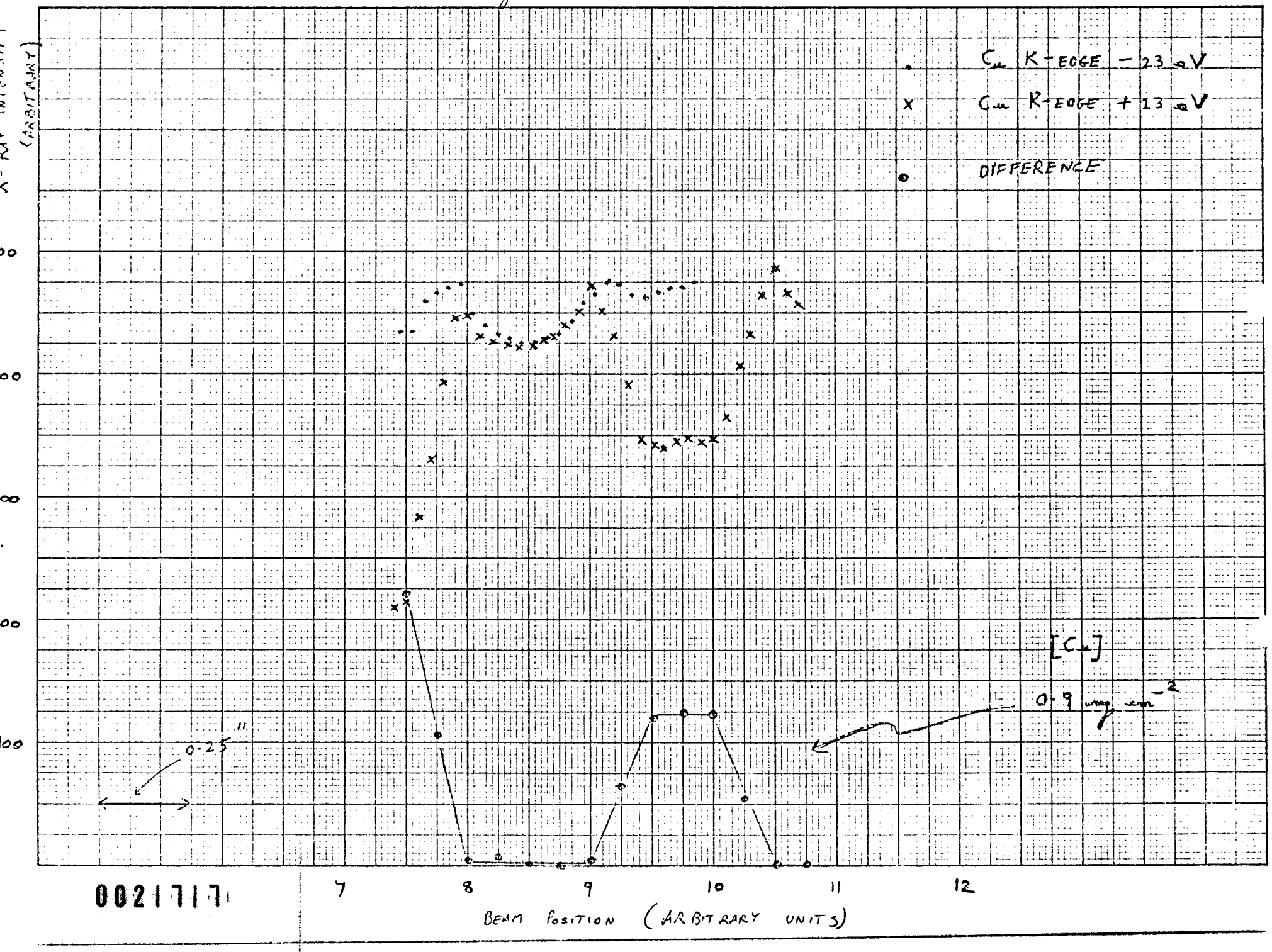

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Fig 3

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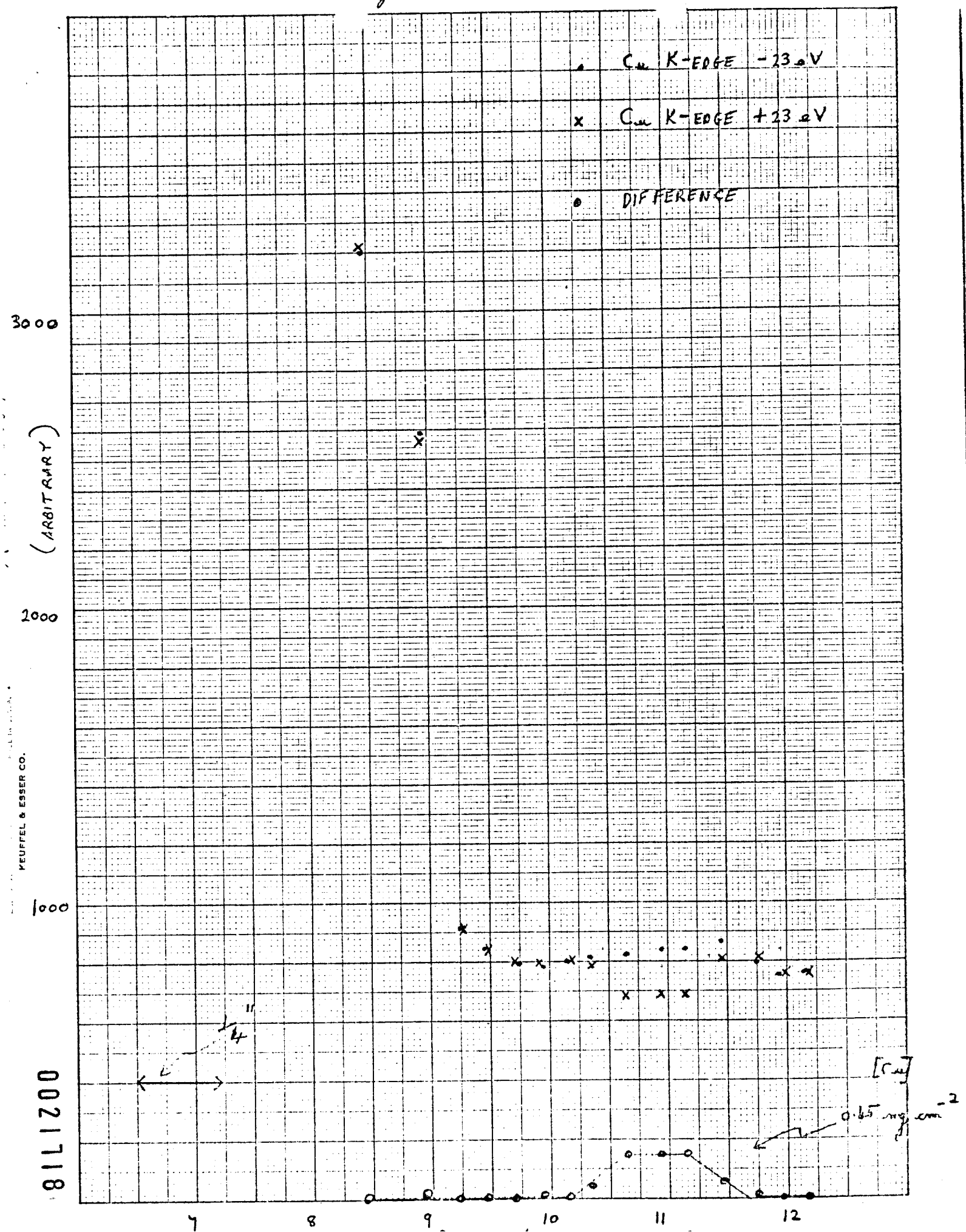

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FIG 4

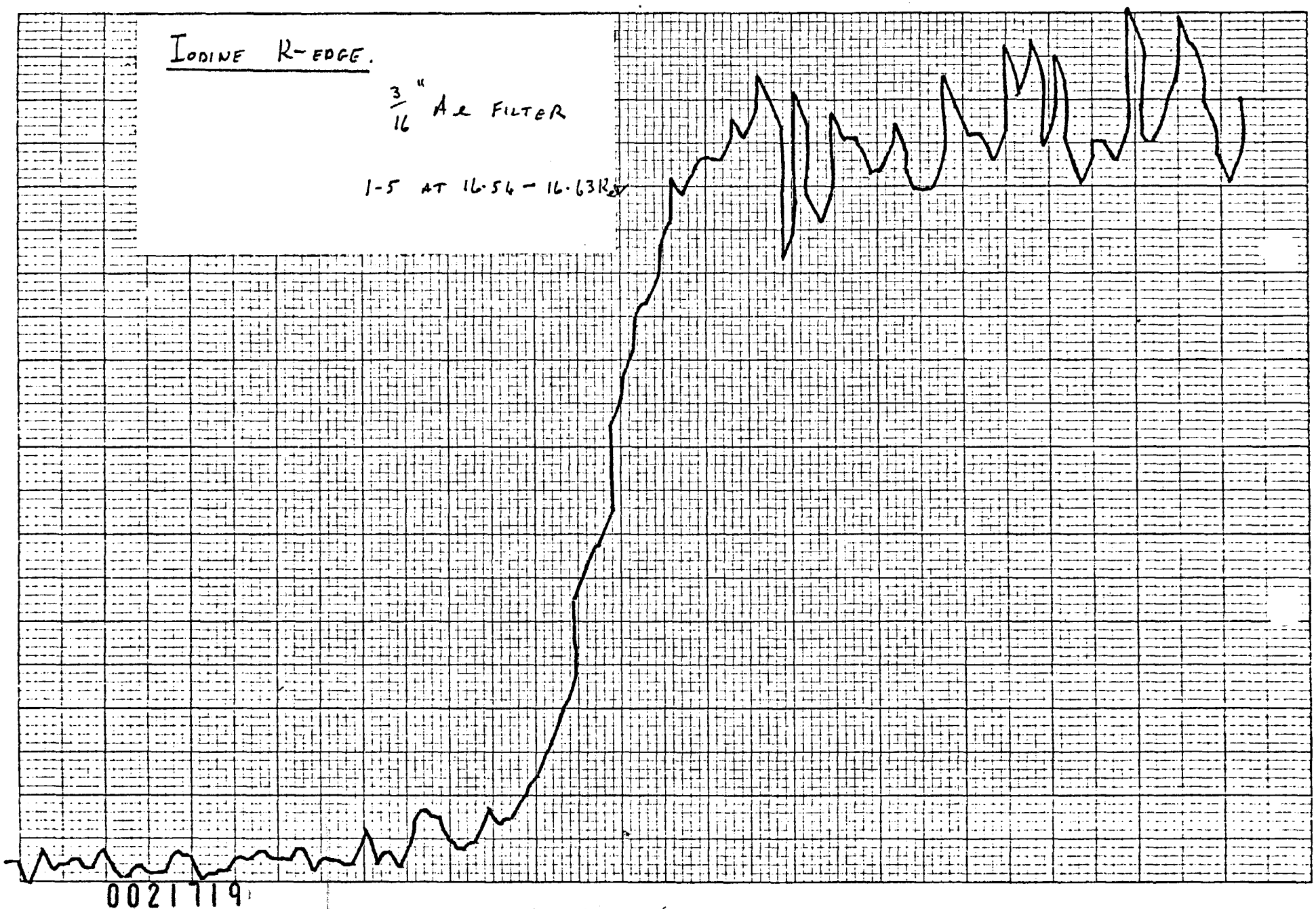
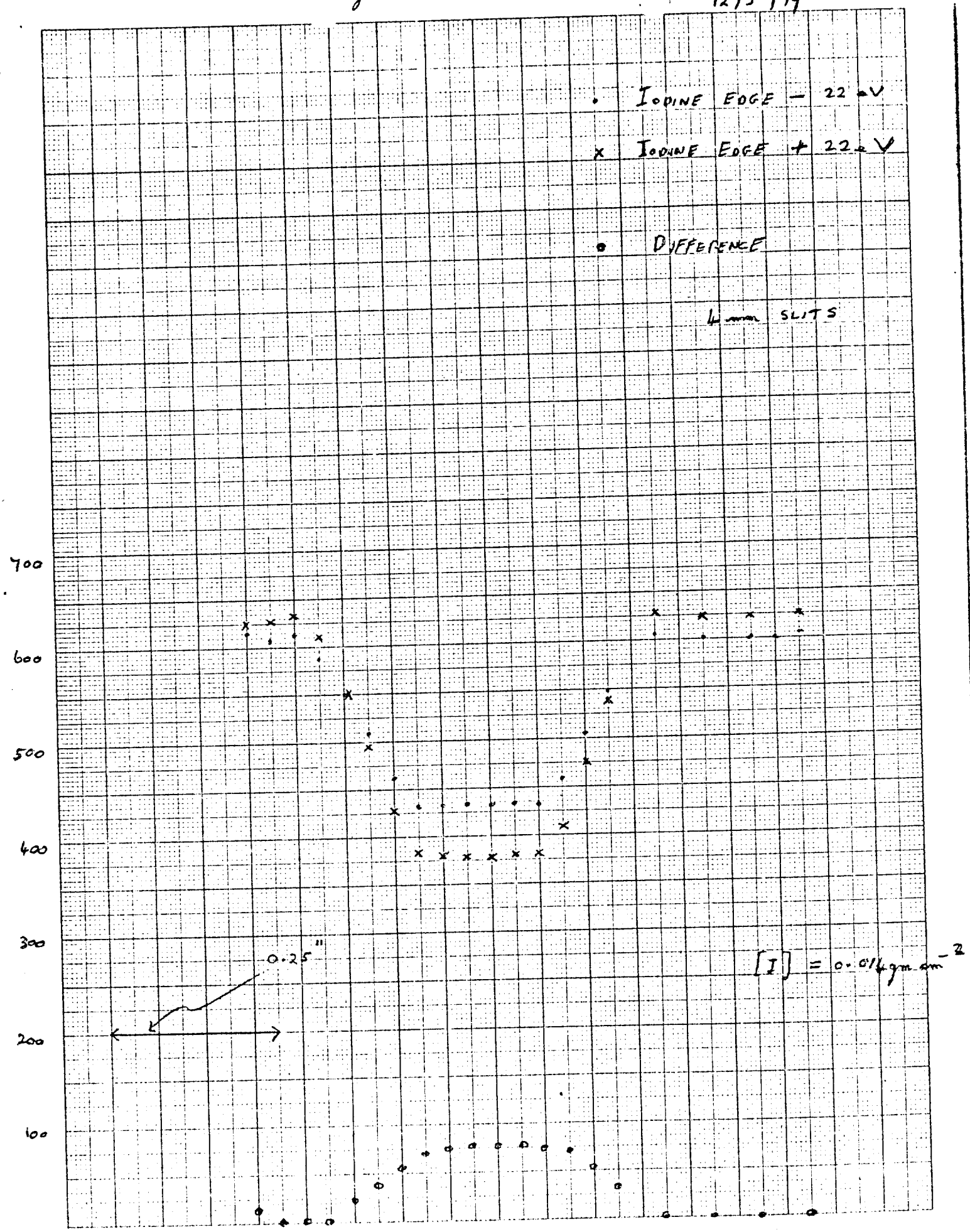


Fig 5

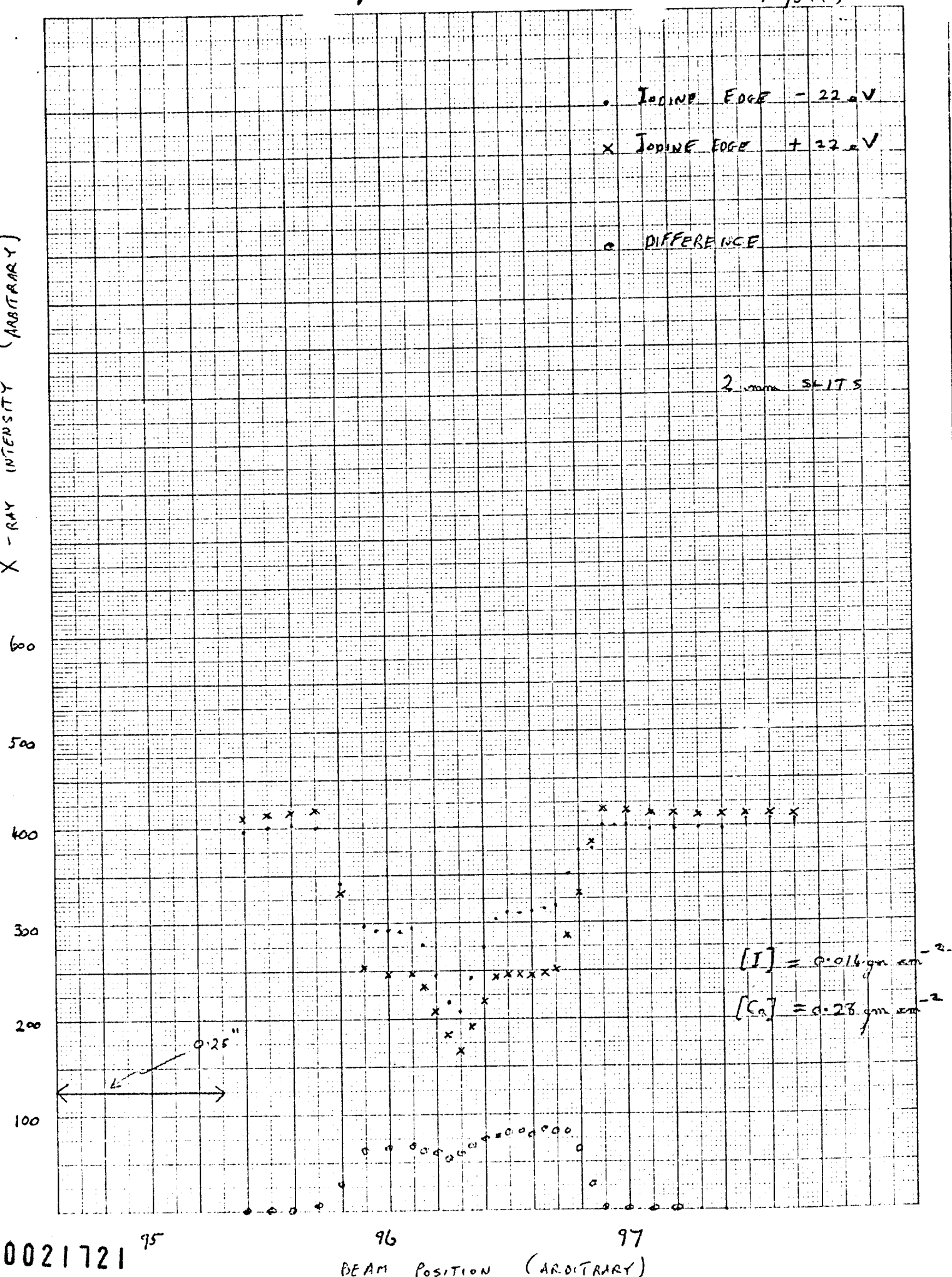
12/5/79



0021720

Fig 6

12/5/79



0021721

W. W. HANSEN LABORATORIES OF PHYSICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

Edward L. Ginzton Laboratory
High Energy Physics Laboratory

Telephone (415) 497-0135

6 November 1979

Professor Arthur I. Bienenstock
Director, Stanford Synchrotron Radiation Laboratory
Stanford, California 94305

Dear Dr. Bienenstock:

We are writing to you in connection with our proposal (SSRL-No. 456B) to study iodine dichromography with monochromatic x-ray beams for angiography. Our immediate purpose is two-fold: (1) to seek approval from you to begin informal experimental work at SSRL this Fall, and (2) to inquire of your need for additional documentation from us to permit such experimentation to take place before the formal review of our proposal in January, 1980.

Our goal, briefly, is to demonstrate the usefulness of the brilliant source of x-rays at SSRL for non-invasive angiography using the technique of iodine dichromography. We submitted our proposal to SSRL on June 27, 1979 and shortly thereafter received six anonymous reviews. Four of these were totally positive, one raised only a minor and easily answered objection, and one was totally negative. In response, principally to the latter review, we submitted an Addendum to our Proposal on August 30, 1979. In return, we received a rebuttal from our original critic, together with a letter from your Proposal Administrator advising us that a reply would not seem useful, although, from a scientific standpoint, this would be very easy for us to prepare.

Since submitting our original Proposal we have proceeded, during the Summer, with the construction and test of the simple apparatus that our initial studies require. These preparations are now nearly complete and we are eager to proceed with the work at SSRL even before our Proposal receives a formal rating. To this end we have asked two Stanford physicians, active in the specialties most likely to benefit from our work, to write to you attesting to the potential clinical usefulness of the invasive technique.

Continued .....

0021722

The preferred beam line for our eventual work, due to the large flux of x-rays close to 33.2 KeV, is the rapidly-tunable hard x-ray beam designated IV-1, but this beam is not essential for preliminary tests. An alternative is the I-5 beam. Further, in order to gain some familiarity with SSRL and our apparatus, it is not essential initially for us to operate at the highest x-ray intensity. We estimate that useful testing of our apparatus, with 33 KeV x-rays, can be done in the I-5 beam at a minimum machine energy of 2.5 GeV. Certain equipment tests can even be done using 10 KeV x-rays at a minimum machine energy of 2 GeV. We are also willing to participate in the check-out and calibration of a monochromatic x-ray beam at the energies necessary for iodine dichromography, since it is our understanding that energies this high have not often been used in the past.

If our request for informal time at SSRL meets with your approval, we propose to keep in touch with your Operation Manager, John Cerino, and others to identify suitable opportunities.

Sincerely yours,

E. Barrie Hughes

E. Barrie Hughes
Spokesman for Proposal SSRL No. 456B

EBH/gs

CC Edward Rubenstein
Robert Hofstadter
William R. Brody
Albert Macovski

0021723

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

November 9, 1979

Dr. E. Barrie Hughes
W. W. Hansen Laboratories
Stanford University

Re: 456B

Dear Dr. Hughes:

Dr. Bienenstock has asked me to answer your letter of 6 November regarding preliminary work on proposal 456B. I understand that you have been in touch with our Operations Manager, John Cerino, on this subject as well. There is no need for further documentation from you to begin this work. We will handle your request for time on this proposal as we would a letter of intent until such time as the proposal is rated.

The high energy time for this fall has been fully scheduled to rated proposals. However, there is time available on several of the x-ray lines at 2.0 GeV. You should let John Cerino know immediately if you want to use some of this time for equipment checks.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

cc: A. Bienenstock
H. Winick

0021724

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

January 7, 1980

Dr. J. R. Cameron
Department of Nuclear Medicine
University of Wisconsin Medical School
Madision, WI 53706

Dear Dr. Cameron:

We are soliciting your advice on the enclosed proposal. As you can see it has been reviewed by several people in the field. Our proposal review panel has met to consider rating this proposal and have requested me to obtain an opinion from you before finalizing their rating. I would very much appreciate your views as soon as possible although I know you will probably be busy on your return from Brazil.

I enclose our referee letter and a rating form as well as all the material on the proposal from Dr. Hughes.

Thanking you in advance for your help,

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

0021725

456 B

STANFORD UNIVERSITY SCHOOL OF MEDICINE • STANFORD, CALIFORNIA 94305 • (415) 497-5771
DEPARTMENT OF CARDIOVASCULAR SURGERY

12/27/79

RECEIVED
DEC 28 1979
S. S. R. L.

Professor Arthur I. Bienenstock
SSRL, SLAC Bin 69

Dear Professor Bienenstock:

I have seen the proposal submitted by E. Barrie Hughes and his co-workers for the study of iodine dichromography with monochromatic X-ray beams for coronary angiography. I would only indicate that this could be a tremendously useful adjunct in the study of patients with coronary artery disease. The financial savings, over the presently available invasive techniques, would be quite significant, and I would guess that vast numbers of individuals could be screened as part of an annual physical examination program. At any rate, we have looked long for non-invasive methods for imaging the coronary arterial system, and this work would appear to show promise in this regard.

Best wishes for the Holiday Season and the New Year.

Sincerely yours,

NE Shumway

Norman E. Shumway, M.D., Ph.D.
Professor and Chairman

NES/rh

0021726

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

November 9, 1979

Dr. E. Barrie Hughes
W. W. Hansen Laboratories
Stanford University

Re: 456B

Dear Dr. Hughes:

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The high energy time for this fall has been fully scheduled to rated proposals. However, there is time available on several of the x-ray lines at 2.0 GeV. You should let John Cerino know immediately if you want to use some of this time for equipment checks.

Sincerely,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

cc: A. Bienenstock
H. Winick

0021727

Cc Katherine
456B

W. W. HANSEN LABORATORIES OF PHYSICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

RECEIVED 11/8/79
NOV 8 1979
S.S.R.L. Office of the Director

Edward L. Ginzton Laboratory
High Energy Physics Laboratory

Telephone (415) 497-0135

6 November 1979

Professor Arthur I. Bienenstock
Director, Stanford Synchrotron Radiation Laboratory
Stanford, California 94305

Dear Dr. Bienenstock:

We are writing to you in connection with our proposal (SSRL-No. 456B) to study iodine dichromography with monochromatic x-ray beams for angiography. Our immediate purpose is two-fold: (1) to seek approval from you to begin informal experimental work at SSRL this Fall, and (2) to inquire of your need for additional documentation from us to permit such experimentation to take place before the formal review of our proposal in January, 1980.

Our goal, briefly, is to demonstrate the usefulness of the brilliant source of x-rays at SSRL for non-invasive angiography using the technique of iodine dichromography. We submitted our proposal to SSRL on June 27, 1979 and shortly thereafter received six anonymous reviews. Four of these were totally positive, one raised only a minor and easily answered objection, and one was totally negative. In response, principally to the latter review, we submitted an Addendum to our Proposal on August 30, 1979. In return, we received a rebuttal from our original critic, together with a letter from your Proposal Administrator advising us that a reply would not seem useful, although, from a scientific standpoint, this would be very easy for us to prepare.

Since submitting our original Proposal we have proceeded, during the Summer, with the construction and test of the simple apparatus that our initial studies require. These preparations are now nearly complete and we are eager to proceed with the work at SSRL even before our Proposal receives a formal rating. To this end we have asked two Stanford physicians, active in the specialties most likely to benefit from our work, to write to you attesting to the potential clinical usefulness of the invasive technique.

Continued .....

0021728

The preferred beam line for our eventual work, due to the large flux of x-rays close to 33.2 KeV, is the rapidly-tunable hard x-ray beam designated IV-1, but this beam is not essential for preliminary tests. An alternative is the I-5 beam. Further, in order to gain some familiarity with SSRL and our apparatus, it is not essential initially for us to operate at the highest x-ray intensity. We estimate that useful testing of our apparatus, with 33 KeV x-rays, can be done in the I-5 beam at a minimum machine energy of 2.5 GeV. Certain equipment tests can even be done using 10 KeV x-rays at a minimum machine energy of 2 GeV. We are also willing to participate in the check-out and calibration of a monochromatic x-ray beam at the energies necessary for iodine dichromography, since it is our understanding that energies this high have not often been used in the past.

If our request for informal time at SSRL meets with your approval, we propose to keep in touch with your Operation Manager, John Cerino, and others to identify suitable opportunities.

Sincerely yours,

E. Barrie Hughes

E. Barrie Hughes
Spokesman for Proposal SSRL No. 456B

EBH/gs

CC Edward Rubenstein
Robert Hofstadter
William R. Brody
Albert Macovski

0021729

SSRL PROPOSAL REVIEW

RECEIVED
SEP 25 1979
S.S.R.L.

Investigators: Dr. E. Barrie Hughes et al

Proposal Number: R 456B
Second report

Title: "Iodine Dichromography With Monochromatic X-ray Beams for Angiography"

Referred to: Prof. Norman A. Baily
Dept. of Radiology
University of California, San Diego
La Jolla, CA. 92037

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

I have read the rebuttal to the original criticisms of the proposed experiment and I should like to comment on these. First, the fact that expensive installations and equipment have been financed for political reasons in remote installations with benefit to very few of us taxpayers does not validate the expenditure of more funds or expense of machine time to go up yet another blind alley. As for efforts to develop compact sources of monochromatic x-rays, this has been an on-going project at the National Bureau of Standards for quite a number of years and there is no doubt that such a source would be valuable. To date, however, no feasible progress in attaining such a source has occurred. The basic properties of digital iodine K-edge dichromography has certainly been demonstrated. I refer you to the open literature and to the following papers by Kruger and associates*: RADIOLOGY, Oct 1977; SPIE PROCEEDINGS, Nov/Dec 1978; MEDICAL PHYSICS, May/June 1977; RADIOLOGY, Jan 1979; SPIE Vol. 167, 1979. These articles definitely show that it is not impossible but that good quality non-blurred images can be made with quasi-monoenergetic x-ray beams, and further that these beams have sufficient intensity to produce images at a rate of 60/sec, and that the radiation dose delivered to the patient is quite low. While the theoretical argument of scatter radiation and signal to noise is certainly valid, the real effect to be considered here is that the use of a highly collimated detector whose detection efficiency will be quite low compared to the method used in the publications referred to above.

*of the University of Wisconsin.

Norman A Baily
Signature of Referee

0021730

PLEASE CHECK

Overall Desirability	Experimenter Competency
( ) *Excellent*	( ) *Excellent*
( ) *Very Good*	( ) *Very Good*
( ) *Good*	( ) *Good*
( ) *Fair*	( ) *Fair*
( ) *Poor*	( ) *Poor*

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administrator,
SSRL, SLAC Bin 69
P. O. Box 4349
Stanford, CA 94305

Are there technical questions to be answered? ( )yes ( )no
If yes, are they ( ) Essential before approval?
( ) Desirable before approval? Comment on back
Are there safety concerns to be answered? ( )yes ( )no
If yes, please describe on back.

RECEIVED
SEP 13 1979
S. S. R. I.

ADDENDUM TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

Co-Investigators: E. Barrie Hughes
Edward Rubenstein
Robert Hofstadter
William R. Brody
Albert Macovski

W. W. Hansen Laboratories of Physics
and
School of Medicine
Stanford University
Stanford, California 94305

0021731

August 30, 1979

I INTRODUCTION

This addendum was written after the receipt of six anonymous reviews of Proposal 456B. Four of these reviews were totally positive, one raised a minor objection and one was totally negative. The minor objection is easily answered: it relates to the use of only inanimate phantoms and the effects of extra-vascular iodine through diffusion in live specimens. The bulk of this addendum is directed at the issues raised in the negative review. These are (a) the utility of a medical facility for coronary arteriography at SSRL alone, (b) the possibility of later providing similar treatment to patients elsewhere, (c) the feasibility (actually the infeasibility) of coronary arteriography by dichromography with existing quasi-monoenergetic x-ray sources and (d) the mistaken impression that the radiation dose to the patient in dichromography will be increased at SSRL relative to the use of quasi-monoenergetic beams.

II THE RESPONSE

The principal purpose of the studies described in Proposal 456B is without question the development of a safe non-invasive method of coronary arteriography. The current method of assessing the condition of the coronary arteries is highly invasive and carries too much risk, discomfort and expense to be used routinely to recognize significant arterial obstruction in asymptomatic patients at high risk for coronary artery disease. For these reasons the invasive diagnostic procedure is practiced in only about 15% of all hospitals and even in these active centers the associated death and morbidity

0021732

rates are too high for the procedure to be used in a screening way. It is therefore restricted in its use to symptomatic patients already known, with high probability, to be suffering from severe coronary artery disease and in probable need of surgical intervention. Even if a successful development effort of a non-invasive method of coronary arteriography resulted in the operation of a diagnostic clinic for coronary artery studies only at SSRL, the impact on the management of this disease in the local area would be substantial. This clinic would be used in the following major ways:

a) The treatment of patients in probable need of surgical intervention who would otherwise be subjected to the invasive diagnostic procedure. The examination of 20 such patients per day, or $\sim$ 5,000 per year, would prevent 25 deaths and 50 serious injuries each year that would otherwise result from the invasive diagnostic examination alone.

b) The follow-up arteriographic examination of surgical patients in order to assess post-operative progress with no further risk of injury.

c) The study of the natural history of coronary artery disease by serial examinations on patients with no previous evidence of this disease.

In fact, the studies identified in item c) above, if conducted only at SSRL, would provide clinical medicine with a truly unique research opportunity. The SSRL facility would, of course, also provide the opportunities identified in items a) - c) above to physicians and researchers in the other areas of angiography. This may be especially important in cerebral arteriography, which currently also carries major risks of stroke and death during invasive examination, but as stated in Proposal 456B there are many arteries and veins whose angiographic examination is of clinical significance.

0021733

If a development effort at SSRL were to succeed, it is then reasonable to expect that this success would soon result in the establishment of similar research and diagnostic clinics at the other sources of synchrotron radiation, both in the United States and abroad. In February 1978, in the Western hemisphere plus Japan, there were thirteen storage rings either in operation (4), in construction (7) or proposed (2) with circulating beam energies in excess of 1 GeV where such a medical facility would be feasible.

Need higher e⁻ energy to get 33 keV [illegible] should have ~10 keV

$E_c = .0165 B E^2$

$E^2 = \frac{10}{.0165 \times 20} = 3$

$E \geq 1.7$ GeV

Another result of an itial success at SSRL would undoubtedly be the stimulation of a considerable technical effort by physicists and engineers to develop a compact source of monochromatic x-rays expressly for medical purposes. Most certainly this source would not require the full intensity of the beam at SSRL. (This question is addressed briefly in Proposal 456B.) Presently, we believe that the most practical and least expensive method of providing an independent source of monochromatic x-rays for medical purposes is to back-scatter laser photons incoherently off the electrons in a small storage ring. If a powerful carbon dioxide laser is used, the storage ring energy required is only 200 MeV. The principle involved, namely inverse Compton scattering, has been used several times to obtain monochromatic γ-rays in high energy physics. At SLAC, for example, beams of laser light are routinely back-scattered off beams of energetic electrons (5 - 22 GeV) to produce monochromatic γ-rays in the range 2 - 10 GeV. At Frascati, Italy, the Adone storage ring, first built in 1967, is now used in conjunction with a powerful argon-ion laser to provide a strong source of monochromatic γ-rays in the range 10 - 100 MeV for particle physics. It may be expected, therefore, that an initial success in the medical arena at SSRL would stimulate an effort to generate monochromatic x-rays for medical purposes at minimum cost

0021734

by this, or an alternative, method. One alternative, but at present more speculative, method is to back-scatter laser photons (from an argon-ion laser) coherently off an electron beam bunched with a spatial structure equal to, or a sub-harmonic of, the wavelength of the laser light. In this way the x-ray yield can be greatly increased relative to incoherent scattering off unbunched electrons so that a 25 MeV electron microtron can be used instead of a storage ring.

At present we are unable to guarantee that medical studies of the type we project for SSRL will be possible at locations other than those selected originally, for other reasons, as the sites for electron storage rings. Should this be so, this limitation on the geographical distribution of facilities would not be uncommon in medicine. It has not prevented the recent development of the positron annihilation camera in nuclear medicine, which must be located adjacent to a proton accelerator capable of providing the required short-lived radioisotopes of ^{11}C, ^{13}N and ^{15}O. Neither has it prevented the establishment of radiotherapy clinics dependent upon beams of negative pi-mesons, heavy ions and neutrons at the large particle accelerators located in Los Alamos, Berkeley or Chicago, respectively. In fact, given the current world-wide demand for synchrotron radiation facilities and the secure position occupied by electron storage rings in particle physics research, it appears that the opportunities for the establishment of medical facilities employing monochromatic x-rays, but dependent upon machines built for other purposes, will not be nearly as restricted in geographical distribution as they have been for other specialized centers utilizing a unique resource.

0021735

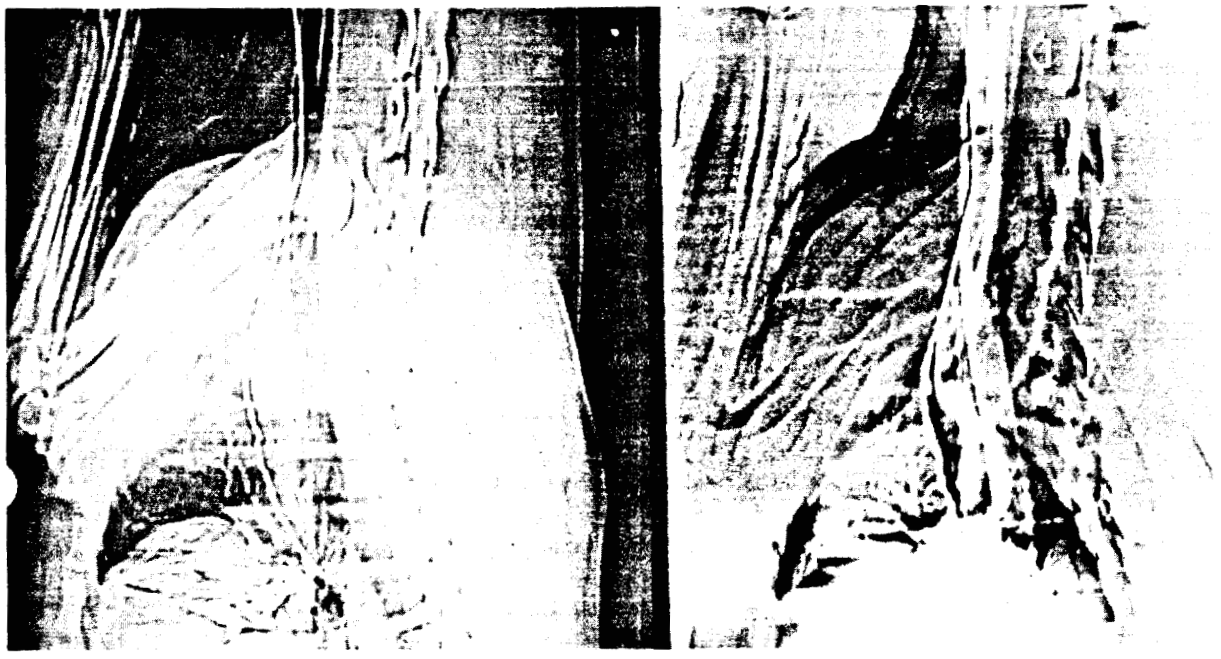
The studies outlined in Proposal 456B comprise a logical first step toward the goal of producing dichromagraphic radiographs of the coronary arteries. The proposal objectives have been deliberately restricted to initial studies with static and inaminate phantoms, in accordance with the stated SSRL preference for short investigations with limited objectives instead of single requests for the study of all questions necessary to achieve a final goal. The limited objective of Proposal 456B is to demonstrate the basic properties of digital iodine K edge dichromography using intense and truly monochromatic x-ray beams before proceeding to the use of more complex phantoms and animate specimens. Certainly, both of the latter will be used in subsequent tests and are immediately avaiable to the experiment team.

Even the limited objectives of Proposal 456B include a study of the visibility of iodinated blood vessels in the presence of extra-vessel background concentrations of iodine. Such backgrounds will indeed occur in animate specimens, but there appears to be no reason why this should preclude arterial examinations if the peripheral venous injection and the x-ray exposures are administered with the proper relative timing. Typically, the radiographs needed for dichromography will be taken on the first or second transits of the injected iodine through the cariovascular system, or within one minute after injection. In contrast, iodine diffusion into the extra-vascular space will occur with a time scale on the order of several minutes and so will not present a major problem. This fact is clearly demonstrated in the photographs below, which show the result of a time subtraction study, by digital

0021736

radiography, of the chest cavity of a dog. The picture on the left, the fast-contrast image, was obtained after the introduction of iodine by catheter, via the superior vena cava, into the right atrium of the heart. An earlier exposure of equal duration, the so-called mask, was also obtained before the introduction of the iodine. The picture on the right is what remains after the mask is subtracted from the post-contrast image. Ideally, it should reveal only the distribution of the con trast agent. Indeed the iodine within the heart, averaged over many cardiac cycles, is clearly seen. The carotid (open arrow) and vertibral (closed arrow) arteries are clearly visualized, as are smaller arteries (to the left) to the forearm and shoulder and even (to the right) iodinated veins. These channels are visible despite their motions during their exposure and are definitely not obscured by any extra-arterial iodine. The incomplete subtractions of the other anatomical structures is due to their non-identical movements during the two exposures.

0021737



Photographs of the chest cavity of a dog obtained during a time subtraction study. On the left is the unsubtracted post-contrast image obtained after the iodine injection. On the right is the difference between the post-contrast image and an earlier exposure, the mask, before the iodine injection.

0021738

While it is true that the feasibility of iodine dichromography using quasi-monoenergetic, or broad-band, beams has already been demonstrated, this does not mean that existing quasi-monoenergetic sources have been used, or indeed can be used, for coronary arteriography. In fact, with conventional x-ray sources this is impossible. The source intensity, after the necessary severe filtration, is totally inadequate. The coronary arteries are not stationary structures. They are in intimate contact with the heart muscle and are therefore in continuous motion. Only a blurred image would result from the use of quasi-monoenergetic x-ray beams. A major advantage of the beam intensity at SSRL is that it is possible to record images fast enough to visualize the coronary arteries in sharp focus. The major arteries, including those not intimately associated with the heart muscle, are involved in a motion of expansion and contraction due to the cardiac cycle and therefore their internal structures are not visible in examinations with quasi-monoenergetic sources. It is likely that the clinical applications of non-invasive procedures with quasi-monoenergetic sources will be restricted to stationary structures, such as the kidneys, gall bladder and thyroid.

The suggestion made by one reviewer of Proposal 456B that the radiation dose delivered to a patient in a dichromographic examination with the monoenergetic x-ray beams at SSRL would substantially exceed that received if quasi-monoenergetic beams are used is most definitely not correct. To the contrary, the radiation dose is minimized through the use of monoenergetic beams because the signal to noise ratio is maximized under these conditions. Moreover, the natural one-dimensional cross sectional profile of the SSRL beam, coupled with the eventual use of a one-dimensional x-ray detector, totally eliminates the problem of scattered radiation that is characteristic of the published technique using quasi-monochromatic x-ray beams. For example, Kelcz et al.[1] has reported that the radiation dose delivered to a patient to achieve a specific

0021739

image contrast is increased by a factor of 25 relative to that needed in the absence of scatter. If a scatter grid is used, the additional dose can be reduced to a factor of about three, but at the expense of a longer exposure time. In all respects the use of monoenergetic beams at SSRL with a matching detector geometry minimizes the radiation dose delivered to a patient in order to achieve a specific signal to noise ratio in the final image using iodine K edge dichromography. The opposite impression received by the one reviewer of Proposal 456B in question could be related to the references made to the work of Ter-Pogossian. In 1956, this author showed that an increased sensitivity to iodine could be obtained if a single quasi-monoenergetic beam at 33 KeV was used instead of a white spectrum of 70 Kvp of radiation. Ter-Pogossian also determined that the use of the softer radiation would cause an increased radiation dose, that this increase was no more than a factor of three for tissue thicknesses up to 20 gm cm^{-2}, and that this increase was well within safe limits. His work in no way relates to the relative radiation dose received in iodine K edge dichromography using, on the one hand, quasi-monoenergetic beams of large linewidth and large energy separation and, on the other hand, truly monochromatic beams with energies immediately adjacent to the iodine K edge.

III SUMMARY

The major advantages that the x-ray beams at SSRL bring to arteriography are as follows:

a) The monochromaticity of the beams maximizes the sensivity to intra-arterial iodine and permits the use of peripheral venous injection.

b) The intensity of the beams permits short exposure times and allows images to be recorded in sharp focus despite the arterial motions associated with the cardiac cycle.

0021740

c) The monochromaticity of the two beams and their very small energy spacing virtually eliminates background signals due to tissue and bone thickness variations.

d) The increased sensitivity to iodine allows the injected concentration of iodine to be reduced, and permits multiple serial injections in a single patient examination.

0021741

REFERENCES

(1) Kelcz, F. and Mistretta, C.A., "Absorption Edge Fluoroscopy Using a Three-Spectrum Technique," Medical Physics 3, 159 (1976).

0021742

SSRL PROPOSAL REVIEW

RECEIVED
AUG 15 1979
S. S. R. L.

Proposal Number 456B

Investigators: Dr. E. Barrie Hughes

Title: "Iodine Dichromography With Monochromatic X-ray Beams For Angiography"

Referred to: Professor Melvin L. Griem
Department of Radiology
University of Chicago
Chicago, Illinois 60637

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

Dr. John Cameron, Director Medical Physics, University of Wisconsin, Madison, Wisconsin, and his colleagues have investigated two-wavelength and three-wavelength techniques for diagnostic imaging using x-rays. The ability to resolve the location of iodine as a contrast agent in the heart to image vascular disease is an extremely sound one. As pointed out, the magnitude of the problem, cardiovascular disease, represents the #1 cause of death in the United States. On page 3 and page 4 of the proposal, the flux of the monochromatic x-ray photons available is described and the methods of detection. Using a crystal detector is described on page 5. The phantoms and methods of testing are also described and straightforward. In my opinion, this is a well designed experiment and proposal which will yield important preclinical information which will ultimately help in detecting and localizing vascular lesions. With such localization, newly developed nonsurgical intravascular techniques have been developed by the Swedish radiologists for the treatment of narrowed and occluded vessels.

0021143

(over)

Signature of Referee

PLEASE CHECK

Overall Desirability	Experimenter Compentency
( ) Excellent	(X) Excellent
(X) Very Good	( ) Very Good
( ) Good	( ) Good
( ) Fair	( ) Fair
( ) Poor	( ) Poor

Are there technical questions to be answered? ( )yes( ) no
If yes, are they ( ) Essential before approval?
( ) Desirable? Comment on back

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administration
SSRL, SLAC Bin 69
P.O. Box 4349
Stanford, CA 94305

I would suggest you seek a second opinion from Dr. John Cameron, University of Wisconsin. I will also seek opinions from Dr. Kunio Doi, Professor of Radiology, University of Chicago. If his opinion is significantly different than mine, I will have him write you directly.

0021744

cc: Katherine
10/29/79

STANFORD UNIVERSITY MEDICAL CENTER
300 PASTEUR DRIVE, STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Surgery
Division of Neurosurgery
John W. Hanbery, M.D., Professor and Executive Head
(415) 497-5572
Gerald D. Silverberg, M.D., Assistant Professor
(415) 497-5574
Frances K. Conley, M.D., Assistant Professor
(415) 497-5575 or 497-5839
Richard H. Britt, M.D., Ph.D.
Clinical Assistant Professor
(415) 497-5575

RECEIVED
OCT 29 1979
S.S.R.L. Office of the Director

October 19, 1979

Professor I. Bienenstock
SSRL, SLAC Bin 69

Dear Dr. Bienenstock:

I am sending you the following letter in support of the proposal (#456B) "A Study of Iodine Dichromography with Monochromatic X-ray Beams for Angiography". Dr. Edward Rubinstein and one of his co-workers have reviewed all of this with me.

The purpose of this letter is to tell you that should such a study prove that it would be feasible to obtain diagnostic cerebral arteriographic studies following intravenous injection of contrast material that this would be a tremendous advance in diagnostic neuroradiology with immediate and wide-spread clinical application. This would provide one further non-invasive technique in screening patients with a wide variety of clinical problems. Hospitalization would not be required for such a study with the obvious financial saving to the patient and third party carriers. This type of study would also be considerably safer than conventional cerebral arteriography which, while we consider it relatively safe, still carries with it a certain percentage of morbidity and mortality.

The technique would be especially useful in the diagnosis of cerebral vascular disorders, including stroke, aneurysms, and arteriovenous malformations. It would also be useful in patients with brain tumors and brain abscess. It would be extremely useful in selected cases of head injury.

The importance of this technique, if successful, would be immediate and enormous on the clinical practice of neurology and neurosurgery.

Yours sincerely,

JOHN W. HANBERY, M.D.
JWH:gc

0021745

SSRL PROPOSAL REVIEW

RECEIVED
AUG 6 1979
S. S. R. L.

Investigators: Dr. E. Barrie Hughes et al

Proposal Number 456B X

Title: "Iodine Dichromography With Monochromatic X-ray Beams For Angiography"

Referred to:
Dr. Norman Zheutlin
Chairman, Dept. of Radiology
Cedars-Sinai Medical Center
8700 Beverly Boulevard
Los Angeles, CA. 90048

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

The project has merit and the non-invasive study should be explored to its fullest.

0021746

Signature of Referee

PLEASE CHECK

Overall Desirability	Experimenter Compentency
( ) Excellent	( ) Excellent
(✓) Very Good	(✓) Very Good
( ) Good	( ) Good
( ) Fair	( ) Fair
( ) Poor	( ) Poor

Are there technical questions to be answered? ( )yes( ) no
If yes, are they ( ) Essential before approval?
( ) Desirable? Comment on back

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administration
SSRL, SLAC Bin 69
P.O. Box 4349
Stanford, CA 94305

SSRL PROPOSAL REVIEW

RECEIVED
JUL 25 1979
S. S. R. L.

Investigators: Dr. E. Barrie Hughes et al

Proposal Number 456B

Title: "Iodine Dichromography With Monochromatic X-ray Beams For Angiography"

Referred to: Dr R. E. Long
Kaiser-Sunset Hospital
4867 Sunset Boulevard
Los Angeles, CA. 90027

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

The proposed research could eventually lead to considerable improvement and advancement in clinical diagnostic radiology techniques. The proposal is well thought out and suggests a very appropriate use of research resources.

If this research proposal is accepted, I would appreciate a copy of the resulting research reports when they are released.

Robert C Long PhD, MD
Signature of Referee

Radiology Dept
Kaiser Sunset Hospital
1505 N. Edgemont Ave
Los Angeles CA 90027

PLEASE CHECK

Overall Desirability	Experimenter Compentency
( ) Excellent	( ) Excellent
(X) Very Good	(X) Very Good
( ) Good	( ) Good
( ) Fair	( ) Fair
( ) Poor	( ) Poor

Are there technical questions to be answered? ( )yes (X) no
If yes, are they ( ) Essential before approval?
( ) Desirable? Comment on back

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administration
SSRL, SLAC Bin 69
P.O. Box 4349
Stanford, CA 94305

(over)

0021741

SSRL PROPOSAL REVIEW

RECEIVED
JUL 23 1979
S. S. R. L.

Proposal Number 456B

Investigators: Dr. E. Barrie Hughes et al

Title: "Iodine Dichromography With Monochromatic X-ray Beams For Angiography"

Referred to: Professor Norman A. Baily
Department of Radiology
University of California, San Diego
La Jolla, CA. 92037

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

This is a completely impractical proposal. As the authors correctly point out angiographic procedures are done routinely in all radiology departments. In order to affect even a small fraction of the practice of radiology large numbers of sources capable ofperforming as well as SSRL's beam would be required. By no stretch of the imagination does the proposed use of the SSRL beam offer an improvement in present diagnostic capabilities to warrant the expenditure of many billions of dollars to establish such facilities. This reviewer therefore feels that the experiment is a waste of valuable beam time since even if the most optimistic predictions of sensitivity were achieved no application of the technique can be expected.

No new knowledge will result from the proposed experiment. Results will only apply to their experimental set-up and will not be generally applicable because of geometric and patient variables. Further, the results obtained using quasi-monoenergetic sources in an identical fashion to that proposed, show that the method is feasible. Therefore, even in this sense the experiment proposed is valueless. Using these much poorer sources, good results using peripheral venous injection have been reported with much lower patient doses than would be required with the proposed technique. Such additional exposure with its attendant risks would negate the benefits gained from the slight reduction in contrast agent concentration possible using the SSRL in comparison to that presently used (peripheral infection) with filtered quasi-monoenergetic sources.

Norman A. Baily
Signature of Referee

0021148

PLEASE CHECK

Overall Desirability	Experimenter Compentency
( ) Excellent	( ) Excellent
( ) Very Good	( ) Very Good
( ) Good	( ) Good
( ) Fair	( ) Fair
(✓) Poor	(✓) Poor

Are there technical questions to be answered? ( )yes( ) no
If yes, are they ( ) Essential before approval?
( ) Desirable? Comment on back

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administration
SSRL, SLAC Bin 69
P.O. Box 4349
Stanford, CA 94305

SSRL PROPOSAL REVIEW

RECEIVED
JUL 23 1979
S. S. R. L.

Proposal Number 456B

Investigators: Dr. E. Barrie Hughes et al

Title: "Iodine Dichromography With Monochromatic X-ray Beams For Angiography"

Referred to: Dr. Robert F. Foran
705 N. Elm Drive
Beverly Hills, CA. 90210

Evaluation: (If you can suggest other qualified referees, their names and institutions would be gratefully accepted along with your review)

This intriguing proposal would seem to have very good potential for producing significant new fundamental data and knowlege. Synchrotron radiation would definitely be needed for the project.

The investigators are entirely unknown to me; I cannot evaluate their competency for accomplishing the project.

For additional opinions, I suggest you contact any or all of the following, listed in order of preference:

Norman Zheutlin, M.D., Chairman, Dept. of Radiology, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, Calif. 90048.
Peter Julien, M.D., Dept. of Radiology, Cedars-Sinai Medical Center
Ran Vas, Ph.D., Director of Biophysics, Dept. of Cardiology, Cedars-Sinai Medical Center
Stephen Halpern, M.D., c/o Non-Invasive Laboratory, Dept. of Cardiology, Cedars-Sinai Med. Center
Neal Buchbinder, M.D., c/o Cardiac Catheterization Lab., Dept. of Cardiology, Cedars-Sinai Med. Center, 8700 Beverly Blvd., Los Angeles, Calif. 90048.

Robert Foran MD
Signature of Referee

PLEASE CHECK

Overall Desirability	Experimenter Compentency (X) SEE ABOVE
( ) Excellent	( ) Excellent
(X) Very Good	(?) Very Good
( ) Good	( ) Good
( ) Fair	( ) Fair
( ) Poor	( ) Poor

Are there technical questions to be answered? (X) yes ( ) no
If yes, are they ( ) Essential before approval?
(X) Desirable? Comment on back

To be fair to the experimenter return within ten days to:
Katherine Cantwell, Proposal Administration
SSRL, SLAC Bin 69
P.O. Box 4349
Stanford, CA 94305

(over)

0021149

I strongly question the advisability or validity of using inanimate phantoms for this project. Background noise signals from tissue and compartment diffusion of the iodinated contrast agent will constitute a major stumbling block for similar investigations in moving models or living subjects. I have serious doubt that direct application of this technique to clinical angiography will result.

0021750

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

July 6, 1979

RECEIVED
JUL 16 1979
S. S. R. L.

Dr. Charles Cantor
Dept. of Chemistry
Columbia University
Box 608, Havenmeyer
New York, New York 10027

Dear Dr. Cantor:

We have just received this biology proposal and are anxious to have it reviewed. Could you please suggest two referees. 456B

1. Melvin L. Griem, Professor
   Department of Radiology
   University of Chicago, Chicago, Il 60637
2. Norman A Baily, Professor
   Department of Radiology
   UCSD La Jolla Calif 92037

Thank you for your attention to this matter.

Sincerely,

Katherine ← TP

Katherine Cantwell
Proposal Administrator

KC/cb Katherine- these names are just wild guesses- you might also try calling the following individuals to see if they will do it or can suggest others:
John Ainsworth, Div'n of Biology and Medicine, Lawrence Berkeley Lab.
Karen K.W. Fu, Department of Radiology, UCSF.
My own naive impression is that this is an outstanding proposal and should be given time as soon as possible but I have to caution that I am really naive when it comes to straight medical applications like this one.

0021751

STANFORD SYNCHROTRON RADIATION LABORATORY

STANFORD LINEAR ACCELERATOR CENTER
P.O. Box 4349, Bin 69
Stanford, California 94305
Telephone: (415) 854-3300, Ext. 2874
TWX: 910-373-1162
Answer Back: STANFRD
STNU A

July 5, 1979

Dr. E. Barrie Hughes
W.W. Hansen Laboratories of Physics
H.E. - 112
Stanford University
Stanford, California 94305

Dear Dr. Hughes:

We have received your proposal entitled "Iodine Dichromography With Monochromatic X-Ray Beams For Angiography". It has been assigned # 456B.

The Proposal Review Panel met June 7th and will not meet again until January, at which time Proposal 456B will be rated. The earliest you will be eligible for beam time is next January.

If you have additional proposals, we will be pleased to receive them.

Sincerely yours,

Katherine Cantwell

Katherine Cantwell
Proposal Administrator

KC/cb

0021752

4563

DATE: May 2, 1979

TO : A. Bienenstock

FROM : H. Winick HW

SUBJECT: Letter of Intent for Hughes, Rubenstein and Hofstadter

Enclosed is a letter of intent given to me today by Barrie Hughes.

I think this is potentially very exciting and important work. I conveyed this reaction to Hughes, but also explained how difficult it will be to assign high energy time until he submits a full proposal.

Let's discuss.

HW:jm
cc: K. Cantwell

0021753

STANFORD UNIVERSITY • OFFICE MEMORANDUM • STANFORD UNIVERSITY • OFFICE MEMORANDUM • STANFORD UNIVERSITY • OFFICE MEMORANDUM

W. W. HANSEN LABORATORIES OF PHYSICS
STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

Edward L. Ginzton Laboratory
High Energy Physics Laboratory

Telephone (415) 497-0135

1 May 1979

Dr. H. Winick, Deputy Director
Stanford Synchrotron Radiation Laboratory

Dear Dr. Winick:

We are writing this Letter of Intent because we believe that the x-ray beams available at SPEAR, and later at PEP, may have invaluable medical applications. At this time, our interest centers on the development of a non-invasive method of coronary arteriography based on the use of monochromatic x-ray beams at energies close to the K absorption edge of iodine. The technique that we advocate is not new. It has been discussed in the literature and even explored in a preliminary way several years ago at SSRL. Nevertheless, at the present time the principle involved is essentially unexploited and the opportunity provided by SSRL for a successful development effort is being ignored. We intend to propose an experimental test of this technique at SSRL. Inevitably, the preparation of the detailed proposal and the acquisition of the appropriate apparatus will take some time. While these prepatory steps are underway we hope to make some progress by conducting development tests with apparatus already in hand. This we would like to do in the Fall of 1979. Therefore, we would like to explore the possibility of such tests with you at an early date.

The motivation for the studies we will propose is easy to understand. Premature coronary artery disease is the major health problem in the United States today. Approximately 500,000 persons die each year from disease of the coronary arteries and many more suffer heart attacks and consequent heart damage. Approximately 50% of all deaths are cardiovascular in origin and one-fourth of all these patients are under 65 years

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Continued

of age. Many of these deaths and serious injuries could be prevented by surgery if a practical screening procedure existed. It is not surprising therefore that coronary artery examinations are increasing annually at a rate of about 20% and that 500,000 were performed last year in the United States alone. The standard procedure for performing coronary arteriography requires catheterization of the artery in question and the injection, by this means, of a concentrated solution of an iodinated organic compound immediately prior to the x-ray examination. This is an highly invasive procedure and carries too much risk to be used in a screening way. It is also too expensive, since it typically requires admission to the hospital for two nights. The catheterization and subsequent rapid intravascular injection of the concentrated contrast medium used in coronary arteriography have associated death and morbidity rates today of 0.5 and 1% respectively. These are much too high to permit arteriography to be used routinely to recognize persons with significant obstruction of the coronary arteries. The cost of each such examination performed today is approximately $2,000, or about $500 million nationwide. There is, therefore, an urgent need to reduce both the risk and the cost of coronary arteriography.

The method we have in mind is familiar to you. It was the subject of Proposal No. 82 at SSRL and is referred to as dichromography. It involves the acquisition of digital radiographs at x-ray energies slightly above and slightly below that of the K absorption edge in iodine at 33.2 KeV and the subsequent subtraction of these two images to achieve maximum contrast in the visualization of the intra-arterial iodine. Estimates suggest that this technique may achieve a sensitivity to iodine on the order of 10^2 - 10^3 times greater than that achieved in present radiological practice. The exact figure will depend on the efficiency of the x-ray detector, which should be as large as possible. If this enhancement is realizable it offers the prospect of coronary arteriography by venous injection and with reduced concentrations of the iodinated compounds. This would eliminate the need for catheterization and substantially reduce both the risk and the cost of the procedure. We estimate that the cost might be on the order of $125.

0021755

Continued

The tests that we would like to do with minimum delay can be done with equipment that is essentially already in hand, but we would like to go immediately to the energy of the K edge in iodine. The initial x-ray detector could be, for example, a single small crystal of bismuth germinate, collimated in order to achieve the necessary fine spatial resolution, and mounted so that it can be automatically scanned through the horizontal width of the beam. The output would be integrated so that the detector could operate without count-rate limitations and the results would be immediately available through the use of an on-line data acquisition minicomputer. Subsequent tests, and the experiment itself, would be done with a real-time radiographic device based on the digital integration of the output of a television camera.

Coronary arteriography is but one of a large number of applications that could benefit from the dichromographic technique. Cerebral arteriography currently carries major risks of stroke and death as a result of the invasion of the root vessels to the brain. In fact, any artery of importance could be studied by this non-invasive means. Neoplasms also exhibit a degree of abnormal and characteristic vascularity. Currently their investigation requires selective arteriograms involving catheterization of the vessels feeding them. Often this is technically impossible and presupposes a knowledge of the presence and location of the neoplasm.

We feel that our proposed study could be of very great benefit in the treatment and prevention of morbidity and death due to a major group of health problems. We intend to submit a detailed proposal to SSRL, but hope to be able to conduct meaningful tests at SSRL in the interim.

Yours sincerely,

E. Barrie Hughes

E. Barrie Hughes
Senior Research Associate

Edward Rubenstein

Edward Rubenstein, M.D.
Associate Dean for Post Graduate Medical Education, and
Professor of Clinical Medicine

EBH/ER/gs

Continued

0021756

Robert Hofstadter

Robert Hofstadter
Max H. Stein Professor of Physics

0021757

PROPOSAL NO._____

Please give a brief a ract of the proposal. Try to nfine yourself to this page.

TITLE: IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

SPOKESPERSON: E. Barrie Hughes

ABSTRACT:

The purpose of this proposal is to demonstrate the value of synchrotron radiation in a specific area of diagnostic radiology. This area, in which our interest centers at this time, concerns the development of a non-invasive method of coronary angiography based on the use of monochromatic x-ray beams at energies close to the K absorption edge of iodine. All other development efforts, with the exception of a preliminary investigation at SSRL, have employed standard commercial x-ray generators and, in consequence, have suffered from the lack of truly monochromatic x-ray beams of adequate intensity. The specific motivation for the proposed studies is an urgent need to reduce both the risk and the cost of coronary arteriography. The proposed method is referred to as dichromography. It involves the acquisition of digital radiographs at x-ray energies slightly above and below that of the K absorption edge in iodine at 33.2 KeV and the subsequent subtraction of these two images to achieve maximum contrast in the visualization of the intra-arterial iodine. Estimates suggest that this technique, at SSRL, may achieve a sensitivity to iodine on the order of 100 - 500 times greater than that achieved in present radiological practice. This proposal calls for the performance of certain tests with minimum delay and with equipment that is already essentially in hand. One-dimensional digital radiographs of inaminate phantoms will be obtained to explore the ultimate sensitivity of dichromography to iodine concentration and other related questions. Future work, based on the success of the presently proposed tests, will employ a real-time radiographic device based on the digital integration of the output of an appropriate x-ray sensor.

0021758

Introduction

Angiography, the radiologic visualization of blood vessels containing contrast media, has become a powerful method of diagnosing disorders involving the circulation of the heart, of the brain, and of other vascular beds. The method provides information not otherwise available. However, the techniques currently in use involve invasive procedures which carry significant risks of morbidity and of mortality. These limitations, together with the high dollar cost of the procedures, have prevented their more widespread use. This is especially true in coronary arteriography, which might otherwise be employed as a screening procedure in certain high-risk populations.

For these reasons we propose a study of the use of the brilliant monochromatic x-ray source at SSRL in non-invasive angiography based on a dichromographic approach. Since the writing of the original Letter of Intent to SSRL on May 1, 1979 (see attachment), Professors William R. Brody and Albert Macovski of the Department of Radiology of the School of Medicine and of the Department of Electrical Engineering at Stanford University have agreed to join the authors of that Letter as members of the experiment team. The research interest of Drs. Brody and Macovski include the development of non-invasive methods of arteriography, which they are actively pursuing in their own laboratory. We expect that the proposed investigation at SSRL, and subsequent work, will benefit significantly from the advice and involvement of these researchers.

0021759

A. Description of Experiment

The purpose of this proposal is to demonstrate the value of synchrotron radiation in angiography. Within this area of diagnostic radiology, our specific interest at this time is centered on the development of a non-invasive method of coronary angiography based on the use of monochromatic x-ray beams at energies close to the K absorption edge of iodine. The principle involved is not new. It was first mentioned in the radiological literature by Jacobson in 1953[1] and in recent years has received most attention from Mistretta and his colleagues at the University of Wisconscin[2-5]. All development efforts however have employed standard commercial x-ray generators and, in consequence, have suffered from the lack of truly monochromatic x-ray beams of adequate intensity. A preliminary investigation was undertaken several years ago at SSRL, using the K absorption edge in copper, but was not pursued[6]. At the present time the principle involved is essentially unexploited and the opportunity provided by SSRL for a successful development effort is being ignored.

One specific motivation for the studies we propose is easy to understand. Premature heart disease is the major health problem in the United States today. Approximately 500,000 persons die each year from disease of the coronary arteries and many more suffer heart attacks and consequent heart damage. Approximately 50% of all deaths are cardiovascular in origin and one-fourth of all these patients are under 65 years of age. Many of these deaths and much of the morbidity could be prevented by surgery if a practical screening procedure existed. It is not surprising therefore that coronary artery examina-

0021760

tions are increasing annually at a rate of about 20% and that 500,000 were performed last year in the United States alone. The standard procedure for performing coronary arteriography requires catheterization of the artery in question and the injection, by this means, of a concentrated solution of an iodinated organic compound immediately prior to the x-ray examination. This is a highly invasive procedure and carries too much risk to be used in a screening way. It is also too expensive, since it typically requires admission to the hospital for two nights. The catheterization and subsequent rapid intravascular injection of the concentrated contrast medium used in coronary arteriography have associated death and morbidity rates today of 0.5 and 1.0% respectively. These are much too high to permit arteriography to be used routinely to recognize persons with significant obstruction of the coronary arteries. The cost of each such examination performed today is approximately $2,000 or about $1,000 million nationwide. There is, therefore an urgent need to reduce both the risk and the cost of coronary arteriography.

The method we propose is referred to as dichromography. Optimally, it involves the acquisition of digital radiographs at x-ray energies slightly above and below that of the K absorption edge in iodine at 33.2 KeV and the subsequent subtraction of these two images to achieve maximum contrast in the visualization of the intra-arterial iodine. Estimates suggest that this technique, at SSRL, may achieve a sensitivity to iodine on the order of 100 - 500 times greater than that achieved in present radiological practice[7]. The exact figure depends on the efficiency of the x-ray detector, which should be as large as possible. If this enhancement is realizable, it offers the

0021761

prospect of coronary arteriography by peripheral venous injection and therefore with reduced concentration of iodinated compounds in the coronary arteries. This would eliminate the need for catheterization and substantially reduce both the risk and the cost of the procedure. The radiation dose incurred by the patient through the use of monocromatic x-rays is increased relative to the use of the typical continuous spectrum of higher mean energy, but is well within the limits of safety. For example, a study by Ter-Pogossian[8] shows that the increase, relative to the use of 70 KVp x-rays, is no more than a factor of three for patient thicknesses up to 20 gm cm^{-2} if the detector response, unlike film, is proportional to the transmitted x-ray intensity.

It has long been recognized that information about the elemental composition of an object can be obtained from the comparison of radiographs taken with different incident x-ray energy spectra[9], or from the measurement of changes in a transmitted x-ray spectrum[10]. Dichromography, by means of which the radiographic sensitivity to iodine is greatly increased, is a special illustration of this principle. It takes advantage of the sharp discontinuity in the x-ray absorption coefficient at the K edge, which in iodine occurs at the relatively high energy of 33.2 KeV. Attempts to implement this idea have been made, but never with monochromatic x-ray beams of the linewidth ($\sim$ 1 eV) and intensity that SSRL provides. Instead, recent investigators have used heavy filtration (90 - 95%) of beams from standard x-ray generators to obtain quasi-monochromatic beams of substantial linewidth ($\sim$ 5000 eV) and limited intensity. In this way they have demonstrated[2] a sensitivity to iodine concentrations as low as $\sim$ 1 mg cm^{-2}. This is already a substantial achievement but has required a considerable effort. The principal complexity, in consequence of the large linewidth and large separation ($\sim$ 10,000 eV) between the peak energies of the two quasi-monoenergetic beams, is the background difference signal due

0021762

to variations in tissue and bone thickness along the possible trajectories through the specimen. Using only two quasi-monoenergetic beams, these difference signals can easily overwhelm the iodine signal and limit the specimens to tissue thickness variations of less than $\sim$ 1 cm and to essentially bone-free regions. A sensitivity to iodine of $\sim$ 1 mg cm^{-2} in the presence of tissue and bone variations of $\sim$ 10 gm cm^{-2} and 2 gm cm^{-2} was achieved only by the use of three quasi-monochromatic beams, each of which required a different filter and a different terminal voltage and current for the x-ray generator[3]. This is a complex procedure, time-consuming, and in need of optimization for each clinical problem.

Clearly, the ideal approach to iodine dichromography is to use two monochromatic x-ray beams, both immediately adjacent to the K absorption edge but one with energy above and one with energy below this edge. In this way the difference signals due to tissue and bone variations are enormously suppressed. For a linewidth of $\sim$ 1 ev and a spacing of $\sim$ 5 eV between the two beam energies, the tissue and bone difference signals are $\sim 5 \times 10^{-2}$%/gm cm^{-2} and 7×10^{-4}%/gm cm^{-} respectively, whereas the iodine difference signal is $\sim$ 3%/mg cm^{-2}. The detectability of iodine difference signals on the order of this size, or less, now depends upon the stability of the x-ray beam intensity and upon the stability and uniformity of the x-ray detector efficiency. At SSRL the stability of the x-ray beam intensity should be excellent. The systematic variation due to the decay of the circulating electron current is not only predictable, but also slow enough to be negligible during the small time required for each exposure. The problem of stability in the detector efficiency is also minimized by the high intensity of the x-ray beams at SSRL. For example, for a stored currentof 30 mA and a beam energy of 3.5 GeV, each detector pixel in a line exposure, $\sim$ 1 mm x 1 mm, will receive $\sim 10^4$ monochromatic x-ray photons in about

0021763

10 μsec. Even if the detection efficiency is only ∿ 1%, it requires only ∿ 1 msec to record this intensity to an accuracy of 1%. The ultimate sensitivity will probably be determined by the residual variations in detector efficiency from pixel to pixel, which it will be important to minimize. No matter what form the detection apparatus takes, it is also clear that the radiographs must be acquired in digital fashion. This will eliminate normalization problems in subtraction, and permit the manipulation, enhancement and display of the difference image in the most appropriate way.

This proposal, to demonstrate the value of monochromatic beams in iodine dichromography, calls for us to perform certain tests with minimum delay and with equipment that is already essentially in hand. The initial x-ray detector will be a single crystal of bismuth germanate, collimated in order to achieve the necessary fine spatial resolution and mounted so that it can be automatically scanned through the horizontal width of the beam. The output will be integrated so that the detector can operate without count-rate limitations and the results will be immediately available through the use of an on-line data acquisition minicomputer. The rudimentary one-dimensional radiographs that we will obtain will therefore be in digital form, in keeping with the methodology that we envision for future work. Future work, based on the success of the presently proposed tests, will employ a real-time radiographic device based on the digital integration of the output of an appropriate x-ray sensor.

The samples that we will use in the presently proposed tests will consist entirely of inaminate phantoms. These phantoms will be designed:

1) to explore the ultimate sensitivity of dichromography to iodine concentration,

2) to demonstrate the suppression of difference signals due to tissue (lucite and water) and bone thickness variations,

0021764

3) to explore the visibility of channels (simulated blood vessels) of various diameters as a function of the iodine concentration within the channel.

and 4) to explore the visibility of iodinated channels in the presence of extra-channel background concentrations of iodine.

The iodine contrast agents that we will employ will be chosen from those in common use today in clinical angiography.

Coronary arteriography is but one of a large number of medical problems that could benefit from the dichromagraphic technique. Cerebral arteriography currently carries major risks of stroke and death as a result of the invasion of the root vessels of the brain. In fact, many arteries and veins of clinical significance could be studied by this non-invasive means. Neoplasms also exhibit a degree of abnormal and characteristic vascularity. Currently their investigation requires selective arteriograms involving catheterization of the vessels feeding them. Often this is technically impossible and presupposes a knowledge of the presence and location of the neoplasms.

We feel that our proposed study could be of very great benefit in the prevention and treatment of morbidity and death due to a major group of health problems. Presently unforseen applications of monochromatic x-ray beams, not necessarily limited to those with energies adjacent to the K absorption edge of iodine (or even to dichromography), may be stimulated by our work. We are also conscious of the efforts elsewhere to apply iodine dichromography to computerized tomography (C.T.)[11]. It may be that the one-dimensional character of the x-ray beams at SSRL is naturally suited to the planar scanning requirement of CT. We are also undeterred by the present availability of intense monochromatic x-ray beams only at laboratories, such as SSRL, located adjacent to a high energy electron storage ring. We feel that medical procedures may be developed at SSRL,

0021765

or at other such laboratories, whose intrinsic value may outweigh this limitation. We are also conscious of the potential use of PEP as a source of readily available x-ray beams. Moreover, we feel that there is a future potential for producing intense monochromatic x-ray beams for medical purposes in machines smaller than SPEAR. These machines may be either single beam storage rings optimized in size and performance for medical applications, or perhaps based upon the interaction of high power laser radiation with intense currents of electrons in small storage rings.

B. Experimental Equipment

The preferred beam line and station for the proposed study is the rapidly-tunable hard x-ray beam designed IV-1 (wiggler). An alternative beam line is that designated I-5. The former is preferred because of its ability to provide a larger flux of x-rays close to 33.2 KeV. Beam energies adjacent to the K edge of iodine will be required.

The experimental apparatus and control equipment will be supplied by the High energy Physics Laboratory (HEPL) at Stanford and will be thoroughly tested before delivery to SSRL. The detector itself will occupy a volume no larger than 24-in. x 24-in. x 24-in. and the associated electronics will be contained in two standard racks.

C. Equipment Delivery Schedule

The experimental equipment will be ready for delivery to SSRL by September 1, 1979. The x-ray detector, associated electronics and control computer are already in hand. All that remains to be done is to construct the mount for the detector and the mechanical device that will allow the detector, or the specimens, to be moved through the x-ray beam in two orthogonal directions under computer control. These tasks, and the necessary software development, will be done during the summer months of 1979.

0021166

D. Previous Experience with the Techniques and Facility

The detector, the associated electronics and the minicomputer that will be used in this study have all been used previously by two members of the experiment team. These individuals have recently built and tested, at SLAC, a γ-ray detector containing close to 200 bismuth germanate crystal elements, each 5 mm x 5 mm x 40 mm. They have also developed an electronic integration module for use with NaI(Tℓ) crystals, and have recently used 49 channels of this circuitry in extensive tests, at SLAC, of a modular array of 49 NaI(Tℓ) modules, each 2½-in. x 2½-in. x 20 in. Minicomputers very similar to that proposed for use at SSRL were used in the performance of both of the above tests. These individuals also have extensive experience in experimental particle physics and have successfully completed major experimental programs at several particle accelerators, including SLAC. In particular, they have been involved in the high energy physics program at SPEAR since the storage ring became operational in late 1972 and are responsible for the precision tests of quantum electrodynamics that have been conducted at SPEAR, as well as several other investigations in the physics of e^+e^- collisions at high energies.

The iodine contrast media and standard medical phantoms are readily available to other members of the experiment team, while specialized phantoms can easily be constructed at HEPL.

0021767

E. Safety Concerns

There are no hazardous materials associated with this study. It may be necessary to use a low energy radioactive source in the test or calibration of our apparatus, but these are readily available at both SLAC and HEPL.

F. Beam Time Required

There are four separable questions of interest in this study; these are listed in Section A. After the initial check-out of the apparatus and procedures in the x-ray beam, which may require four shifts, we estimate that the exploration of each of the four questions of interest may also occupy about four shifts. The total time estimate is, therefore, 20 shifts, to which we should add a contingency of 10 shifts for the usual unpredictable problems. The overall time estimate is therefore 30 shifts, which should be delivered in blocks of between 3 - 4 shifts at a time.

G. Data Analysis Requirements

We intend to analyze the data from this study with the minicomputer that will be used to acquire the data. This computer is a DEC LS1-11 system with a fortran compiler and a memory capacity of 30 kilobits. Any analysis that we find to be more appropriate for a larger computer will be done either on the SLAC or campus computers at our own expense.

0021768

REFERENCES

(1) Jacobson, B., "Dichromatic Absorption Radiography: Dichromography," Acta Radiologica 39, 437 (1953).

(2) Mistretta, C.A., Ort, M.G., Kelcz, F., Cameron, J.R., Sieband, M.P. and Crummy, A.B., "Absorption Edge Fluoroscopy Using Quasi-Monoenergetic X-ray Beams," Invest. Radiol. 8, 402 (1973).

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(5) Kruger, R.A., Mistretta, C.A., Crummy, A.B., Sackett, J.F., Goodsitt, M.M., Riederer, S.J., Houk, T.L., Shaw, C-G and Fleming, D., "Digital K edge Subtraction Radiography," Radiology 125, 242 (1977).

(6) Chu, G., Doniach, S., Hastings, J., Marshall, B., Salsburg, B. and Freeman, W., "Dichromography: An Application of Synchrotron Radiation to Medical Diagnostic Radiology," Stanford Synchrotron Radiation Laboratory: Proposal No. 82, 1976.

(7) Doniach, S, and Pierce, D., "The Uses of Synchrotron Radiation for Medical Diagnostics," Stanford-SLAC Synchrotron Radiation Laboratory Report No. 1 (unpublished), 1971.

(8) Ter-Pogossian, M., "Monochromatic Roentgen Rays in Contrast Media Roentgenography," Acta Radiol. 45, 313 (1956).

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(9) Jacobson, B., "X-ray Spectrophometry in Vivo," Am. J. Roentgenol., Rad. Therapy and Nuclear Med. 91, 202 (1964).

(10) Alvarez, R.E. and Macovski, A., "Energy-selective Reconstructions in X-ray Computerized Tomography," Phys. Med. and Biol. 21, 733 (1976).

(11) Riederer, S.J. and Mistretta, C.A., "Selective Iodine Imaging Using K Edge Energies in Computerized X-ray Tomography," Medical Physics 4, 464 (1977).

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(This form must be submitted with every SSRL Proposal)

This proposal is a new proposal (X) or a replacement ( ) for proposal No._____.

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_____ X-ray-materials & chemistry _____ VUV X X-ray-biology

456B

DATE RECEIVED: RECEIVED JUL 5 1979 S.S.R.L.

To be filled in at SSRL

1. TITLE (less than 10 words)

IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

2. List of Collaborators (underline spokesperson)

Name	Full Address	Telephone Numbers Office	Home
E. Barrie Hughes	W. W. Hansen Laboratories of Physics H. E-112 Stanford U.	497-0135	368-2771
Edward Rubenstein	Stanford U. Med. Center; Dept. of Medicine	497-7188	342-1888
Robert Hofstadter	Physics Department	497-0281	326-6711
William R. Brody	Stanford U. Med. Center; Dept. of Radiology and Electrical Engineering Department	497-5226	325-1709
Albert Macovski	Electrical Engineering Department and Stanford U. Med. Center; Dept. of Radiology	497-2708	854-3681

(All Stanford University, Stanford, Cal. 94305)

3. Experimental Station (see list in Proposal Guidelines, Figure 2)
a) First Choice IV-1 (wiggler) Alternates I-5
If there are no alternates state reason in proposal.

4. Estimated Beam Time Required in 8 hour Shifts:

Stored Beam Energy (GeV)	1.5	2	≥2.5	3	≥3.5
Estimated Optimal Total Shift Requirement			30		

Minimum Lead Time Required: --days -- weeks -- months Ready in ~~September~~ OCTOBER 1979

5. Describe any special conditions which make it desirable to run the experiment on dedicated time (stored current ≥ 100 mA at any energy, reduced emittance).

NONE

6. For experiments on Vacuum Beam Lines: Please list all samples you expect to insert into the vacuum system (and also the lead time needed for preparation) and also any construction materials and components not generally considered to be UHV materials or components. Detail must be given in the proposal.

NONE

7. List all potentially hazardous procedures and equipment, including all toxic, radioactive, or explosive materials, and furnish detailed safety procedures in the proposal. *Agreement to bring these materials to SSRL must be obtained from J. Cerino, Operations Mana least one week prior to the date of arrival.*

NONE

8. What equipment or materials do you expect to be provided by SSRL?

NONE

9. What is the source of funding for your experimental work. If Government Agency please specifiy grant or contract number.

HANSEN LABORATORY RESERVE FUNDS.
SPECIAL PROJECTS FUND, DEPARTMENT OF MEDICINE (E.R.).
GENERAL MOTORS RESEARCH GRANT (R.H.).

0021771

Please give a brief abstract of the proposal. Try to confine yourself to this page.

TITLE: IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

SPOKESPERSON: E. Barrie Hughes

ABSTRACT:

The purpose of this proposal is to demonstrate the value of synchrotron radiation in a specific area of diagnostic radiology. This area, in which our interest centers at this time, concerns the development of a non-invasive method of coronary angiography based on the use of monochromatic x-ray beams at energies close to the K absorption edge of iodine. All other development efforts, with the exception of a preliminary investigation at SSRL, have employed standard commercial x-ray generators and, in consequence, have suffered from the lack of truly monochromatic x-ray beams of adequate intensity. The specific motivation for the proposed studies is an urgent need to reduce both the risk and the cost of coronary arteriography. The proposed method is referred to as dichromography. It involves the acquisition of digital radiographs at x-ray energies slightly above and below that of the K absorption edge in iodine at 33.2 KeV and the subsequent subtraction of these two images to achieve maximum contrast in the visualization of the intra-arterial iodine. Estimates suggest that this technique, at SSRL, may achieve a sensitivity to iodine on the order of 100 - 500 times greater than that achieved in present radiological practice. This proposal calls for the performance of certain tests with minimum delay and with equipment that is already essentially in hand. One-dimensional digital radiographs of inaminate phantoms will be obtained to explore the ultimate sensitivity of dichromography to iodine concentration and other related questions. Future work, based on the success of the presently proposed tests, will employ a real-time radiographic device based on the digital integration of the output of an appropriate x-ray sensor.

0021772

Introduction

Angiography, the radiologic visualization of blood vessels containing contrast media, has become a powerful method of diagnosing disorders involving the circulation of the heart, of the brain, and of other vascular beds. The method provides information not otherwise available. However, the techniques currently in use involve invasive procedures which carry significant risks of morbidity and of mortality. These limitations, together with the high dollar cost of the procedures, have prevented their more widespread use. This is especially true in coronary arteriography, which might otherwise be employed as a screening procedure in certain high-risk populations.

For these reasons we propose a study of the use of the brilliant monochromatic x-ray source at SSRL in non-invasive angiography based on a dichromographic approach. Since the writing of the original Letter of Intent to SSRL on May 1, 1979 (see attachment), Professors William R. Brody and Albert Macovski of the Department of Radiology of the School of Medicine and of the Department of Electrical Engineering at Stanford University have agreed to join the authors of that Letter as members of the experiment team. The research interest of Drs. Brody and Macovski include the development of non-invasive methods of arteriography, which they are actively pursuing in their own laboratory. We expect that the proposed investigation at SSRL, and subsequent work, will benefit significantly from the advice and involvement of these researchers.

0021773

A. Description of Experiment

The purpose of this proposal is to demonstrate the value of synchrotron radiation in angiography. Within this area of diagnostic radiology, our specific interest at this time is centered on the development of a non-invasive method of coronary angiography based on the use of monochromatic x-ray beams at energies close to the K absorption edge of iodine. The principle involved is not new. It was first mentioned in the radiological literature by Jacobson in 1953[1] and in recent years has received most attention from Mistretta and his colleagues at the University of Wisconscin[2-5]. All development efforts however have employed standard commercial x-ray generators and, in consequence, have suffered from the lack of truly monochromatic x-ray beams of adequate intensity. A preliminary investigation was undertaken several years ago at SSRL, using the K absorption edge in copper, but was not pursued[6]. At the present time the principle involved is essentially unexploited and the opportunity provided by SSRL for a successful development effort is being ignored.

One specific motivation for the studies we propose is easy to understand. Premature heart disease is the major health problem in the United States today. Approximately 500,000 persons die each year from disease of the coronary arteries and many more suffer heart attacks and consequent heart damage. Approximately 50% of all deaths are cardiovascular in origin and one-fourth of all these patients are under 65 years of age. Many of these deaths and much of the morbidity could be prevented by surgery if a practical screening procedure existed. It is not surprising therefore that coronary artery examina-

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tions are increasing annually at a rate of about 20% and that 500,000 were performed last year in the United States alone. The standard procedure for performing coronary arteriography requires catheterization of the artery in question and the injection, by this means, of a concentrated solution of an iodinated organic compound immediately prior to the x-ray examination. This is a highly invasive procedure and carries too much risk to be used in a screening way. It is also too expensive, since it typically requires admission to the hospital for two nights. The catheterization and subsequent rapid intravascular injection of the concentrated contrast medium used in coronary arteriography have associated death and morbidity rates today of 0.5 and 1.0% respectively. These are much too high to permit arteriography to be used routinely to recognize persons with significant obstruction of the coronary arteries. The cost of each such examination performed today is approximately $2,000 or about $1,000 million nationwide. There is, therefore an urgent need to reduce both the risk and the cost of coronary arteriography.

The method we propose is referred to as dichromography. Optimally, it involves the acquisition of digital radiographs at x-ray energies slightly above and below that of the K absorption edge in iodine at 33.2 KeV and the subsequent subtraction of these two images to achieve maximum contrast in the visualization of the intra-arterial iodine. Estimates suggest that this technique, at SSRL, may achieve a sensitivity to iodine on the order of 100 - 500 times greater than that achieved in present radiological practice[7]. The exact figure depends on the efficiency of the x-ray detector, which should be as large as possible. If this enhancement is realizable, it offers the

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prospect of coronary arteriography by peripheral venous injection and therefore with reduced concentration of iodinated compounds in the coronary arteries. This would eliminate the need for catheterization and substantially reduce both the risk and the cost of the procedure. The radiation dose incurred by the patient through the use of monocromatic x-rays is increased relative to the use of the typical continuous spectrum of higher mean energy, but is well within the limits of safety. For example, a study by Ter-Pogossian[8] shows that the increase, relative to the use of 70 KVp x-rays, is no more than a factor of three for patient thicknesses up to 20 gm cm^{-2} if the detector response, unlike film, is proportional to the transmitted x-ray intensity.

It has long been recognized that information about the elemental composition of an object can be obtained from the comparison of radiographs taken with different incident x-ray energy spectra[9], or from the measurement of changes in a transmitted x-ray spectrum[10]. Dichromography, by means of which the radiographic sensitivity to iodine is greatly increased, is a special illustration of this principle. It takes advantage of the sharp discontinuity in the x-ray absorption coefficient at the K edge, which in iodine occurs at the relatively high energy of 33.2 KeV. Attempts to implement this idea have been made, but never with monochromatic x-ray beams of the linewidth ($\sim$ 1 eV) and intensity that SSRL provides. Instead, recent investigators have used heavy filtration (90 - 95%) of beams from standard x-ray generators to obtain quasi-monochromatic beams of substantial linewidth ($\sim$ 5000 eV) and limited intensity. In this way they have demonstrated[2] a sensitivity to iodine concentrations as low as $\sim$ 1 mg cm^{-2}. This is already a substantial achievement but has required a considerable effort. The principal complexity, in consequence of the large linewidth and large separation ($\sim$ 10,000 eV) between the peak energies of the two quasi-monoenergetic beams, is the background difference signal due

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to variations in tissue and bone thickness along the possible trajectories through the specimen. Using only two quasi-monoenergetic beams, these difference signals can easily overwhelm the iodine signal and limit the specimens to tissue thickness variations of less than $\sim$ 1 cm and to essentially bone-free regions. A sensitivity to iodine of $\sim$ 1 mg cm^{-2} in the presence of tissue and bone variations of $\sim$ 10 gm cm^{-2} and 2 gm cm^{-2} was achieved only by the use of three quasi-monochromatic beams, each of which required a different filter and a different terminal voltage and current for the x-ray generator[3]. This is a complex procedure, time-consuming, and in need of optimization for each clinical problem.

Clearly, the ideal approach to iodine dichromography is to use two monochromatic x-ray beams, both immediately adjacent to the K absorption edge but one with energy above and one with energy below this edge. In this way the difference signals due to tissue and bone variations are enormously suppressed. For a linewidth of $\sim$ 1 ev and a spacing of $\sim$ 5 eV between the two beam energies, the tissue and bone difference signals are $\sim 5 \times 10^{-2}$%/gm cm^{-2} and 7×10^{-4}%/gm cm^{-} respectively, whereas the iodine difference signal is $\sim$ 3%/mg cm^{-2}. The detectability of iodine difference signals on the order of this size, or less, now depends upon the stability of the x-ray beam intensity and upon the stability and uniformity of the x-ray detector efficiency. At SSRL the stability of the x-ray beam intensity should be excellent. The systematic variation due to the decay of the circulating electron current is not only predictable, but also slow enough to be negligible during the small time required for each exposure. The problem of stability in the detector efficiency is also minimized by the high intensity of the x-ray beams at SSRL. For example, for a stored currentof 30 mA and a beam energy of 3.5 GeV, each detector pixel in a line exposure, $\sim$ 1 mm x 1 mm, will receive $\sim 10^4$ monochromatic x-ray photons in about

I told this to Hughes, Hofstadter et al.

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10 μsec. Even if the detection efficiency is only ∿ 1%, it requires only ∿ 1 msec to record this intensity to an accuracy of 1%. The ultimate sensitivity will probably be determined by the residual variations in detector efficiency from pixel to pixel, which it will be important to minimize. No matter what form the detection apparatus takes, it is also clear that the radiographs must be acquired in digital fashion. This will eliminate normalization problems in subtraction, and permit the manipulation, enhancement and display of the difference image in the most appropriate way.

This proposal, to demonstrate the value of monochromatic beams in iodine dichromography, calls for us to perform certain tests with minimum delay and with equipment that is already essentially in hand. The initial x-ray detector will be a single crystal of bismuth germanate, collimated in order to achieve the necessary fine spatial resolution and mounted so that it can be automatically scanned through the horizontal width of the beam. The output will be integrated so that the detector can operate without count-rate limitations and the results will be immediately available through the use of an on-line data acquisition minicomputer. The rudimentary one-dimensional radiographs that we will obtain will therefore be in digital form, in keeping with the methodology that we envision for future work. Future work, based on the success of the presently proposed tests, will employ a real-time radiographic device based on the digital integration of the output of an appropriate x-ray sensor.

The samples that we will use in the presently proposed tests will consist entirely of inaminate phantoms. These phantoms will be designed:

1) to explore the ultimate sensitivity of dichromography to iodine concentration,

2) to demonstrate the suppression of difference signals due to tissue (lucite and water) and bone thickness variations,

0021778

3) to explore the visibility of channels (simulated blood vessels) of various diameters as a function of the iodine concentration within the channel.

and 4) to explore the visibility of iodinated channels in the presence of extra-channel background concentrations of iodine.

The iodine contrast agents that we will employ will be chosen from those in common use today in clinical angiography.

Coronary arteriography is but one of a large number of medical problems that could benefit from the dichromagraphic technique. Cerebral arteriography currently carries major risks of stroke and death as a result of the invasion of the root vessels of the brain. In fact, many arteries and veins of clinical significance could be studied by this non-invasive means. Neoplasms also exhibit a degree of abnormal and characteristic vascularity. Currently their investigation requires selective arteriograms involving catheterization of the vessels feeding them. Often this is technically impossible and presupposes a knowledge of the presence and location of the neoplasms.

We feel that our proposed study could be of very great benefit in the prevention and treatment of morbidity and death due to a major group of health problems. Presently unforseen applications of monochromatic x-ray beams, not necessarily limited to those with energies adjacent to the K absorption edge of iodine (or even to dichromography), may be stimulated by our work. We are also conscious of the efforts elsewhere to apply iodine dichromography to computerized tomography (C.T.)[11]. It may be that the one-dimensional character of the x-ray beams at SSRL is naturally suited to the planar scanning requirement of CT. We are also undeterred by the present availability of intense monochromatic x-ray beams only at laboratories, such as SSRL, located adjacent to a high energy electron storage ring. We feel that medical procedures may be developed at SSRL,

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or at other such laboratories, whose intrinsic value may outweigh this limitation. We are also conscious of the potential use of PEP as a source of readily available x-ray beams. Moreover, we feel that there is a future potential for producing intense monochromatic x-ray beams for medical purposes in machines smaller than SPEAR. These machines may be either single beam storage rings optimized in size and performance for medical applications, or perhaps based upon the interaction of high power laser radiation with intense currents of electrons in small storage rings.

B. Experimental Equipment

The preferred beam line and station for the proposed study is the rapidly-tunable hard x-ray beam designed IV-1 (wiggler). An alternative beam line is that designated I-5. The former is preferred because of its ability to provide a larger flux of x-rays close to 33.2 KeV. Beam energies adjacent to the K edge of iodine will be required.

The experimental apparatus and control equipment will be supplied by the High energy Physics Laboratory (HEPL) at Stanford and will be thoroughly tested before delivery to SSRL. The detector itself will occupy a volume no larger than 24-in. x 24-in. x 24-in. and the associated electronics will be contained in two standard racks.

C. Equipment Delivery Schedule

The experimental equipment will be ready for delivery to SSRL by September 1, 1979. The x-ray detector, associated electronics and control computer are already in hand. All that remains to be done is to construct the mount for the detector and the mechanical device that will allow the detector, or the specimens, to be moved through the x-ray beam in two orthogonal directions under computer control. These tasks, and the necessary software development, will be done during the summer months of 1979.

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D. Previous Experience with the Techniques and Facility

The detector, the associated electronics and the minicomputer that will be used in this study have all been used previously by two members of the experiment team. These individuals have recently built and tested, at SLAC, a γ-ray detector containing close to 200 bismuth germanate crystal elements, each 5 mm x 5 mm x 40 mm. They have also developed an electronic integration module for use with NaI(Tℓ) crystals, and have recently used 49 channels of this circuitry in extensive tests, at SLAC, of a modular array of 49 NaI(Tℓ) modules, each 2½-in. x 2½-in. x 20 in. Minicomputers very similar to that proposed for use at SSRL were used in the performance of both of the above tests. These individuals also have extensive experience in experimental particle physics and have successfully completed major experimental programs at several particle accelerators, including SLAC. In particular, they have been involved in the high energy physics program at SPEAR since the storage ring became operational in late 1972 and are responsible for the precision tests of quantum electrodynamics that have been conducted at SPEAR, as well as several other investigations in the physics of e^+e^- collisions at high energies.

The iodine contrast media and standard medical phantoms are readily available to other members of the experiment team, while specialized phantoms can easily be constructed at HEPL.

0021781

E. Safety Concerns

There are no hazardous materials associated with this study. It may be necessary to use a low energy radioactive source in the test or calibration of our apparatus, but these are readily available at both SLAC and HEPL.

F. Beam Time Required

There are four separable questions of interest in this study; these are listed in Section A. After the initial check-out of the apparatus and procedures in the x-ray beam, which may require four shifts, we estimate that the exploration of each of the four questions of interest may also occupy about four shifts. The total time estimate is, therefore, 20 shifts, to which we should add a contingency of 10 shifts for the usual unpredictable problems. The overall time estimate is therefore 30 shifts, which should be delivered in blocks of between 3 - 4 shifts at a time.

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REFERENCES

(1) Jacobson, B., "Dichromatic Absorption Radiography: Dichromography," Acta Radiologica 39, 437 (1953).

(2) Mistretta, C.A., Ort, M.G., Kelcz, F., Cameron, J.R., Sieband, M.P. and Crummy, A.B., "Absorption Edge Fluoroscopy Using Quasi-Monoenergetic X-ray Beams," Invest. Radiol. 8, 402 (1973).

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(7) Doniach, S, and Pierce, D., "The Uses of Synchrotron Radiation for Medical Diagnostics," Stanford-SLAC Synchrotron Radiation Laboratory Report No. 1 (unpublished), 1971.

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(11) Riederer, S.J. and Mistretta, C.A., "Selective Iodine Imaging Using K Edge Energies in Computerized X-ray Tomography," Medical Physics 4, 464 (1977).

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ADDENDUM II TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

Co-Investigators: E. Barrie Hughes
Edward Rubenstein
Robert Hofstadter
William R. Brody
Albert Macovski

W. W. Hansen Laboratories of Physics
and
School of Medicine
Stanford University
Stanford, California 94305

0021785

March 1980

The preparation of this document was prompted by our receipt of the expert review requested by the SSRL Program Review Panel in January 1980. We will give our response to each of the items raised, but we wish first to remark that the scope of this latest review seems to go considerably beyond that of the six earlier reviews conducted in the period July - August 1979. The proposal under review was written, upon the advice of the Directorate of SSRL, not for the immediate purpose of securing sufficient beam time and facilities to take coronary arteriograms in patients, but only to conduct the first stages of such a program. This is specifically stated on page 5 of our Proposal, as is our intention to employ only inanimate phantoms at this time. The limited scope of our first proposal seems to have been well-understood by the earlier reviewers, four of whom gave us their unqualified endorsement. We are not at all surprised that the recent expert reviewer did not find a complete technical discussion of exactly how we intend to acquire coronary images in patients at SSRL. We regarded these details as appropriate for future proposals. At the time we wrote our current Proposal we had identified solutions to some of the technical problems related to the realization of a diagnostic clinic for coronary angiography at SSRL, but not to all of them. Since that time we have continued to study these problems, often in consultation with the SSRL staff, and at the present time we feel that we have practical solutions to all of the major problems. Not surprisingly, our project has been in a dynamic state of development for the past nine months, and we expect to communicate the results of these efforts to the Program Review Panel at the appropriate time in the context of new proposals. We did not feel it wise to delay the execution of the specific fundamental tests called for in our first proposal until our total development effort was conceptually complete and we hope therefore that the Program Review Panel, and the Directorate of SSRL, will continue to review our first proposal with these thoughts in mind, or instruct us otherwise.

0021786

Clearly, we agree with the opinion of the expert reviewer that coronary arteriography cannot be done using the quasi-monoenergetic x-ray beams provided by standard x-ray sources. This is explicitly stated on page 7 of the Addendum to our Proposal that we submitted to SSRL on August 30, 1979.

Contrary to the claim of the expert reviewer, the instrumentation that we propose to use to obtain our initial one-dimentional radiographs is fully described on page 5 of our Proposal. It is also described on page 1 of the report we submitted to SSRL on December 20, 1979 describing the results of our first informal tests at SSRL, which were obtained with exactly this instrumentation. Obviously, for the reasons spelled out in the introductory paragraph of this document, we did not include a specific description of the instrumentation that we will need in due course to accumulate digital images rapidly in patients without the need for horizontal scanning.

We do agree with the claim of the expert reviewer that in order to visualize iodine within the coronary arteries it will be necessary to record each pair of digital images, i.e., above and below the K-edge, in a time short compared to the periodic motion of these structures. His estimate of about 30 msec for this time is quite correct. This is precisely why coronary arteriography cannot be done using quasi-monoenergetic sources derived from standard x-ray sources, which are insufficiently intense. We fully recognize this specific problem and have discussed it several times with the SSRL staff. It poses no fundamental practical difficulty, but its solution is also totally irrelevant to the realization of the objectives of our current proposal, all of which involve phantoms that are inanimate and static. Our eventual solution is to rotate, or to oscillate, the crystal monochromator at the requisite frequency ($\sim$ 30 Hz) by the small angular amount ($\sim 0.001^{\circ}$) necessary to step the transmitted beam back and forth through the iodine K-edge.

Another fundamental misconception held by the expert reviewer is that he expected we would eventually scan line-by-line through the complete coronary field of interest entirely at one x-ray energy before switching the energy and repeating the scan. He is correct in pointing out the severe limitations of this method. However, we have never had any intention of operating in this manner. We intend, at the proper time, to propose the use of an efficient linear array of detection elements encompassing the full width of the field of interest. This is the natural detector configuration for use at SSRL and, in addition, eliminates the familiar scatter background of standard radiology. In conjunction with Dr. George Brown of SSRL, we have conceived a method by which the horizontally planar x-ray beam may be scanned vertically through

0021781

the field of interest (in contrast to moving the patient vertically through the horizontal x-ray beam). We intend, however, to use a scanning time longer than the cardiac cycle, but it must be emphasized that this relatively long scanning time will not result in a blurred image. Each line exposure, due to the high x-ray intensity, will occupy only a few milliseconds. The x-ray energy is then switched, within about 30 msec, and the second exposure is made. Each pair of line exposures occurs within 30 msec, a period within which the heart is essentially stationary. Upon completion of each exposure pair, the beam (or the patient) is moved vertically by the required spatial element and the procedure repeated. The lack of blurring is governed by the line-pair exposure time and not by the total frame time. This is a direct analog of photographic cameras with focal plane shutters which are free of blurring despite relatively long exposure times of the scanning slit. The price paid for this effect is that all portions of the image do not represent the same time interval. A subtle distortion is generated due to motion (the cardiac cycle), but this does not represent blurring. For example, a horizontally moving vessel, which would otherwise be blurred, is reproduced in good focus at a slight inclination since the top and bottom are scanned at different times.

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The same principle is also illustrated by the series of photographs in Fig. 2. The first frame (a) is a standard coronary arteriogram obtained in projection with a normal exposure time ($\sim$ 0.01 sec). The subject is again a dog and the iodine is again introduced invasively. The second frame (b) represents an integration over four seconds, with the resultant severe blurring

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and almost total loss of arterial detail. The third frame (c) is also taken over the same four seconds, where a line scan has been simulated by a vertically scanned horizontal slit. As is shown, the original detail is restored despite the motion. The streak artifacts are due to the non-uniform motion of the manually scanned slit.

The misunderstanding by the expert reviewer of our x-ray detection efficiency is 1% is hard to anticipate but easy to correct. Any x-ray detector that we have proposed, or will propose, for use at SSRL will have an efficiency of essentially 100%. The current proposal calls for the use of a bismuth germanate (BGO) crystal 3 mm in thickness, which corresponds to approximately 38 x-ray mean free paths at 30 KeV. Although the precise thickness of our BGO crystal is specified on page 1 of our Informal Test Report to SSRL, it is true that it is not explicitly stated in our Proposal. Our excuse for this omission must be our awareness of the excellent stopping power of BGO for 30 KeV x-rays and our implicit assumption that just the stated use of BGO would, by itself, clearly signal an excellent detector efficiency to the thoughtful reader. In fact, a BGO crystal thin enough ($\sim$ 0.01 mm) to have low detection efficiency ($<$ 10%) for 30 KeV x-rays would be about 30 times thinner than the minimum thickness ($\sim$ 0.25 mm) presently available.

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We agree with the expert reviewer's remark that if the time occupied by a complete set of line scans at one energy followed by a second complete set of line scans at a second energy should collectively occupy more than about 30 msec, that a temporal subtraction methodology, using standard x-ray tubes, will produce cardiac images of comparable quality. Having said this however, we can repeat that we do not intend to acquire our cardiac images in this way. Images acquired by either of the two methods just outlined will be hopelessly blurred due to cardiac motion and be useless from the standpoint of visualizing the coronaries.

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We also agree with the second academic point raised by the expert reviewer that, in the absence of motion (obviously impossible in coronary arteriography), the iodine sensitivity provided by time subtraction exceeds that provided by K-edge subtraction. This occurs because the small reduction in iodine contrast due to the subtraction of the image taken below the K-edge is avoided. Clearly, the situations of vital clinical interest in which patient motion can be so totally suspended as to realize this small benefit must be few in number, and are obviously totally disconnected to our area of interest where motion is ever-present and unavoidable.

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0021791

Fig. 1

0021792

(a) (b) (c)

Fig. 2

0021793

ADDENDUM II TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

Co-Investigators: E. Barrie Hughes

Edward Rubenstein

Robert Hofstadter

William R. Brody

Albert Macovski

W. W. Hansen Laboratories of Physics
and
School of Medicine
Stanford University
Stanford, California 94305

0021794

March 1980

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0021795

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We do agree with the claim of the expert reviewer that in order to visualize iodine within the coronary arteries it will be necessary to record each pair of digital images, i.e., above and below the K-edge, in a time short compared to the periodic motion of these structures. His estimate of about 30 msec for this time is quite correct. This is precisely why coronary arteriography cannot be done using quasi-monoenergetic sources derived from standard x-ray sources, which are insufficiently intense. We fully recognize this specific problem and have discussed it several times with the SSRL staff. It poses no fundamental practical difficulty, but its solution is also totally irrelevant to the realization of the objectives of our current proposal, all of which involve phantoms that are inanimate and static. Our eventual solution is to rotate, or to oscillate, the crystal monochromator at the requisite frequency ($\sim$ 30 Hz) by the small angular amount ($\sim 0.001^{\circ}$) necessary to step the transmitted beam back and forth through the iodine K-edge.

Another fundamental misconception held by the expert reviewer is that he expected we would eventually scan line-by-line through the complete coronary field of interest entirely at one x-ray energy before switching the energy and repeating the scan. He is correct in pointing out the severe limitations of this method. However, we have never had any intention of operating in this manner. We intend, at the proper time, to propose the use of an efficient linear array of detection elements encompassing the full width of the field of interest. This is the natural detector configuration for use at SSRL and, in addition, eliminates the familiar scatter background of standard radiology. In conjunction with Dr. George Brown of SSRL, we have conceived a method by which the horizontally planar x-ray beam may be scanned vertically through

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0021800

Fig. 1

0021801

(a) (b) (c)

Fig. 2

ADDENDUM II TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

Co-Investigators: E. Barrie Hughes

Edward Rubenstein

Robert Hofstadter

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Stanford, California 94305

0021803

March 1980

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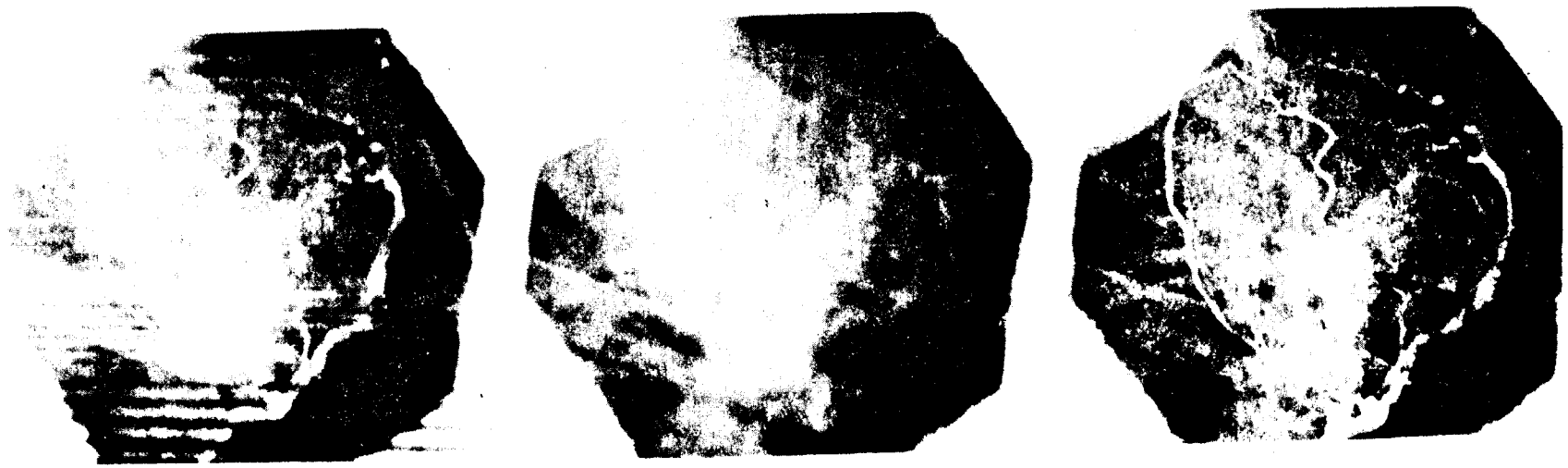
0021809

Fig. 1

0021810



(a) (b) (c)

Fig. 2

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S. S. R. L.

ADDENDUM TO PROPOSAL 456B

"A STUDY OF IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY"

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I INTRODUCTION

This addendum was written after the receipt of six anonymous reviews of Proposal 456B. Four of these reviews were totally positive, one raised a minor objection and one was totally negative. The minor objection is easily answered: it relates to the use of only inanimate phantoms and the effects of extra-vascular iodine through diffusion in live specimens. The bulk of this addendum is directed at the issues raised in the negative review. These are (a) the utility of a medical facility for coronary arteriography at SSRL alone, (b) the possibility of later providing similar treatment to patients elsewhere, (c) the feasibility (actually the infeasibility) of coronary arteriography by dichromography with existing quasi-monoenergetic x-ray sources and (d) the mistaken impression that the radiation dose to the patient in dichromography will be increased at SSRL relative to the use of quasi-monoenergetic beams.

II THE RESPONSE

The principal purpose of the studies described in Proposal 456B is without question the development of a safe non-invasive method of coronary arteriography. The current method of assessing the condition of the coronary arteries is highly invasive and carries too much risk, discomfort and expense to be used routinely to recognize significant arterial obstruction in asymptomatic patients at high risk for coronary artery disease. For these reasons the invasive diagnostic procedure is practiced in only about 15% of all hospitals and even in these active centers the associated death and morbidity

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rates are too high for the procedure to be used in a screening way. It is therefore restricted in its use to symptomatic patients already known, with high probability, to be suffering from severe coronary artery disease and in probable need of surgical intervention. Even if a successful development effort of a non-invasive method of coronary arteriography resulted in the operation of a diagnostic clinic for coronary artery studies only at SSRL, the impact on the management of this disease in the local area would be substantial. This clinic would be used in the following major ways:

a) The treatment of patients in probable need of surgical intervention who would otherwise be subjected to the invasive diagnostic procedure. The examination of 20 such patients per day, or $\sim$ 5,000 per year, would prevent 25 deaths and 50 serious injuries each year that would otherwise result from the invasive diagnostic examination alone.

b) The follow-up arteriographic examination of surgical patients in order to assess post-operative progress with no further risk of injury.

c) The study of the natural history of coronary artery disease by serial examinations on patients with no previous evidence of this disease.

In fact, the studies identified in item c) above, if conducted only at SSRL, would provide clinical medicine with a truly unique research opportunity. The SSRL facility would, of course, also provide the opportunities identified in items a) - c) above to physicians and researchers in the other areas of angiography. This may be especially important in cerebral arteriography, which currently also carries major risks of stroke and death during invasive examination, but as stated in Proposal 456B there are many arteries and veins whose angiographic examination is of clinical significance.

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If a development effort at SSRL were to succeed, it is then reasonable to expect that this success would soon result in the establishment of similar research and diagnostic clinics at the other sources of synchrotron radiation, both in the United States and abroad. In February 1978, in the Western hemisphere plus Japan, there were thirteen storage rings either in operation (4), in construction (7) or proposed (2) with circulating beam energies in excess of 1 GeV where such a medical facility would be feasible.

Another result of an itial success at SSRL would undoubtedly be the stimulation of a considerable technical effort by physicists and engineers to develop a compact source of monochromatic x-rays expressly for medical purposes. Most certainly this source would not require the full intensity of the beam at SSRL. (This question is addressed briefly in Proposal 456B.) Presently, we believe that the most practical and least expensive method of providing an independent source of monochromatic x-rays for medical purposes is to back-scatter laser photons incoherently off the electrons in a small storage ring. If a powerful carbon dioxide laser is used, the storage ring energy required is only 200 MeV. The principle involved, namely inverse Compton scattering, has been used several times to obtain monochromatic γ-rays in high energy physics. At SLAC, for example, beams of laser light are routinely back-scattered off beams of energetic electrons (5 - 22 GeV) to produce monochromatic γ-rays in the range 2 - 10 GeV. At Frascati, Italy, the Adone storage ring, first built in 1967, is now used in conjunction with a powerful argon-ion laser to provide a strong source of monochromatic γ-rays in the range 10 - 100 MeV for particle physics. It may be expected, therefore, that an initial success in the medical arena at SSRL would stimulate an effort to generate monochromatic x-rays for medical purposes at minimum cost

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by this, or an alternative, method. One alternative, but at present more speculative, method is to back-scatter laser photons (from an argon-ion laser) coherently off an electron beam bunched with a spatial structure equal to, or a sub-harmonic of, the wavelength of the laser light. In this way the x-ray yield can be greatly increased relative to incoherent scattering off unbunched electrons so that a 25 MeV electron microtron can be used instead of a storage ring.

At present we are unable to guarantee that medical studies of the type we project for SSRL will be possible at locations other than those selected originally, for other reasons, as the sites for electron storage rings. Should this be so, this limitation on the geographical distribution of facilities would not be uncommon in medicine. It has not prevented the recent development of the positron annihilation camera in nuclear medicine, which must be located adjacent to a proton accelerator capable of providing the required short-lived radioisotopes of ^{11}C, ^{13}N and ^{15}O. Neither has it prevented the establishment of radiotherapy clinics dependent upon beams of negative pi-mesons, heavy ions and neutrons at the large particle accelerators located in Los Alamos, Berkeley or Chicago, respectively. In fact, given the current world-wide demand for synchrotron radiation facilities and the secure position occupied by electron storage rings in particle physics research, it appears that the opportunities for the establishment of medical facilities employing monochromatic x-rays, but dependent upon machines built for other purposes, will not be nearly as restricted in geographical distribution as they have been for other specialized centers utilizing a unique resource.

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The studies outlined in Proposal 456B comprise a logical first step toward the goal of producing dichromagraphic radiographs of the coronary arteries. The proposal objectives have been deliberately restricted to initial studies with static and inaminate phantoms, in accordance with the stated SSRL preference for short investigations with limited objectives instead of single requests for the study of all questions necessary to achieve a final goal. The limited objective of Proposal 456B is to demonstrate the basic properties of digital iodine K edge dichromography using intense and truly monochromatic x-ray beams before proceeding to the use of more complex phantoms and animate specimens. Certainly, both of the latter will be used in subsequent tests and are immediately avaiable to the experiment team.

Even the limited objectives of Proposal 456B include a study of the visibility of iodinated blood vessels in the presence of extra-vessel background concentrations of iodine. Such backgrounds will indeed occur in animate specimens, but there appears to be no reason why this should preclude arterial examinations if the peripheral venous injection and the x-ray exposures are administered with the proper relative timing. Typically, the radiographs needed for dichromography will be taken on the first or second transits of the injected iodine through the cariovascular system, or within one minute after injection. In contrast, iodine diffusion into the extra-vascular space will occur with a time scale on the order of several minutes and so will not present a major problem. This fact is clearly demonstrated in the photographs below, which show the result of a time subtraction study, by digital

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radiography, of the chest cavity of a dog. The picture on the left, the fast-contrast image, was obtained after the introduction of iodine by catheter, via the superior vena cava, into the right atrium of the heart. An earlier exposure of equal duration, the so-called mask, was also obtained before the introduction of the iodine. The picture on the right is what remains after the mask is subtracted from the post-contrast image. Ideally, it should reveal only the distribution of the con trast agent. Indeed the iodine within the heart, averaged over many cardiac cycles, is clearly seen. The carotid (open arrow) and vertibral (closed arrow) arteries are clearly visualized, as are smaller arteries (to the left) to the forearm and shoulder and even (to the right) iodinated veins. These channels are visible despite their motions during their exposure and are definitely not obscured by any extra-arterial iodine. The incomplete subtractions of the other anatomical structures is due to their non-identical movements during the two exposures.

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Photographs of the chest cavity of a dog obtained during a time subtraction study. On the left is the unsubtracted post-contrast image obtained after the iodine injection. On the right is the difference between the post-contrast image and an earlier exposure, the mask, before the iodine injection.

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While it is true that the feasibility of iodine dichromography using quasi-monoenergetic, or broad-band, beams has already been demonstrated, this does not mean that existing quasi-monoenergetic sources have been used, or indeed can be used, for coronary arteriography. In fact, with conventional x-ray sources this is impossible. The source intensity, after the necessary severe filtration, is totally inadequate. The coronary arteries are not stationary structures. They are in intimate contact with the heart muscle and are therefore in continuous motion. Only a blurred image would result from the use of quasi-monoenergetic x-ray beams. A major advantage of the beam intensity at SSRL is that it is possible to record images fast enough to visualize the coronary arteries in sharp focus. The major arteries, including those not intimately associated with the heart muscle, are involved in a motion of expansion and contraction due to the cardiac cycle and therefore their internal structures are not visible in examinations with quasi-monoenergetic sources. It is likely that the clinical applications of non-invasive procedures with quasi-monoenergetic sources will be restricted to stationary structures, such as the kidneys, gall bladder and thyroid.

The suggestion made by one reviewer of Proposal 456B that the radiation dose delivered to a patient in a dichromographic examination with the monoenergetic x-ray beams at SSRL would substantially exceed that received if quasi-monoenergetic beams are used is most definitely not correct. To the contrary, the radiation dose is minimized through the use of monoenergetic beams because the signal to noise ratio is maximized under these conditions. Moreover, the natural one-dimensional cross sectional profile of the SSRL beam, coupled with the eventual use of a one-dimensional x-ray detector, totally eliminates the problem of scattered radiation that is characteristic of the published technique using quasi-monochromatic x-ray beams. For example, Kelcz et al.[1] has reported that the radiation dose delivered to a patient to achieve a specific

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image contrast is increased by a factor of 25 relative to that needed in the absence of scatter. If a scatter grid is used, the additional dose can be reduced to a factor of about three, but at the expense of a longer exposure time. In all respects the use of monoenergetic beams at SSRL with a matching detector geometry minimizes the radiation dose delivered to a patient in order to achieve a specific signal to noise ratio in the final image using iodine K edge dichromography. The opposite impression received by the one reviewer of Proposal 456B in question could be related to the references made to the work of Ter-Pogossian. In 1956, this author showed that an increased sensitivity to iodine could be obtained if a single quasi-monoenergetic beam at 33 KeV was used instead of a white spectrum of 70 Kvp of radiation. Ter-Pogossian also determined that the use of the softer radiation would cause an increased radiation dose, that this increase was no more than a factor of three for tissue thicknesses up to 20 gm cm^{-2}, and that this increase was well within safe limits. His work in no way relates to the relative radiation dose received in iodine K edge dichromography using, on the one hand, quasi-monoenergetic beams of large linewidth and large energy separation and, on the other hand, truly monochromatic beams with energies immediately adjacent to the iodine K edge.

III SUMMARY

The major advantages that the x-ray beams at SSRL bring to arteriography are as follows:

a) The monochromaticity of the beams maximizes the sensivity to intra-arterial iodine and permits the use of peripheral venous injection.

b) The intensity of the beams permits short exposure times and allows images to be recorded in sharp focus despite the arterial motions associated with the cardiac cycle.

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c) The monochromaticity of the two beams and their very small energy spacing virtually eliminates background signals due to tissue and bone thickness variations.

d) The increased sensitivity to iodine allows the injected concentration of iodine to be reduced, and permits multiple serial injections in a single patient examination.

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REFERENCES

(1) Kelcz, F. and Mistretta, C.A., "Absorption Edge Fluoroscopy Using a Three-Spectrum Technique," Medical Physics 3, 159 (1976).

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(This form must be submitted with every SSRL Proposal)

This proposal is a new proposal (X) or a replacement ( ) for proposal No._____.

Check most appropriate Review Panel:

_____X-ray-materials & chemistry _____VUV __X__X-ray-biology

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DATE RECEIVED: RECEIVED JUL 5 1979 S.S.R.L.

To be filled in at SSRL

1. TITLE (less than 10 words)

IODINE DICHROMOGRAPHY WITH MONOCHROMATIC X-RAY BEAMS FOR ANGIOGRAPHY

2. List of Collaborators (underline spokesperson)

Name	Full Address	Telephone Numbers Office	Home
E. Barrie Hughes	W. W. Hansen Laboratories of Physics	497-0135	368-2771
Edward Rubenstein	Stanford U. Med. Center; Dept. of Medicine	497-7188	342-1888
Robert Hofstadter	Physics Department	497-0281	326-6711
William R. Brody	Stanford U. Med. Center; Dept. of Radiology and Electrical Engineering Department	497-5226	325-1709
Albert Macovski	Electrical Engineering Department and Stanford U. Med. Center; Dept. of Radiology	497-2708	854-3681

(All Stanford University, Stanford, Cal. 94305)

3. Experimental Station (see list in Proposal Guidelines, Figure 2)
a) First Choice IV-1 (wiggler) Alternates I-5
If there are no alternates state reason in proposal.

4. Estimated Beam Time Required in 8 hour Shifts:

Stored Beam Energy (GeV)	1.5	2	≥2.5	3	≥3.5
Estimated Optimal Total Shift Requirement	___	___	30	___	___

Minimum Lead Time Required: ___days ___weeks ___months Ready in ~~September~~ OCTOBER 1979

5. Describe any special conditions which make it desirable to run the experiment on dedicated time (stored current ≥ 100 mA at any energy, reduced emittance).

NONE

6. For experiments on Vacuum Beam Lines: Please list all samples you expect to insert into the vacuum system (and also the lead time needed for preparation) and also any construction materials and components not generally considered to be UHV materials or components. Details must be given in the proposal.

NONE

7. List all potentially hazardous procedures and equipment, including all toxic, radioactive, or explosive materials, and furnish detailed safety procedures in the proposal. *Agreement to bring these materials to SSRL must be obtained from* J. Cerino, Operations Manag *least one week prior to the date of arrival.*

NONE

8. What equipment or materials do you expect to be provided by SSRL?

NONE

9. What is the source of funding for your experimental work. If Government Agency please specifiy grant or contract number.

HANSEN LABORATORY RESERVE FUNDS.
SPECIAL PROJECTS FUND, DEPARTMENT OF MEDICINE (E.R.).
GENERAL MOTORS RESEARCH GRANT (R.H.).

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