Harper Grace Hospitals
Harper Hospital Division

July 18, 1985

U.S. Nuclear Regulatory Commission
Region III
Materials Licensing Branch
799 Roosevelt Rd.
Glen Ellyn, IL. 60137

Re: Control No. 79162

Dear Mr. Mideria:

In reference to our phone conversation on Wednesday, July 17, 1985, concerning our amendment for establishment of a Regional Cerebral Blood Flow Laboratory, I have attached the following items that you requested: 1) Standard rCBF Clinical Protocol, 2) Literature concerning the Harshaw System 400.

As we discussed, the extreme sensitivity of this diagnostic procedure will not tolerate a leakage of Xenon-133 gas in excess of a few percent of the administered dose. It is for this reason that extra protective measures such as those listed as "Specific steps taken to minimize 133 Xenon leakage" within the enclosed clinical protocol are taken. Therefore, due to the sensitivity of this procedure and the extra protective measures taken, we request that our leakage rate of 10%, which is noted in parts 5 and 6 of our amendment application, be approved and our amendment granted.

If you have any further questions or require any additional information, please contact me.

Sincerely,

Thomas M. Kumpuris, M.S.

Thomas M. Kumpuris, M.S.
Nuclear Medical Physicist

TMK:do
cc: Roger Higgens, Ph.D.
Curtis Smith
J. Muz, M.D.

3990 John R., Detroit, Michigan 48201

STANDARD rCBF CLINICAL PROTOCOL

Regional Cerebral Blood Flow Analysis (rCBF) is a noninvasive quantitative measurement of cerebral hemodynamics. The method has been used for:

1. Management of critically injured patients (head trauma)
2. Evaluating patients for extracranial/intracranial bypass (superficial temporal to middle cerebral artery bypass)
3. Diagnosis of migraine
4. Evaluation of carotid endarterectomy
5. Evaluation of strokes

Normal subjects and category 4 and 5 patients (above) will be tested at Harper Hospital.

The normal procedure:

1. The purpose of the procedure, its investigational or diagnostic nature, the apparatus and the approximate length of the testing period are all explained.
2. The appropriate consent form is signed by the subject.
3. Hair clips, earrings or other head adornments are removed. A disposable paper cap is placed on the subjects head for hygenic purposes. The subject is placed supine on a stretcher.
4. A close-fitting, comfortable face mask is selected and located over the subjects mouth and nose. Careful

selection of the appropriate face mask is a key step in the elimination of gas leakage during the study. The face mask is held in place by carefully adjustment of the elastic retainers.

5. The subject is allowed a ten minute acclimatization period before the test is started.
6. The subjects head is carefully positioned within the probe holder helmet (the probes are initially locked in a withdrawn position). The position of the helmet in relation to bony landmarks is carefully adjusted. Each probe is advanced until it presses lightly against the scalp without discomfort to the subject. Each probe is locked in place.
7. A corrugated plastic tube is used to connect the face mask to the gas delivery/extraction device. The subject is allowed to adjust to the new situation.
8. The delivery unit is charged with 133 Xe to a concentration of approximately 12 mci/litre (requires approximately 30 mci load).
9. The data collection program is initiated and the subject unknowingly inhales a 133 Xe and air mixture for one minute.
10. At the end of this period the subject is switched to breathing room air and the expired gases are collected in an activated charcoal filter within the

delivery/extraction unit. The build up of radio activity within the filter is measured and displayed on the collection device. Alarms are fitted to indicate impending filter saturation.

11. At the end of the washout period (15 minutes including 1 minute of inhalation) the test is concluded. The probes are withdrawn from the subjects head, the face mask is removed and the subject allowed to sit up.
12. A brachial blood pressure is taken and 3 milliltres of blood drawn for hemoglobin and PCO_2 determinations.

Specific steps take to minimize 133 Xe leakage:

1. Careful subject selection: only cooperative, conscious, coherent subjects will be tested.
2. The nature of the study will be carefully explained, particularly the need to remain still to ensure a leak free mask/face junction.
3. Difficult mask fitment may be overcome by the use of suitable gap-filling material (uncooked pancake batter). Subjects with beards and moustaches may be required to shave.
4. A suitable fan may be mounted above and behind the helmet in such a way that any 133 Xe gas would be blown away from the scintillation detector in order to minimize extraneous contamination and to provide the subject with a less claustrophobic environment during

the study.

5. A suitable 133 Xe leakage monitor, Xenogard, will be located in the testing area and will be in operation during the study.
6. 133 Xe will not be stored in the testing area.
7. Appropriate air supply and extraction rates will be maintained in order that, should a leak occur, the leak will be confined to the study room and not spread to adjacent areas.
8. Appropriate documentation of isotope use, background activity and cumulative exposure will be maintained.

SYSTEM 400™ INTRODUCES QUANTITATIVE AND FUNCTIONAL rCBF MEASUREMENT PLUS ADVANCED XENON DELIVERY.

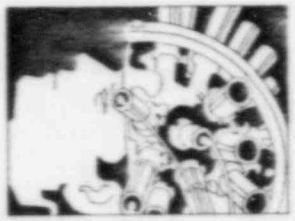
About Harshaw and rCBF.
As the world's leading producer of nuclear radiation detectors and related electronic components, Harshaw has been a major contributor to the science of nuclear medicine.

As the discipline has matured, Harshaw has continued as a prolific contributor of supportive equipment and expertise, including the first systems specifically designed for nuclear medicine and clinical applications.

By the early 1970's thousands of Harshaw "application designed" detectors were in the field, many of them being applied to laboratory and clinical investigations of Regional Cerebral Blood Flow — rCBF.

The logical extension of Harshaw's early work in rCBF analysis was the introduction of the world's first **complete** rCBF system, including software with analysis capability to complement detector and electronic assemblies.

In 1975 this goal was achieved with installation of the first complete computer-based rCBF analysis system at the Baylor College of Medicine in Houston, Texas. Although this system was later relocated, it is still in daily operation, having performed over 7000 rCBF studies to date.



rCBF: QUANTITATIVE MEASUREMENT OF CEREBRAL HEMODYNAMICS.

The Harshaw rCBF System provides **quantitative** functional information unobtainable by alternate investigative procedures. In fact, an important rCBF application is demonstration of the **effects** of structural abnormalities identified by CT, ultrasound, angiography and scintillation camera studies.

Other methodologies for measuring cerebral hemodynamics have included positron emission tomography (PET), single photon emission computerized tomography (SPECT), multiprobe analysis (MFA) and CT using non-radioactive Xenon. While these methodologies have some merit for rCBF analysis, inhalation MFA has demonstrated superior clinical practicality in terms of initial and ongoing costs, radiation safety and simplicity of procedure.

A Vital Diagnostic Tool.
In addition to demonstrating the functional effects of structural abnormalities, rCBF is a vital diagnostic tool for:

■ management of critically injured patients (Head Trauma) ■ evaluation of normal pressure hydrocephalus (NPH) ■ evaluation of candidates for ECAC bypass ■ diagnosis of migraine ■ evaluation of carotid endarterectomy ■ diagnosis of CVA ■ diagnosis of dementia.

Non-Invasive Methodology.
A face mask is placed over the patient's nose and mouth. As the patient relaxes in a supine position, his head is placed in the transparent probe holder. Probes are then inserted into the holder in a symmetrical configuration.

The patient breathes a Xenon-133/air mixture for one minute, followed by a 10-14 minute washout period breathing room air. During this period, the head probes monitor the uptake and washout of Xenon-133.

The entire patient procedure — which is routinely performed by nuclear medicine or general medicine technologists — takes approximately 20 minutes.

The computer analyzes the data and determines grey flow, white flow and other diagnostic parameters.

Xenon-133: Safe and Convenient.
Xenon-133 is a radioactive isotope produced by fission of Uranium-235. It is an isotope of elemental Xenon, a non-radioactive noble gas that is physiologically inert except for anesthetic properties at high concentrations.

Extensive diagnostic use has been made of Xenon-133 in nuclear medicine for evaluation of pulmonary function and lung imaging. It is physiologically inactive in recommended concentrations. No contraindications are known, and no adverse reactions specifically attributable to Xenon-133 have been reported.

Xenon-133 has a half-life of 5.31 days. It is supplied as a gas in break-sealed glass ampules and can be shipped anywhere in the world by common carrier.

INTRODUCING THE NEW HARSHAW rCBF SYSTEM 400.

With the introduction of the System 400, Harshaw again moves the leading edge of rCBF technology a significant step forward.

Designed to simplify operation, while it extends application and analysis capabilities, the key features of this unique system offer major performance benefits.

■ Helmet Probe Holder provides reproducible probe positioning for serial studies ■ New Xenon Delivery System accommodates even patients on life support ■ New Software reduces analysis time ■ Menu-Driven Operator Controls simplify operation ■ Digital Gain Stabilization ensures accurate calibration ■ Inhalation or IV Methodology provides maximum flexibility in study selection ■ Graphic Display assists in data interpretation ■ Compact Hardware requires less floor space

Advanced new Xenon delivery unit.
The Xenon-133 delivery unit incorporated in Harshaw's complete rCBF System was specifically designed to satisfy demands for more stringent than modified pulmonary ventilation/perfusion units previously used. It incorporates all the features necessary for consistent, reproducible and accurate rCBF measurement.

The System 400 is totally shielded for operator safety. It readily accommodates the **shallow breather** because of its low dead volume, the **hyperventilating subject** because of its efficient Xenon trapping system, and the **patient requiring breathing assistance** because it can be connected to any respirator having an external exhalation valve with controller.

For the most efficient use of Xenon-133, patients rebreathe Xenon/air from a closed container. Since rebreathing-type systems can suffer O_2 depletion, provision is made for **automatic oxygen replenishment.** The testube also permits maintaining the same O_2 concentration used in the patient's ventilator for rCBF studies at the life-support patient.

An activity concentration meter calibrated in millicuries/liter ensures economical Xenon usage, an important consideration at high case loads.

Selectable inhalation or intravenous injection.
The two methodologies for non-invasive measurement of rCBF are Xenon-133 inhalation and IV injection, with inhalation being the most often used.

Both methods yield essentially the same final results, while IV injection may be elected for patients with impaired pulmonary function who might not absorb sufficient Xenon-133 through inhalation.

Because the Harshaw System 400 is software controlled, the user need only push a button to automatically adjust system operation for either infusion method.

Head probes.
The design of the head probes used in the System 400 reflects Harshaw's 30-plus years' experience in nucleas detector technology. Rugged, reliable, lightweight and well-shielded from background radiation and electromagnetic interference, these probes meet all rCBF performance requirements.

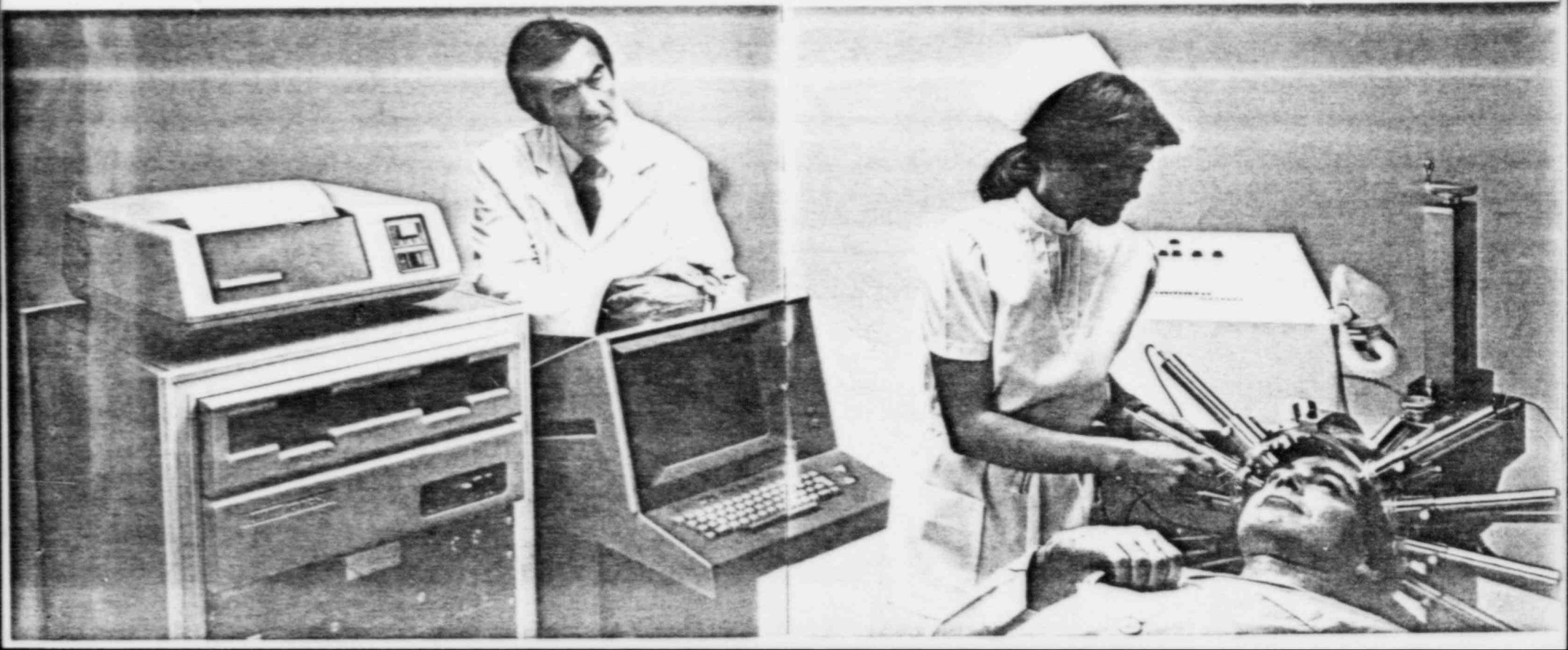
Harshaw's probes incorporate a 1/2" diameter by a 3/4" thick NaI(Tl) detector and a photomultiplier in a stainless steel housing with a thin foil entrance window. Lead-lined stainless steel interchangeable collimators with a 5/8" inside diameter by 1" straight bore attach to the probes.

These detector/collimator dimensions are selected for the optimum sensitivity/spatial resolution ratio.

Helmet probe holder and stand.
The combination of helmet probe holder and portable stand assures reproducible probe positioning. Both height and angle of the helmet assembly are adjustable to accommodate patient position.

This reproducible probe positioning is the most efficient means of acquiring rCBF data and permits rCBF measurement to be performed even on patients lying on a gurney. The lightweight assembly is readily moved out of room traffic when necessary.

The transparent construction of the helmet permits precise positioning of the head probes perpendicularly against the scalp. The helmet is easily fitted to the patient, and its reproducible probe positioning is particularly advantageous for serial studies. When in place, the probes are securely held by retaining collars fitted with lock screws, which provide additional shielding for the head probes, reducing the effects of scattered radiation.



COMPUTERIZED OPERATION FOR FAST, ACCURATE rCBF MANAGEMENT.

Graphic display assists in data interpretation.
A 16-channel rCBF study yields more than 125 items of CBF-related information, thus making graphical presentation a practical necessity.

Some investigators prefer rCBF interpretation based on asymmetry of opposing head probes and variance from hemispheric mean values (1)(2). Others prefer variance from normal values since a great deal of information has been published in the literature about "normal" values (3)(4). To serve both schools of thought, Hasshaw software offers the user a choice of two graphic display formats.

The first format portrays a single hemispheric outline with opposing head probes represented as a single square. The calculated value for each probe is placed within its respective half of the square. To simplify left/right comparison of measurements, all odd-numbered probes are located on the patient's left hemisphere, and even-numbered probes on the right.

The second display format incorporates an outline of each hemisphere, with individual head probes represented as a square. To the right of each square is the calculated measurement for a particular study, and to the left is the "normal" value ± one standard deviation. The "normal" values used are the Baylor Normals (5), which are divided into decades of life to facilitate comparison. These "normals" are a composite of men and women without "risk" factors.

Hard copy unit.
The hard copy unit can be used to reproduce any information which is displayed on the computer terminal, but is normally used for pertinent data summation charts and graphic displays. Since this may involve five or more pages of information, Hasshaw's rCBF System uses a plain paper electrostatic copy unit to quickly and silently reproduce desired information at a speed of ten seconds per page.

"Application designed" electronics.
The System 400 electronics were designed for rCBF application. Even personnel with limited experience in nuclear medical electronics can operate this system. Digital gain stabilization, which ensures accurate energy calibration, is an example of this design philosophy.

Interchangeable plug-in modules are used in each head probe channel, permitting the user to correct system malfunctions should they occur. This reduces downtime and service calls.

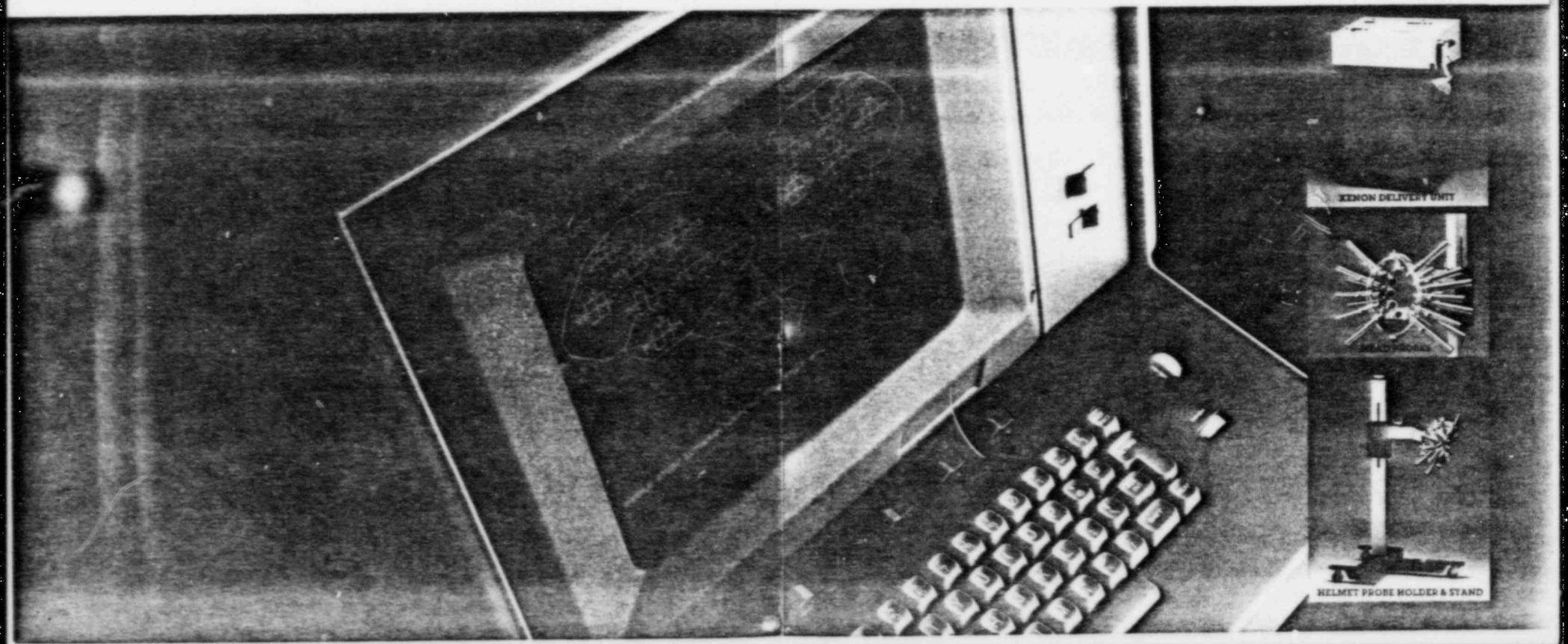
Energy centerline and window width settings for all channels are accomplished with common controls and calibrated in keV for ease of operation.

New software reduces analysis time.
Hasshaw software utilizes the variable metric algorithm developed by Fletcher (6) and recommended by Obrist (7). It is written in Fortran IV and implemented under the DEC RT-11* operating system. Analysis speed is an important consideration, both in high patient volume and serial study situations.

*Digital Equipment Corp., Maynard, MA.

"Menu-driven" controls simplify operation.
Hasshaw's rCBF software is written in "menu-driven" format for ease of operation. This, plus software control of all functions — including the Xenon delivery unit — greatly reduces the time necessary to establish operator familiarity.

In the menu format, operator interaction with the System 400 is based on a series of simple questions displayed on the computer screen. The questions and responses are structured in a logical sequence requiring minimal operator education.



TOTAL COMPUTERIZED SYSTEM SUPPORT.

Digital gain stabilization.
This feature is unique to the System 400. With its many years of experience in nuclear radiation detectors and rCBF, Harshaw recognized early that a fast and accurate method of calibration was necessary in an MPA system containing as many as 32 detectors.

Digital gain stabilization automatically adjusts individual detector amplification gain, resulting in energy calibration far more precise than that obtainable by other means. It ensures accurate calibration even by personnel whose experience with nuclear radiation detectors is limited.

Disc drive.
Storage of patient data in both analyzed and raw form for future reference is necessary in rCBF analysis. Floppy discs have proven to be the most practical storage medium for rCBF applications, with superior access and retrieval speed, reliability and cost effectiveness.

The Harshaw System 400 features a dual drive floppy disc system, which provides backup in case of a drive failure. In normal operation, the system provides convenience of one drive dedicated to program entry and the other to data storage.

Computer selection.
Since the Harshaw rCBF System is totally software controlled, the computer is a functional element, not limited to data analysis. In fact, part of the acquisition electronics and controls for the Xenon delivery system are installed in the computer. This makes consideration of substitute computers or off-line analysis impractical.

Selection of the appropriate computer involves consideration of the entire computational package, including the terminal, data storage medium, interfacing to data acquisition electronics, hard copy device and software.

The entire package must be selected to operate together and perform the task within acceptable time frame and cost parameters. Whether the computer has a 16, 32 or 64K byte memory is immaterial if the "package" meets your objectives.

The DEC LSI-11* microprocessor has shown itself a practical choice in terms of speed, cost and operational flexibility when used in the System 400.

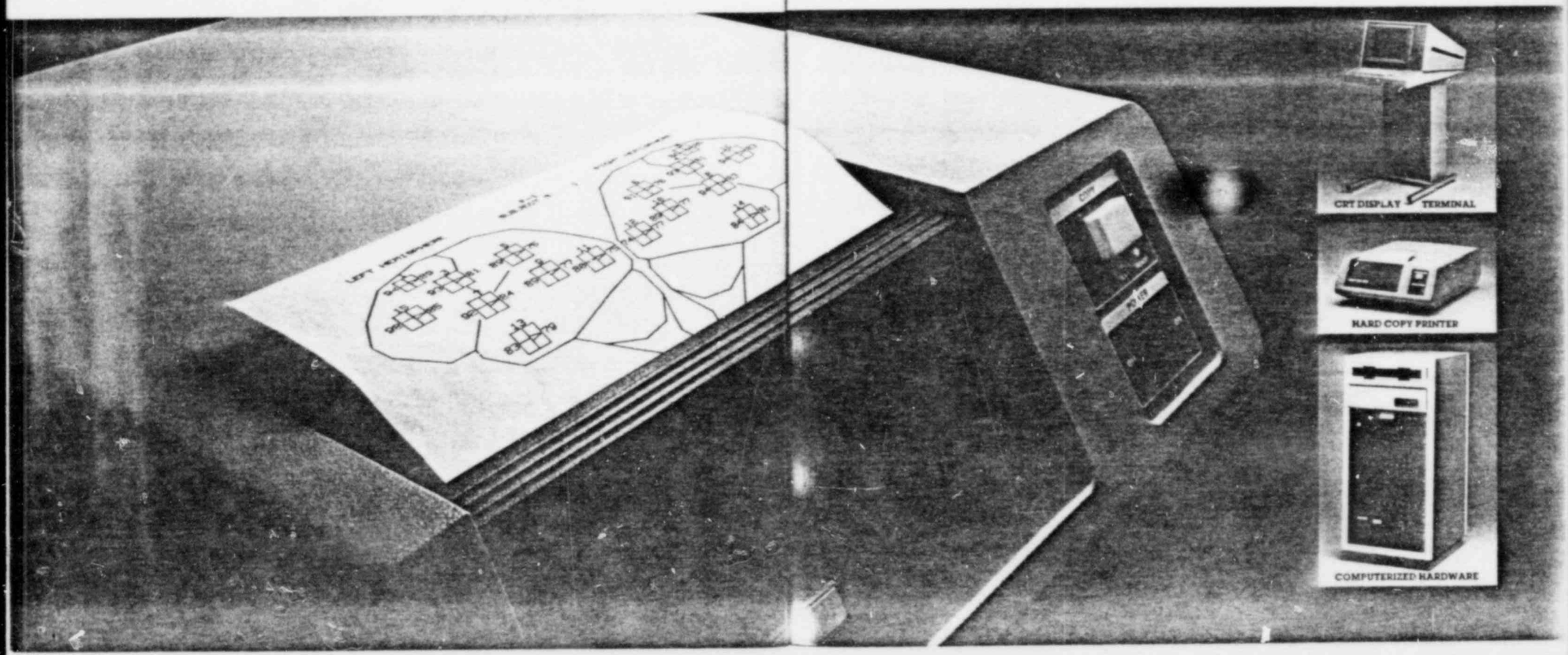
*Digital Equipment Corp., Maynard, MA.

Compact hardware requires less floor space.
The modularity of the Harshaw System 400 components permits practical installation in as little as 64 square feet (6 square meters) of floor space. Because of its mobility, installation in Intensive Care is common.

Harshaw provides complete system support.
The new System 400 brings all the components you need for advanced rCBF analysis together in a system designed for top performance and backed by superior service. Technical assistance and replacement parts are available worldwide within as little as 24 hours.

Complete on-site installation and customer training are provided by Harshaw technicians. Clinical reports on newly identified rCBF applications and other technical data are periodically provided without charge.

For complete details on how Harshaw can bring your clinical and research rCBF analysis capabilities to the forefront of technology, call or write to arrange an appointment in your laboratory or clinic.



Footnotes:

1. Paulson O. B.: Regional Cerebral Blood Flow in Apoplexy Due to Occlusion of the Middle Cerebral Artery. NEUROLOGY 20:63-77, 1970.

2. Fieschi E., Des Rosiers M.: Cerebral Blood Flow Measurements in Stroke. In Ross Russell RW (ed): CEREBRAL ARTERIAL DISEASE. London, Churchill Livingston, 1976, pp. 85-106.

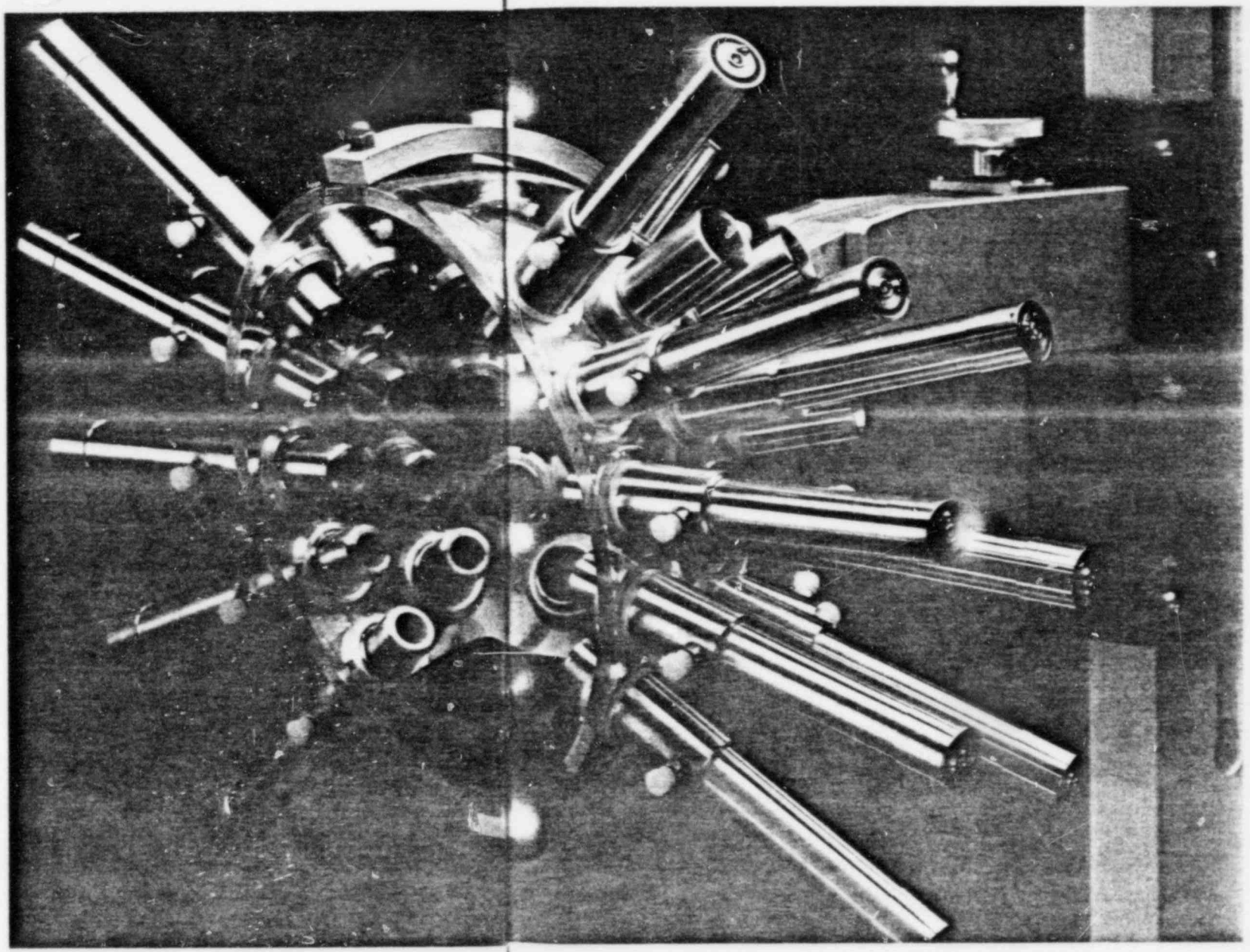
3. McHenry L. C., Jr., Mettory J., et al: Xenon-133 Inhalation Method for Regional Cerebral Blood Flow Measurement: Normal Values and Test-Retest Results. STROKE 9:395-399, 1978.

4. Naritomi H., Meyer J. S., et al: Effects of Advancing Age on Regional Cerebral Blood Flow. ARCHIVES OF NEUROLOGY 36:410-416, 1979.

5. These values are derived from participants in the longitudinal study of aging in cerebral vascular disease under the auspices of J. S. Meyer, M.D. and T. Shaw, Ph.D., Veterans Administration Medical Center, Division of Cerebral Vascular Research, Houston, Texas.

6. Fletcher R.: A New Approach to Variable Metric Algorithms. COMPUTER J 13:317-322, 1970.

7. Obrist W. D., Thompson H. K., Jr., Wang H. S., et al: Regional Cerebral Blood Flow Estimated by Xenon-133 Inhalation. STROKE 6:245-256, 1975.



CONVERSATION RECORD

TIME

DATE 6/19/85

TYPE ☐ VISIT ☐ CONFERENCE ☒ TELEPHONE ☐ INCOMING ☒ OUTGOING

ROUTING

NAME/SYMBOL	INT

Location of Visit/Conference:

NAME OF PERSON(S) CONTACTED OR IN CONTACT WITH YOU	ORGANIZATION (Office, dept., bureau, etc.)	TELEPHONE NO.
Tom Kompurias, HP	Harper-Grace Hosp.	313/494-9381
		494-8417

SUBJECT Xenon-133 amendment

SUMMARY ① Your calculations for concentrations of Xe-133 in restricted areas and unrestricted areas use an assumed loss rate of 10% which is too low. Calculations should use a 20% loss rate.

② The concentrations in restricted areas using 20% seem to produce adequate results, but the results of calculations using 20% loss rate in unrestricted areas are slightly higher than NRC requirements.

a.) Submit new calculations:

1. use 20% loss and
2. you should either:
   a.) increase exhaust or
   b.) lower per patient dose (20mCi) or
   c.) decrease number of studies ~~or~~
   ~~d.) increase from a dome~~.

Note: Xenon is vented to the outside via stack

ACTION REQUIRED

License must respond in 30 days in writing with control # 79162

NAME OF PERSON DOCUMENTING CONVERSATION

SIGNATURE J R Made

DATE 6/19/85

ACTION TAKEN

SIGNATURE

TITLE

DATE

50271-101 ☆ GPO : 1981 O - 361-526 (7221) CONVERSATION RECORD OPTIONAL FORM 271 (12-76) DEPARTMENT OF DEFENSE