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DEUTERATION IN SLOW NEUTRON RADIOGRAPHY OF BIOLOGICAL MEDIA

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ABSTRACT

Contrasts in slow neutron radiography of biological media can be improved by replacing hydrogen with deuterium in various tissues. Muscle and bone exposed to D_2O readily exchange hydrogen for deuterium. If fully deuterated, their linear attenuation coefficients are reduced from approximately 3.4 and 2.3 cm^{-1} to 0.5 and 0.5 cm^{-1}, respectively. Fatty tissues, however, have little tendency to deuterate, and the linear attenuation coefficients remain approximately 3.5 cm^{-1}. Slow neutron radiographs of deuterated-biological specimens show the fat distribution with contrasts exceeding those of conventional roentgenography.

Calculations show that with a 50-70% hydrogen-deuterium exchange, slow neutron radiography of specimens as thick as the adult human arm or leg could be done without excessive radiation dose. However, clinical application of this technique cannot be recommended at this time because of the toxic effects of D_2O. Deuterating isolated segments of the body may have clinical applications in the future; however, deuteration with slow neutron radiography, at present, is feasible only as a medical research procedure. A suitable source for investigating research uses for deuteration within a medical institution may be a moderated ^{252}Cf neutron source assembly.

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INTRODUCTION

Slow neutron radiographs usually do not show contrasts between soft tissues of similar density and thickness.[1-6] However, it has been observed[5] that by exposing specimens to heavy water, improved contrasts between some tissues can be induced. These contrasts are due to deuteration, the selective replacement of hydrogen by deuterium.

Studies of the use of heavy water as a biological contrast agent for slow neutron radiography were conducted jointly by the Medical College of Georgia and the Savannah River Laboratory. This research was part of a recently concluded effort to investigate the potential that neutron radiography might have for both biological research and clinical diagnosis.

The use of deuteration as a contrast-inducing process and some of the potential applications to non-clinical research are described in this report. The constraints of absorbed radiation dose and heavy water toxicity on the clinical use of deuteration are considered. The use of moderated neutrons from ^{252}Cf sources for neutron radiography in medical research is also discussed.

SUMMARY

The selective exchange of hydrogen for deuterium reduces the attenuation of slow neutrons in tissue because the absorption and scattering cross sections are much larger for hydrogen than for deuterium. After deuteration, fatty tissues have been imaged with high contrast against surrounding muscle, bone, and most body fluids. The contrasts are caused by an almost total lack of hydrogen-deuterium exchange when fats are exposed to heavy water. Thus, the fats remain neutron opaque in the much more radiolucent medium of muscle and bone where high levels of exchange occur.

Possible research applications of deuteration include: tumor pathology, yellow bone marrow visualization, direct imaging of the distribution of myelinated nerve tissue, and selective imaging where contrasts are induced by obstructing deuteration artificially. For example, if dextran is added to a D_2O-glucose-saline solution which is infused into the head of a living rat, all organs except the brain cells and the aqueous humor of the

eye are extensively deuterated. Subsequent radiographs show the brain and eye with relatively high contrast against the surrounding tissues.

Pathological specimens can be deuterated by soaking the specimens in D_2O. Living research animals can be deuterated by intra-peritoneal or intra-arterial injections of D_2O.

Application of slow neutron radiography with deuteration to clinical diagnosis of human disease is hindered by two interrelated problems: radiation dose limitations and heavy water toxicity. The thickness of tissue that can be penetrated by slow neutrons, within the clinical constraints of dose and exposure time, is increased as hydrogen is replaced by deuterium. Deuteration decreases the number of incident neutrons required to take a given radiograph and also the absorbed dose per neutron. With a hydrogen-deuterium exchange of 50-70%, a part as thick as an adult human arm or leg could be radiographed without incurring an unreasonable dose.

Techniques to diminish the toxic effects of heavy water on living specimens at high deuteration levels have not been developed to the degree required for human use. The technique of deuterating isolated regions of the body, if developed, might make clinical applications possible. Hydrogen-deuterium exchange levels as high as 50% have been obtained in the heads of living rats without apparent harm to the animals.

Californium-252 could be used as a neutron source in research; however, it is not recommended for clinical applications. Any economically feasible ^{252}Cf assembly (approximately 100 mg maximum) probably would not have sufficient beam flux to be useful clinically.

DISCUSSION

PROCEDURE

Most of the neutron radiographs of this report were taken with the thermal neutron beam emitted through the thermal column of the Standard Pile at the Savannah River Laboratory. The beam was collimated by the 3-in.-diameter central thimble with a flight path of 93 in. from midcore to the edge of the thermal column. The radiography station was 83 in. further out where the beam flux was approximately 3×10^6 neutrons/(cm^2)(sec) when the reactor was operated at a power of 8 kw.

The transfer detection technique was used for recording the neutron images.[4] With this method, a latent image is made by inducing beta activity in a thin metallic foil that is placed behind the object. The foil is then placed in contact with an x-ray emulsion. This transfer technique was used because a high gamma-ray flux accompanied the neutron beam and would have caused interfering gamma images in any direct method of recording images using radiographic film.

An antiscatter grid[7] was placed between the object and the foil (usually dysprosium with a 2.3 hr half-life) to minimize image interference from neutrons scattered within the object. The exposure data for the neutron and x-radiographs shown in this report are summarized in Table I.

TABLE I

PHYSICAL FACTORS FOR RADIOGRAPHS

Neutron Radiographs

Figure	Specimen	Neutron Source	Film[a]	Incident Fluence, neutrons/cm^2
1	Tumors	Standard Pile	NS-54T	2.3×10^8
2	Human Finger	Standard Pile	NS-54T	4.0×10^9
3	Rat Head	Standard Pile	NS-54T	8.0×10^8
4	Rat Leg	Georgia Tech Research Reactor	AA	1.7×10^{10}

X-Radiographs[b]

Figure	Specimen	Control Settings KVP	mA	Sec
1	Tumors	24	300	1
2	Human Finger	20	300	5
3	Rat Head	20	300	4
4	Rat Leg	20	300	4

[a] All film exposures by transfer to 0.010-in. dysprosium foil.

[b] All X-radiographs taken with conventional mammography techniques[8] at 30-in. FSD.

INDUCED CONTRASTS OF DEUTERATION AND RESEARCH APPLICATIONS

Hydrogen nuclei are mostly responsible for the attenuation of neutrons as they traverse normal tissues. Deuterium absorbs and scatters far fewer neutrons than hydrogen. If the hydrogen-deuterium exchange within tissues during exposure to D_2O is significant, the linear attenuation coefficients of the tissues are reduced (Table II). Under certain circumstances, adjacent organs may have different degrees of exchange. Thus, radiographic contrasts between the organs may be altered by exposing them to heavy water. For example, the linear attenuation coefficients of fats are not affected appreciably by deuteration,[5] presumably because of the hydrophobic characteristics of most fats. If adjacent non-fatty tissues, such as muscle and bone, are deuterated, the linear attenuation coefficients of these tissues are decreased to values as low as 0.5 cm^{-1} while the coefficients of the fatty tissues remain as high as 3.5 cm^{-1} (Table II). Because muscle and bone are easily deuterated, high contrasts between these tissues and fatty tissues are seen in neutron radiographs of deuterated specimens.

The contrasts caused by deuteration have the following potential research applications: 1) the nondestructive visualization of fat in and about tumors, 2) the direct imaging of yellow bone marrow, 3) the direct imaging of myelineated nerve tissue concentrations in brain slices, and 4) the imaging of certain anatomical structures by selectively deuterating the tissues surrounding these structures and by using deuteration in combination with positive contrast agents.

TABLE II

COMPARISON OF THEORETICAL LINEAR ATTENUATION COEFFICIENTS OF 0.025-eV NEUTRONS IN NORMAL AND DEUTERATED TISSUES[a]

	Linear Attenuation Coefficients, cm^{-1}		
	Muscle	Bone	Fat
Without Deuteration			
Hydrogen	3.26	2.06	3.28
All Other Elements	0.17	0.27	0.18
Total	3.43	2.33	3.46
With Deuteration			
Deuterium	0.32	0.21	3.28[b]
All Other Elements	0.17	0.27	0.18
Total	0.49	0.48	3.46

[a] The element composition of muscle and fat is from Ref. 9, and that of bone cortex is from Ref. 2. The neutron cross sections are from Ref. 10.

[b] Assumes no hydrogen-deuterium exchange.

Tumor Histology

X-ray and neutron radiographs of two tissue slices that were soaked in heavy water for 24 hours are compared to histological sections for tissue identification in Figure 1. The lower radiographs are of a lymph node imbedded in fat. In the conventional X-ray, the lymph node is somewhat more opaque than the surrounding fatty tissues; in the neutron radiograph, the fatty tissues are more opaque. With the improved contrast in the neutron radiograph, another small lymph node as well as several small vessel-like structures to the side of the two nodes can be seen.

The upper radiographs in Figure 1 show a similar comparison using tissue from an adenocarcinoma of the colon that has a small collection of fat at the tip of the specimen. The contrast between the fat and the other tissues is more noticeable in the neutron radiograph.

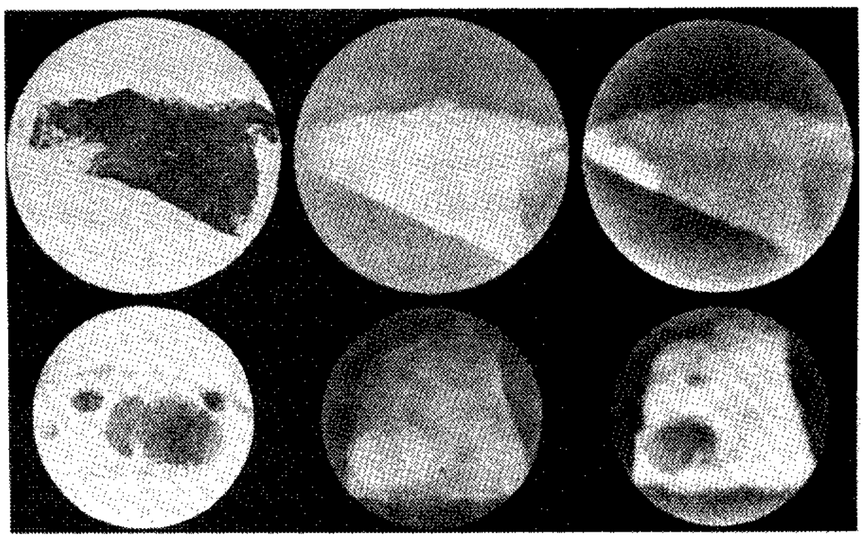


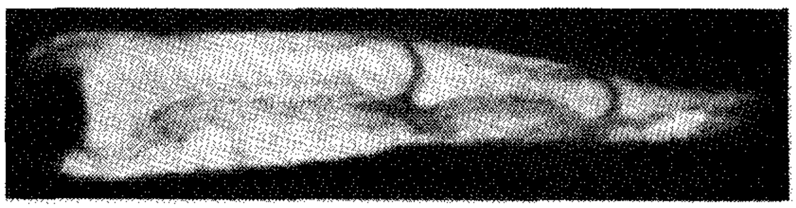
FIG. 1 X-RAY, NEUTRON RADIOGRAPH, AND HISTOLOGICAL SECTION OF DEUTERATED TISSUES

Yellow Bone Marrow Visualization

The ability to image yellow bone marrow directly is unique to slow neutron radiography. Figure 2 is a comparison of X-ray and neutron radiographs of a human finger specimen that was soaked in heavy water for 48 hours before being radiographed. The neutron radiograph shows the radio-opacity of the fatty bone marrow in strong contrast to the radiolucency of the bone cortex and the connective tissues in the joints.

Direct Imaging of the Distribution of Myelinated Nerve Tissue

A 1-cm brain slice was soaked in heavy water for 24 hours and was then radiographed. As anticipated, the myelinated white matter was somewhat more opaque than the grey matter. Destruction of the fatty myelin in nervous system disorders could perhaps be visualized in this manner during pathology investigations.



NEUTRON RADIOGRAPH

X-RADIOGRAPH

FIG. 2 X-RAY AND NEUTRON RADIOGRAPH OF DEUTERATED HUMAN FINGER SPECIMEN

Selective Imaging

Figure 3 is a comparison of X-ray and slow neutron radiographs of a rat's head. The radiographs were made after a heavy water-dextran solution* was infused into both carotid arteries over a 4-hr. period. All of the tissues except the eyes, brain, and retro-orbital fat became radiolucent to neutrons; therefore, these structures show high contrast. This did not occur when glucose and saline alone in heavy water was used for the arterial perfusion. Dextran may have interfered with the hydrogen-deuterium exchange across the blood-brain and blood-aqueous humor barriers.[11,12] This technique could possibly be used to investigate drugs and other factors affecting the integrity of the blood-brain and blood-aqueous humor barriers.

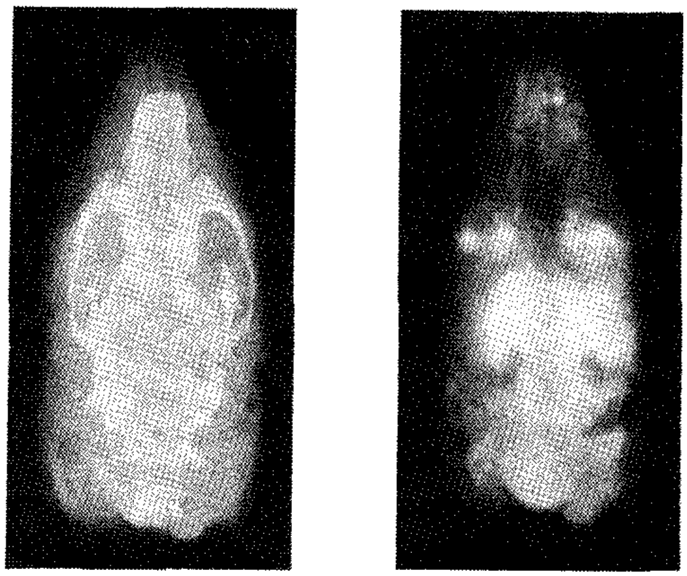


FIG. 3 X-RAY AND NEUTRON RADIOGRAPH OF DEUTERATED RAT HEAD SPECIMEN

Another method of inducing tissue contrasts is in the double contrast arteriogram in Figure 4. Neutron opaque gadolinium oxide was injected into the arteries of a rat. Most of the surrounding tissues were then made radiolucent by soaking the specimen in heavy water for 24 hours. The neutron radiograph shows an improvement in the visualization of the arterial structures that were hidden by bone in the conventional roentgenographs (particularly the caudal, tibial and digital arteries).

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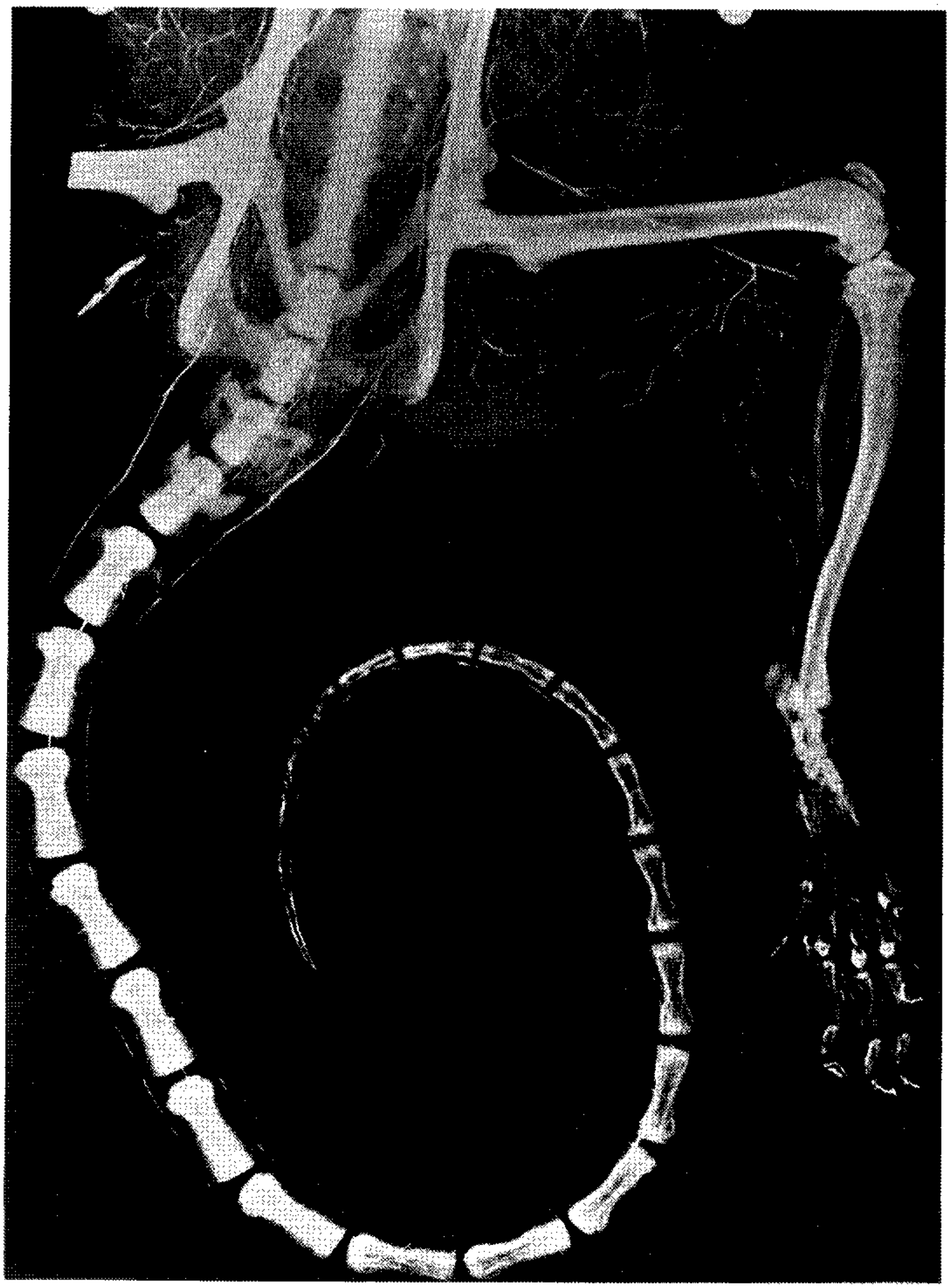
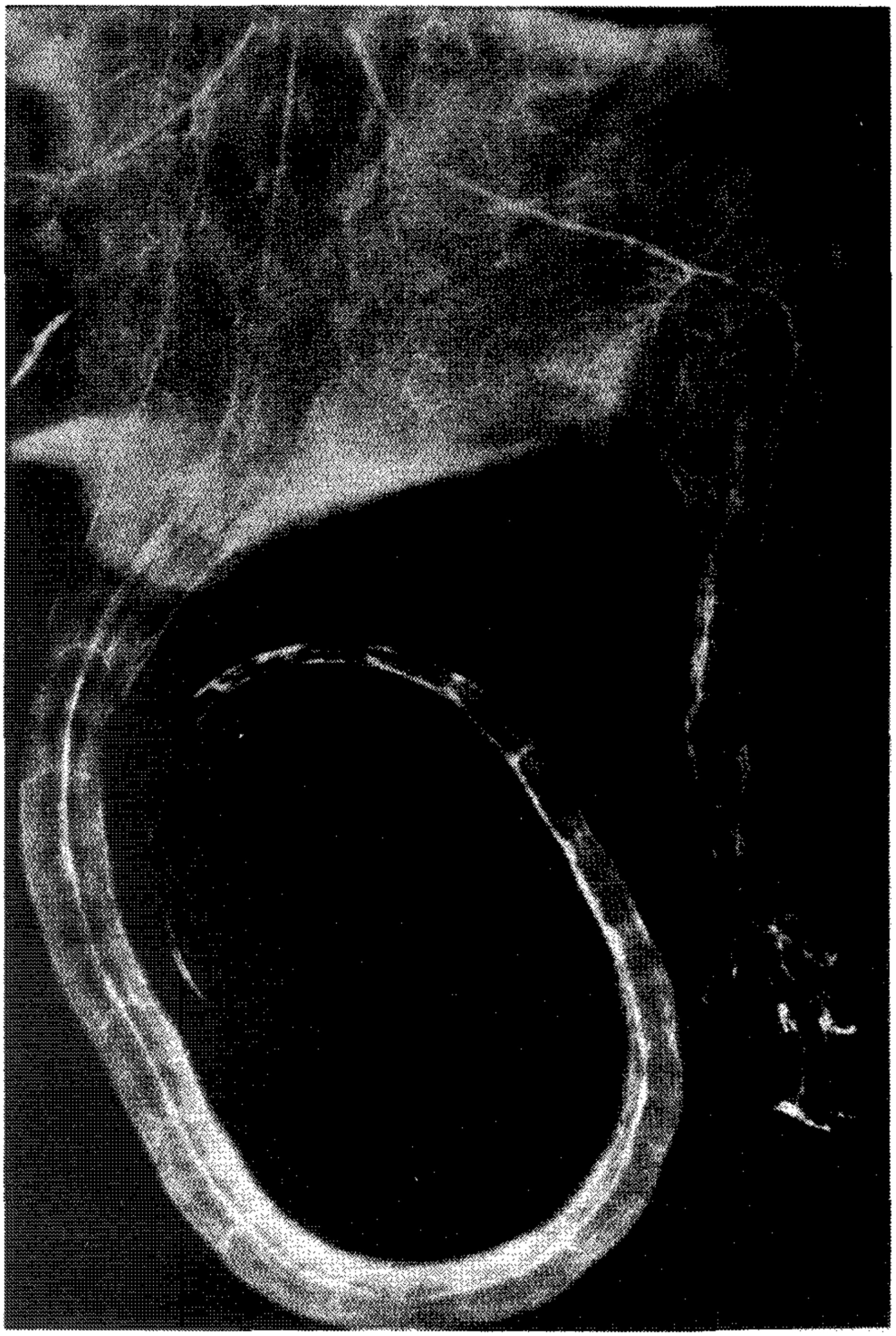
* 5 grams of medium molecular weight (75,000) dextran, 5 grams of glucose, and 0.9 grams of sodium chloride in 100 cc of 99.87% pure heavy water.



X-RADIOGRAPH

FIG. 4 ARTERIOGRAM OF RAT LEG, PAW, AND TAIL WITH Gd_2O_3 AS A POSITIVE CONTRAST AGENT



NEUTRON RADIOGRAPH

FIG. 4 (Continuation)

Other Applications

The improved contrasts in neutron radiography by deuteration may possibly be used to determine the replacement of red with yellow bone marrow, the hydrogen content of tumors, the effectiveness of a given artery in the delivery of hydrogenous fluids across vessel walls into adjacent tissues and endodontic disease processes.

CLINICAL CONSTRAINTS

For certain research purposes, neutron dose and heavy water toxicity may not be important. Clinical use of deuteration, however, will be severely restricted by these two constraints.

Neutron Dose

Slow neutrons are unable to penetrate more than 2-3 cm of normal tissues without delivering unreasonably large radiation doses.[1-6] Deuteration reduces neutron dose because the linear attenuation coefficients are reduced and the $^1H(n,\gamma)$ reaction does not occur. Thus, a smaller incident neutron fluence is required for a given exit fluence (i.e., fewer incident neutrons will be required to take a radiograph of a given specimen). The $^1H(n,\gamma)$ reaction that is responsible for part of the absorbed neutron dose is replaced by a deuterium capture reaction in which only negligible amounts of radioactive tritium are produced.

Statistical arguments show that the neutron exposure and the detector efficiency must be such that at least 10^7 neutrons/cm^2 are recorded to produce an adequate radiograph.[13] A similar requirement for the detected gamma fluence has been shown for conventional roentgenographs.[14] In Figure 5, the calculated dose from thermal neutrons received at the surface of a water density tissue (muscle) is shown as a function of the tissue thickness and the percent of hydrogen replaced by deuterium, assuming that 10^7 n/cm^2 reach a 100% efficient detector. (For actual detector efficiencies, the required dose is the indicated dose divided by the efficiency.) Scattered neutrons are assumed to be removed before reaching the detector (i.e., narrow beam geometry), and the dose per unit fluence is assumed to be caused by only the $^1H(n,\gamma)$ and $^{14}N(n,p)$ reactions.[15]

With high temperature moderation techniques, the average energy of the neutron beam can be raised, and smaller doses are possible because of the reduced attenuation of the higher-energy neutrons.[16]

The efficiency of the transfer detection technique with 0.010-in. dysprosium foils (used for all of the neutron radiographs of this report) is estimated to be no higher than 17%. Efficiencies approaching 100% are possible with such detectors as ^6LiF-ZnS(Ag) scintillating mixtures. If the deuteration level were 100%, objects of muscle and bone as thick as 15-20 cm could be radiographed within clinically acceptable dose limitations. However, humans cannot tolerate such a high deuteration level. The absorbed radiation dose, and thus the acceptability of slow neutron radiography for clinical diagnosis, will depend very sensitively on the maximum deuteration level that can be tolerated.

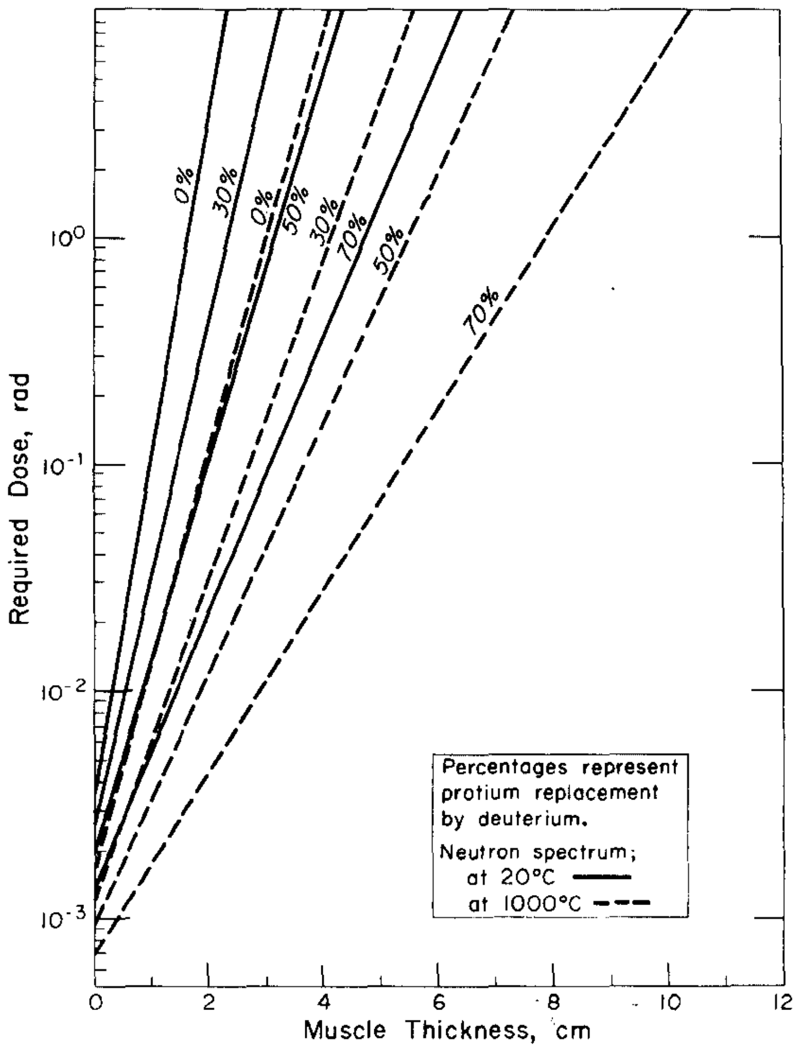


FIG. 5 SURFACE DOSE AS A FUNCTION OF TISSUE THICKNESS AND HYDROGEN-DEUTERIUM EXCHANGE

Heavy Water Toxicity

Heavy water has been shown to have significant toxic effects[17,18] on many types of organisms, including mammals. Because of this, the toxicity limitations must be established before deuteration techniques can be used clinically. The toxic effects of chronic ingestion of heavy water have been extensively studied,[18] and the main points are summarized in Table III. If deuteration is to be used clinically, the heavy water will probably be administered in a single dose rather than by chronic ingestion. Because little information is available on single dose administration, single dose toxicity was studied.

Whole Body Gross Toxicity. Single dose injections, with heavy water saline, were administered to rats intraperitoneally, intravenously, and in combinations of both methods. Rats survived injections of heavy water that did not exceed 40% of their body fluid weight; death occurred with injections >40%. The total non-lethal replacement of hydrogen by deuterium was ≤30%, determined by examining muscle, blood, and urine samples. The relationship between the time following intraperitoneal injection and the deuterium concentration in these samples is shown in Figure 6.

A maximum concentration of 30% is probably not sufficient for clinical use of deuteration in neutron radiography. Figure 5 indicates that only a 5-cm-thick tissue specimen could be radiographed at 30% deuteration with a dose of 5 rads even with the 1000°C neutron spectrum.

Isolated Region Gross Toxicity. Hydrogen replacement may be increased if the heavy water is confined to a segment of a rat's body following injection. Deuteration levels as high as 50% in the muscle of the hind limbs did not cause death, when heavy water-saline was injected through a catheter inserted below the ligated abdominal aorta superior to the bifurcation. The return flow was drained through a catheter inserted into the inferior vena cava. Similar D_2O concentrations in the brains of rats did not cause death when heavy water-saline was injected into the carotid arteries.

The upper limit on deuteration of the heads of rats without lethal effects was not determined.

TABLE III

CHRONIC INGESTION OF HEAVY WATER BY SMALL MAMMALS

Replacement[a]	Effect	Reversible
<15%	No gross effects	--
15-20%	Hyperexcitability	Yes
20-25%	Frequent convulsions	Yes
30%	Comatose	Usually
>30%	Death	--

[a] % of body fluids replaced with D_2O.

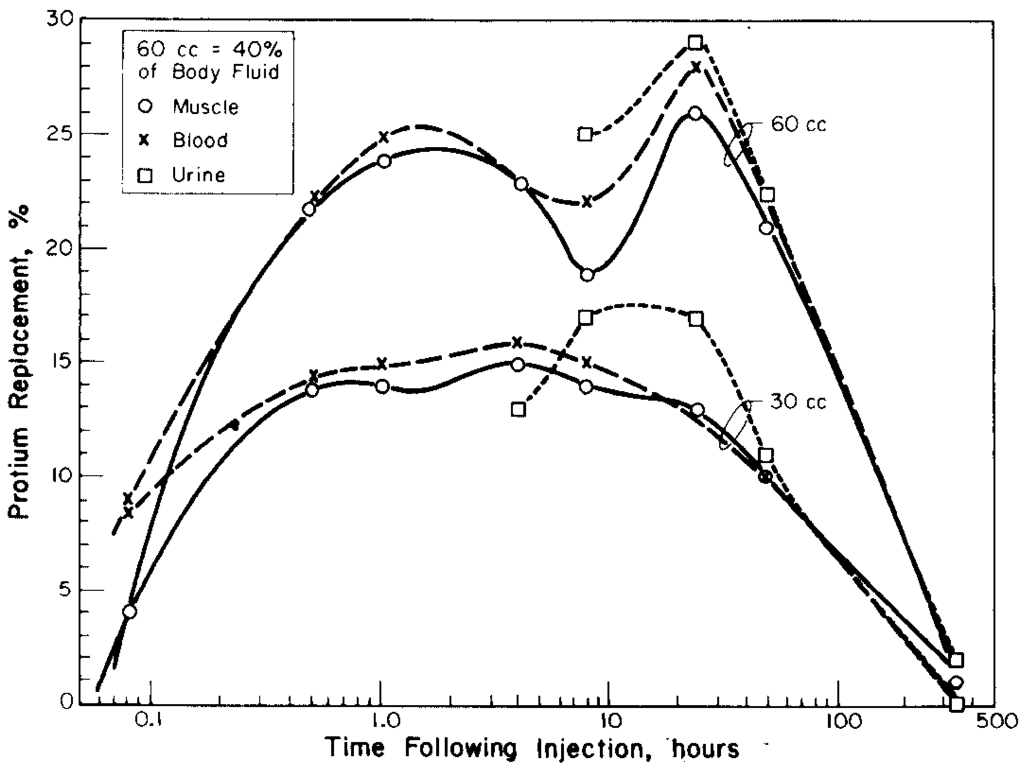


FIG. 6 PROTIUM REPLACEMENT FOLLOWING PERITONEAL HEAVY WATER INJECTION IN RATS

RESEARCH NECESSARY TO DEVELOP CLINICAL USE OF DEUTERATION

Isolated segment infusion experiments indicate that portions of rats can be deuterated to at least 50% levels. It has not been determined whether such a level could be obtained in the extremities of humans, but if it were, radiographs of limbs as thick as 7 cm would be possible with a high, though still clinically acceptable, dose of 5 rads (Figure 5). Higher levels of deuteration would increase the penetrable thickness within acceptable radiation dose limits.

Some of the research necessary to establish clinical uses for deuteration as a contrast-inducing process in slow neutron radiography are:

- Determining the upper limit of deuteration in isolated segments in research animals

- Determining the sub-lethal effects of deuteration of isolated segments on mitotic, enzymatic, and metabolic processes, et al.

- Determining techniques for isolating and deuterating segments of the human body

- Demonstrating clinical advantages of deuteration over more conventional techniques

^{252}Cf APPLICATION

^{252}Cf might be used in a moderating assembly as a neutron source for slow neutron beams. Such beams would be sufficiently intense for medical research applications of slow neutron radiography with deuteration; however, the source strength may be too small for clinical applications.

The usefulness of a moderated ^{252}Cf neutron source depends on the thermal flux levels attainable at the radiography site. A thermal flux of 0.0205 neutrons/(cm^2)(sec) can be obtained in the middle of a polyethylene sphere of 20 cm radius from a ^{252}Cf emitter of one fast neutron/sec.[19] ^{252}Cf emits 2.34×10^{12} neutrons/(sec)(g);[20] thus, a midcore thermal flux of 4.8×10^{10} neutrons/(cm^2)(sec) could be obtained from a 1 g source. Calculations by F. J. McCrosson at Savannah River show that a homogeneous mixture of enriched ^{235}U and H_2O, at an effective multiplication constant of K = 0.980 and with a 17 cm radius, boosts the thermal flux at the midcore to about 2×10^{11} neutrons/cm^2-sec per gram of ^{252}Cf.

The imaging of finely detailed structures of biological media needs at least the resolution capabilities of the Savannah River radiography facility. The reduction in flux in the usable beam from the midcore of a ^{252}Cf assembly should be similar to the reduction observed in the Savannah River facility, where the ratio of the midcore to radiography station flux is approximately 8×10^4. Thus, the flux obtained at the radiography station from the moderated neutron emission of 1 g of ^{252}Cf boosted by the k = 0.980 $^{235}U\text{-}H_2O$ mixture should be about 2.6×10^6. (This multiplication is about the maximum that can be used without requiring that the system have the same safeguards as reactors.)

The neutron radiograph of the rat head (Figure 3) was taken with a total incident neutron fluence of 7.8×10^8 neutrons/cm^2. If 100 mg of ^{252}Cf (about the largest economically feasible amount) were used in the flux enhancing assembly discussed, this radiograph would have required an exposure of 50 minutes, which is well within the saturation limits imposed by the half-lives of the most useful transfer image recording foils such as dysprosium (2.35 hours).

Thus meaningful research on the biological aspects of deuteration can be carried out with a ^{252}Cf source in a multiplying system. However, this output is too small for use in a clinical facility. The human extremities are two to four times thicker than the rat head sample and would require prohibitively long exposure times. Therefore, ^{252}Cf is not likely to be a useful source for any potential clinical applications of slow neutron radiography.

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