

## BROOKHAVEN NATIONAL LABORATORY

## MEMORANDUM

Records Holding Area  
 REPOSITORY Bldg. 494

DATE: June 16, 1960

COLLECTION Protocols - Clinical

TO: Ctte on Use of Radioactive Isotopes  
in Patients

BOX No. 4

FROM: W. L. Hughes

FOLDER Human Protocols 1950-1963

SUBJECT: Request for approval of use of  
isotope in patient.1. Title

Administration of I<sup>131</sup>-labeled iododeoxyuridine for the external measurement of the proliferative activities of human tissues. *Project Request H-65*

2. Investigators

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3. General Statement

The purpose of this study is to develop a diagnostic procedure using I<sup>131</sup>-deoxyuridine (I\*DU) for the estimation of cell proliferation in the human by external measurement of radioactivity. Such a procedure should be a useful tool for gauging the effects of x-rays either at a diagnostic or at a therapeutic level or, in fact, for quantitating any treatment based on inhibiting new cell formation. If sufficient resolution in whole-body scanning can be achieved, differential estimation in several proliferating tissues, including neoplasms, may be possible. For this purpose the positron scanner now being designed by Dr. Robertson should be readily adaptable. (The BNL cyclotron can prepare the positron-emitting I<sup>124</sup> of 4.5 d half-life.)

Biochemically, this technic depends upon the incorporation of I\*DU into the DNA which must be synthesized as a prerequisite to cell division. I\*DU appears to behave like thymidine when injected. It rapidly leaves the blood stream of mice and distributes throughout the body tissues. Most of it is then excreted during the first 24 hours as breakdown products. The remainder (about 10% of the injected dose) remains as an integral part of DNA. However, after several days this "permanent" activity also starts to decline presumably through maturation and death of labeled cells as in the intestinal mucosa which may contain up to half of the "permanent" activity.

We propose the initial injection of 20  $\mu$ c into patients of limited life expectancy and unlikely to procreate. Activity retained and excreted will be measured by the whole-body counter and attempts will be made to observe localization in various parts of the body. At a suitable time after I\*DU injection, a much smaller dose of I<sup>133</sup> will be injected to estimate the residual iodide pool so that its effect on apparent localization can be assessed. With this preliminary information, we will re-estimate the dose to target organs and then propose the use of larger doses of greater diagnostic utility.

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#### 4. Isotopes

$I^{131}$  0.6 mev  $\beta$ , 0.36 mev  $\gamma$ , 8.1 d half-life

$\rightarrow Xe^{131}$  (stable)

$I^{133}$  1.3 mev  $\beta$ , 0.538 mev  $\gamma$ , 21 hr. half-life

$\rightarrow Xe^{133}$  (5 d half-life - rapidly expired)

obtained carrier-free in 0.1 N NaOH from BNL reactor, neutralized, diluted with I.V. saline, and autoclaved in vaccine bottles before administration.

Compound:  $I^{131}$ -deoxyuridine (I\*DU) prepared by reacting Oak Ridge carrier-free  $I^{131}$  (iodide) with deoxyuridine in dilute nitric acid. Purified by anion-exchange chromatography to a radioisotopic purity of greater than 90% as measured by co-crystallization with carrier IDU.

Specific Activity of I\*DU: greater than 1 mc/mg.

Radioactive Assay: This will be performed on a duplicate vial in a gamma ray spectrometer prior to injection.

Vehicle: Solution in 0.01 M acetic acid, neutralized, diluted with NaCl, and sterilized by heat (autoclave) in vaccine bottles.

Route of Administration: I.V.

Pharmacology: I\*DU is not particularly toxic. The LD50 in mice is approximately 2 g/kg (Prusoff). We are preparing material with a specific activity greater than 1 mc/mg so that we will be injecting less than 0.1 mg. This is one-millionth of the dose per kg. which is toxic for mice. Furthermore, I\*DU has been administered by Welch in 50-gram amounts to patients as an anti-cancer agent.

Iodouracil (not radioactive) causes mutations in B. coli. This is presumably because its incorporation into DNA results in mistakes in the information code. While this effect has not been reported for mammals, it must be presumed to operate, and therefore may also restrict the use of I\*DU in persons with procreative expectancy.

#### 5. Radiation Dosage

Whole-Body Dose:  $I^{133}$  - ca. 0.2 mr from 1  $\mu$  injected.  $I^{131}$  (I\*DU) after intravenous injection initially disappears from the mouse (via urine) with a half-time of 2 hr. This is close to the half-time of iodide and, in fact, much of the activity in urine is iodide. Therefore, let us assume an excretion rate similar to iodide for the fast component in humans or a half-time of 10 hr. If the initial concentration of this component is 1  $\mu$ /kg, in infinite time it will give a radiation dose of 8 mr, assuming uniform distribution.\* Patients will receive Lugol's solution continuously to block thyroidal accumulation of radiiodide.

\* assuming "g" factor of 125 - see attached sheet

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Dose to Labeled Organs: The small intestine may contain up to half of the "permanent" radioactivity. Assuming it to be a sphere with a mass of 1 kg, it can be seen that it will receive essentially all of the beta dose from its contained radioactivity and ~~less than one-third of the~~ *only a fraction* gamma dose. The infinite beta dose for  $I^{131}$  with a physical half-life of 8.1 days is about 118 mr for 1  $\mu\text{c}/\text{kg}$ . ~~One-third of the~~ gamma dose in infinite time would be about 30 mr for 1  $\mu\text{c}/\text{kg}$ .<sup>\*</sup> Therefore, the total dose from the permanent activity will be less than 150 mr for 1  $\mu\text{c}/\text{kg}$ .

Values for a standard man:

G.I. tract - 2000 g - 2.9% body weight  
Bone marrow  
  red - 1,500 g  
  yellow - 1,500 g

Therefore, assuming about 1 kg of bowel heavily labeled, we would be allowed about 2  $\mu\text{c}$  of  $I^{131}$  permanently concentrated in this volume. Similarly, for the bone marrow we would be allowed about 6  $\mu\text{c}$  of permanent activity.

The above calculations assume uniform distribution throughout the tissue in question. Actually those nuclei which are labeled will receive somewhat higher doses from their contained radiation. This effect is not as large as might be envisaged since the beta energy from  $I^{131}$  is so great that only a very small percentage is expended within the labeled nucleus. (We estimate that this amounts to only one-third of the dose from the uniform beta flux.) Furthermore, since the labeling time is very short, many nuclei in any tissue will completely escape labeling due to the asynchrony in cell division.

Total Dose: This will then be somewhat less than the sum of the doses calculated under "Whole-Body Dose" and "Dose to Labeled Organs." Thus, if we injected 10  $\mu\text{c}$  of  $I^{131}$  into a 70-kg man and 9  $\mu\text{c}$  were rapidly excreted as iodide, the dose from the iodide component would be 1.0 mr. If half of the remaining microcurie was built into the intestine, the total dose from this would be 75 mr (calculated as in "Dose to Labeled Organs"). Therefore, the total dose to the intestine would be about 80 mr, and the dose to other less heavily labeled tissue would be less.

#### 6. Health Physics Aspect

The precautions applied will be the same as for  $I^{131}$  as iodide since the hazards for internal emission are the same and the possibility of contamination is largely through excreted iodide. Urine and feces are to be collected for counting.

\* Hine + Brownell p 854 give "g" at center of 1kg sphere as 90. Average "g" will then be about 50 with resultant infinite dose of 30 mr for  $1\mu\text{c}/\text{kg}$ .

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Hughes, Gitlin and Farr - IDU- June 16, 1960

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