O.R.

Panel on Generator Production
Isotopes Vienna 5/11-15/70

ACRH--1000-212
CONF-700517--5

LEGAL NOTICE

This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Atomic Energy Commission, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

MASTER

Preparation and Control of ^{99m}Tc Radiopharmaceuticals

Katherine A. Lathrop

Department of Radiology and the Argonne Cancer Research Hospital,*
University of Chicago, Chicago, Illinois 60637 U.S.A.

Methods of preparation have evolved considerably since the first administration of $\text{Na}^{99m}\text{TcO}_4$ to a human late in 1961 (1). A brief description of this evolution may be useful since it has resulted entirely from efforts to produce for intravenous use sterile solutions that are free of pyrogenic, chemical, radiochemical and radionuclidic contaminants, and to minimize radiation exposure to all persons involved in preparation and administration of the radiodiagnostic agents, as well as to the patient.

The first ^{99m}Tc generator was produced by the Brookhaven National Laboratory (2) and consisted of a small column of inorganic ion-exchanger, aluminum oxide, supported by a scintered glass filter, on which fission product $\text{NH}_4^{99}\text{MoO}_4$ had been adsorbed, and from which the ^{99m}Tc daughter was removed by elution with 1 N HNO_3 or HCl . All subsequent ion-exchange ^{99m}Tc generators have been basically of the same design. Also eluted with the ^{99m}Tc were some long-lived fission products associated with the ^{99}Mo and some aluminum from the column which precipitated on neutralization of the eluate to make it suitable for intravenous use. Most of the radionuclidic contamination, including small quantities of ^{99}Mo , and the aluminum could be removed by extracting the ^{99m}Tc into methyl-ethyl-ketone from 5 N sodium hydroxide. The ketone was removed by evaporation and the dry $\text{Na}^{99m}\text{TcO}_4$ was taken up in any desired volume of sterile isotonic NaCl , or processed to other chemical forms (3). This extraction procedure, although a simple chemical manipulation, complicated the preparation beyond what most nuclear medicine laboratories were prepared to undertake at that time.

The Brookhaven laboratories found it possible to remove most of the contaminating radionuclides from the ^{99}Mo solution before application to the ion-exchange column. The problem with precipitated aluminum hydroxide

Operated by the University of Chicago for the United States Atomic Energy Commission.

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

109

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

vanished along with the necessity for neutralization when reports from Hammersmith Hospital (4) showed that isotonic NaCl eluted the ^{99m}Tc as efficiently as did inorganic acids. With these improvements, the ion-exchange generator became a satisfactory source of $\text{Na}^{99m}\text{TcO}_4$ for intravenous use except that some kind of sterilization before administration remained necessary. Several systems which, with reasonable assurance, produced sterile, pyrogen-free solutions of $\text{Na}^{99m}\text{TcO}_4$ suitable for brain scanning or thyroid function studies, were developed by the radiopharmaceutical companies, who, by this time, had taken on manufacture of ^{99m}Tc generators. These solutions were, however, not well suited for the dynamic flow studies which many laboratories were finding of diagnostic usefulness, because these studies require injection of the radioactivity in a small volume to act as a bolus in the blood stream. The required ^{99m}Tc in a sufficiently small volume could be available only during the early life of the generator. In addition to this problem, another was introduced with increased use of the generators. Sufficient fission-product ^{99}Mo could not be made available to meet the demand and manufacturers turned to use of neutron-activated molybdenum to supply their need for ^{99}Mo . In order to place sufficient quantities of ^{99}Mo in the generator, chemically large amounts of molybdenum must be used, resulting in bulkier columns from which enough molybdenum is eluted to be grossly evident in some chemical processing and whose biological inertness has yet to be proved for all cases (i.e., molybdenum sulfide). Development of the sterile ion-exchange generator has been accompanied by development of sterile pre-prepared kits to which the sterile eluate is added to make other chemical forms of ^{99m}Tc .

While these developments were taking place, the additional purification of the ^{99m}Tc eluate by methyl-ethyl-ketone extraction continued to be used at the University of Chicago's Argonne Cancer Research Hospital as a safeguard against ^{99}Mo contamination and as a convenience in allowing the patient dose to be maintained at approximately one milliliter. Since extensive testing in these laboratories showed that no more than 50 or 60% of the ^{99m}Tc from ^{99}Mo decay could be obtained from any of the available generators, it was decided to eliminate use of the ion-exchange generator and to produce ^{99m}Tc directly from a liquid-extraction generator (5). Advantages of this course are: 1) cost of ^{99m}Tc is reduced considerably below the cost for the same quantity of ^{99m}Tc from an ion-exchange generator; 2) patient doses are held to a volume of about 1 ml to allow bolus injection; and 3) contamination with Mo is eliminated. Disadvantages are: 1) more highly skilled personnel are required; and 2) responsibility for testing for sterility, pyrogenicity, and radiochemical purity resides entirely within the individual laboratory rather than being borne wholly or in part by the manufacturer. These disadvantages seem likely to disappear with the successful development of a closed-system, entirely automated liquid-extraction generator now nearing completion by one manufacturer (6). Several larger hospitals with research orientation, and some radiopharmaceutical companies have initiated use of the liquid-extraction generator during the last year or two.

A third development in the supply of ^{99m}Tc radiodiagnostic agents to nuclear medicine facilities has been the establishment of centrally located processing laboratories from which on-call deliveries are made within the

service area. In this way solutions ready for intravenous injection are available to the scanning laboratory with all responsibility for quality testing being taken by the supplier.

Three distinct means are, thus, presently available to provide the nuclear medicine laboratory with ^{99m}Tc : 1) Use of an ion-exchange generator to produce sterile $\text{Na}^{99m}\text{TcO}_4$ with employment of this sterile solution for conversion to other ^{99m}Tc radiodiagnostic agents, perhaps with pre-prepared sterile kits. 2) Use of a liquid-extraction generator to produce dry $\text{Na}^{99m}\text{TcO}_4$ which is then converted to the various agents. 3) Use of completely finished preparations delivered from a central processing laboratory. The form in which a particular nuclear medicine facility chooses to have its ^{99m}Tc agents supplied depends, of course, on its particular needs, including such considerations as the number of patient examinations which are made per day; what facilities and personnel are available; whether ^{99m}Tc is used exclusively for established patient studies or is used, in addition, for investigational studies of new agents in animals and humans. The three types of supply for ^{99m}Tc radiodiagnostic agents may have developed in response to the needs of three kinds of nuclear medicine facilities: 1) The hospital with medium or heavy patient load may find it most economical to buy ion-exchange generators and sterile preparation kits. 2) The hospital with heavy patient load and strong research interest in preparation of new radioactive agents may find it economically advantageous to hire a radiopharmacist and devote space and equipment to a radiopharmacy. 3) The small hospital with light patient load will probably find that the most economical course is to purchase injectable solutions provided it is located within a service area. The distinction is less clear-cut than stated, of course, and the choice of supply must be evaluated in terms of the actual situation.

Whatever method of supply is used, responsibility must be taken at some point to assure sterility, apyrogenicity, efficacy, and chemical, radiochemical and radionuclidic purity of the final product injected into the patient. Present guide-lines for making such tests were written for pharmaceutical manufacturers and nonradioactive parenterals produced in large quantities. The radioactive pharmaceuticals presently included in the U. S. Pharmacopeia and National Formulary (i.e., those incorporating ^{32}P , ^{51}Cr , ^{57}Co , ^{60}Co , ^{125}I , ^{131}I , ^{198}Au , ^{203}Hg) are all relatively long-lived compared with the 6 hour half-life of ^{99m}Tc . Standards of testing for these materials have been relaxed to allow their use prior to completion of the ten-day sterility tests. This variation in procedure, although helpful, is not sufficient in actual practice when dealing with radioisotopes whose half-lives are a few hours or less. Relatively large volumes are prepared with radionuclides having much longer half-lives, such as those mentioned, so that the required test volume is only a small fraction of the total. Individual patient doses, or multiple doses for a few patients, are necessarily made with the short-lived materials which must be used within a few hours. It becomes unrealistic if the patient dose is about 1 ml, and the entire batch is about 10 ml (to be used for 9 or 10 patients) to double the volume, and consequently the ^{99m}Tc used and the radiation dose to the pharmacist, in order to allow testing in conformity with the volumes specified by the U. S. Pharmacopeia. The present attitude of the United States Food and Drug Administration, although no official recommendations have been written, affords the recognizably essential protection needed for the patient, and is

compatible with the actual use of very short-lived materials, so that all their advantages are gained without assumption of the risks associated with lack of pretesting. By this procedure, the radiodiagnostic agent is produced in a sterile closed-system using reagents pretested for sterility and pyrogens. The system must be thoroughly tested for repeated reliability and uniformity of product before it is employed to produce the radiodiagnostic agent for use in human beings. It must also be challenged at intervals during use to insure that performance has not been impaired.

As an example of the procedures used for production of ^{99m}Tc radio-diagnostic agents, the routines followed at the University of Chicago Hospitals and Clinics will be described in detail. These are not presented as being superior to any of the many published in the nuclear medicine literature, but only as methods that have proved highly satisfactory for several years in this laboratory.

1. Separation of ^{99m}Tc from ^{99}Mo in a liquid-extraction generator

The schematic diagram of the generator is shown in figure 1. ^{99}Mo is dissolved in 25 ml of 5 N NaOH. The operational procedure is: Turn on vacuum, place container with 25 ml of methyl-ethyl-ketone under outlet arm of separatory funnel, adjust stopcock 1 to control flow, open stopcock 2, open stopcock 5 to air. As soon as MEK has been drawn into separatory funnel, close stopcock 5 to air and open slightly to reservoir to draw ^{99}Mo solution into funnel. Mix phases vigorously for 2 to 3 min, by bubbling air through extraction chamber controlling air flow with stopcock 1. Allow phases to separate by closing stopcocks 5 and 2, and opening stopcock 1. Return aqueous layer to reservoir by opening stopcock 5 (may be accelerated by opening stopcock 3). Close stopcock 5 when interface reaches stopcock, then open to allow MEK to drain through Al_2O_3 . Open stopcock 5 to reservoir to drain aqueous solution from tubing into reservoir. Turn off vacuum, close stopcock 5 and open stopcock 3 to air. Stopcock 4 is for loading and unloading ^{99}Mo solution, which may also be done at stopcock 5, thus eliminating stopcock 4. The MEK solution is assayed in a calibrated ion-chamber for ^{99m}Tc , and used as required to prepare the various ^{99m}Tc agents. Some of the solution is saved at intervals for radionuclidic purity determination using a scintillation spectrometer and a multi-channel analyzer. A record of extraction and use data such as is shown in figure 2, is very helpful in organizing the production schedule and in predicting future requirements for ^{99}Mo .

In general only one preparation of each agent is made each day, so that sterility and radiochemical purity may be determined for each. A constant check on these parameters seems desirable in assessing any untoward reaction or distribution of radioactivity in the patient. No organisms have been cultured from patient preparations in about three years of constant sterility testing. The chromatographic test for radiochemical purity aids in keeping the pharmacist aware of the necessary precision required to achieve uniformity of preparation and in assessing patient scans. Representative chromatogram tracings are shown in figure 3 for each of the ^{99m}Tc agents described below. The record used for these tests is shown in figure 4. Part II of this record, the test for efficacy, is always used for a new preparation until confidence has been established in its biological

UNIVERSITY OF CHICAGO HOSPITALS & CLINICS
SECTION OF NUCLEAR MEDICINE

DIAGRAM FOR LIQUID-LIQUID EXTRACTION OF ^{99m}Tc FROM ^{99}Mo

Unpublished work from Argonne Cancer Research Hospital
University of Chicago

Figure 1

- 6 -
Figure 2

⁹⁹Mo - ^{99m}Tc EXTRACTION DATA: Week of _____

UNIVERSITY OF CHICAGO HOSPITALS & CLINICS
SECTION OF NUCLEAR MEDICINE

⁹⁹Mo reference No. _____

MONDAY

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by							

TUESDAY

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by							

WEDNESDAY

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by							

THURSDAY

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by							

FRIDAY

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by							

DATE:

Extraction Number	1	2	3	ml's MEK Used			
Assay Time					1	2	3
mCi/ml				TcO ₄ ⁻			
Total ml's				Tc-S			
mCi's total				Tc-Fe			
Calc'd mCi's ⁹⁹ Mo				Tc-alb.			
^{99m} Tc % yield							
Control Number							
Prepared by

← origin
solvent front →

Figure 3

Figure 4

UNIVERSITY OF CHICAGO HOSPITALS & CLINICS SECTION OF NUCLEAR MEDICINE	RADIOISOTOPE PHARMACY RADIOCHEMICAL, BIOLOGICAL AND STERILITY RECORD																																																																																																																																																																																																																																																																																																						
I. CHROMATOGRAPHY: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>date tested _____</div> <div>time on _____</div> <div>time off _____</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>solvent system _____</div> <div>lot number _____</div> <div>normal R_f _____</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>R_f & % of total:</div> <div>1 _____</div> <div>2 _____</div> <div>3 _____</div> <div>4 _____</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>Tested by _____</div> <div>Reported by _____</div> </div>																																																																																																																																																																																																																																																																																																							
II. BIOLOGICAL DATA: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>date tested _____</div> <div>tested by _____</div> <div>reported by _____</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>animal used _____</div> <div>ml's used _____</div> <div>injection route _____</div> <div>time injected _____</div> <div>time sacrificed _____</div> </div> <div style="margin-top: 10px;"> Tissues sampled & counts/time: 1. _____ 2. _____ 3. _____ 4. _____ 5. _____ </div>																																																																																																																																																																																																																																																																																																							
III. BACTERIOLOGICAL DATA: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>date inoculated _____</div> <div>inoculated by _____</div> </div> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th rowspan="3">Date</th> <th rowspan="3">°C</th> <th colspan="6">Thioglycollate, Lot No: _____</th> <th rowspan="3">°C</th> <th colspan="6">Sabouraud, Lot No: _____</th> <th rowspan="3">Read by</th> </tr> <tr> <th colspan="6">Tube Identification</th> <th colspan="6">Tube Identification</th> </tr> <tr> <th>1</th> <th>2</th> <th>3</th> <th>IC</th> <th>SC</th> <th>1</th> <th>2</th> <th>3</th> <th>IC</th> <th>SC</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> <div style="margin-top: 10px; font-size: small;"> Record + for growth; - for no growth. IC = inoculated control. SC = sterile control. </div> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div>Month _____ Day _____ Year _____</div> <div>Day of Week _____</div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>Radiopharmaceutical _____</div> <div>Control Number _____</div> </div>		Date	°C	Thioglycollate, Lot No: _____						°C	Sabouraud, Lot No: _____						Read by	Tube Identification						Tube Identification						1	2	3	IC	SC	1	2	3	IC	SC																																																																																																																																																																																																																																																																
Date	°C			Thioglycollate, Lot No: _____							°C	Sabouraud, Lot No: _____						Read by																																																																																																																																																																																																																																																																																					
				Tube Identification								Tube Identification																																																																																																																																																																																																																																																																																											
		1	2	3	IC	SC	1	2	3	IC		SC																																																																																																																																																																																																																																																																																											

distribution pattern. A detailed record for the materials used is kept for each preparation, similar to the two shown in figures 5 and 6, as an aid in tracing any changes in character of the radiodiagnostic agent.

2. Preparation of $\text{Na}^{99}\text{TcO}_4$ solution. Place the required volume of MEK solution in a sterile container and evaporate to dryness in a stream of filtered air by gentle heating on a hot plate. Add the desired volume of sterile pyrogen-free isotonic saline and shake briefly. Take up the solution in a sterile syringe and filter into a second sterile syringe through a sterile $0.2\ \mu$ membrane filter.

3. Preparation of $^{99m}\text{Tc-S}$ colloid. Place the required volume of MEK solution in a sterile container and evaporate to dryness in a stream of filtered air by gentle heating on a hot plate. Add 0.5 ml per patient dose of a 1% solution of pharmaceutical grade gelatin in 1 N HCl that has been prepared immediately before use. Heat gently to dissolve gelatin. Add 10 ml of H_2S gas per patient dose and allow to stand at room temperature for 15 minutes. (The H_2S is measured in a syringe fitted with a teflon-lined, three-way needle adapter inserted into the stopper closing the reaction vessel.) Adjust solution to pH 5.5 to 6 with 1 N NaOH. (This adjustment must be made carefully so that pH 6 is not exceeded which will result in formation of pertechnetate ion.) Take up the solution in a sterile syringe and filter into a second sterile syringe through a sterile $0.45\ \mu$ membrane filter fitted with a microfiber glass prefilter. Yield should be 90 to 95% and the volume about 1 ml per patient dose.

4. Preparation of $^{99m}\text{Tc-Fe}^{++}$ complex. Place the required volume of MEK solution in a sterile container with teflon-coated magnetic stirring bar. Evaporate to dryness in stream of filtered air by gentle heating on a hot plate. Add 2 ml of 20% HCl, 0.2 ml 5% ascorbic acid and 0.2 ml FeCl_2 in 20% HCl (200 μg Fe). Using magnetic stirrer and pH meter, add 5 N NaOH until solution reaches pH 3. Then add 1 N NaOH to pH 7.5. Take up in sterile syringe and filter into a second sterile syringe through a sterile $0.2\ \mu$ membrane filter. Final volume is 3.5 to 4 ml.

5. Preparation of $^{99m}\text{Tc-albumin}$ solution. Place the required volume of MEK solution in a sterile container with a teflon-coated magnetic stirring bar. Evaporate to dryness with gentle heat from a hot plate in a stream of filtered air. Add 1 ml of 2.5 N HCl and 0.5 ml of 5% ascorbic acid solution. Allow to stand at room temperature 30 min or longer to reduce pertechnetate. Add with mixing 0.1 ml of 1% albumin solution. (This is a sterile solution prepared by diluting sterile normal human serum albumin, 12.5 g/50 ml, with sterile saline, 1 ml to 25.) Mix for 15 min and add 0.2 ml of 10 N NaOH to bring to about pH 1. Using pH meter add 1 N NaOH to pH 6. Pass through a small sterile anion-exchange column in chloride phase to remove pertechnetate. Take up eluate in sterile syringe and filter into second sterile syringe through a $0.2\ \mu$ membrane filter.

6. Preparation of $^{99m}\text{Tc-albumin}$ microspheres. To a sterile vial containing 2 mg albumin microspheres (Minnesota Mining and Manufacturing Company) and a teflon-coated magnetic stirring bar, add 0.1 ml 2% Tween-80 solution in isotonic NaCl. Stir well and add 1.7 ml sterile $\text{Na}^{99m}\text{TcO}_4$.

PREPARATION AND DISPENSING RECORD
PERTECHNETATE

NaCl solution: Manufacturer _____

Preservative _____ Concentration _____

Manufacturer _____

Assay:	mCl's/ml	time	total ml's	total mCl's	% yield
--------	----------	------	------------	-------------	---------

[illegible]

Day of Week

Control Number

Figure 6

UNIVERSITY OF CHICAGO HOSPITALS & CLINICS SECTION OF NUCLEAR MEDICINE			PREPARATION AND DISPENSING RECORD Tc-S COLLOID			
MEK solution:						
mCi's used		control number				
GELATIN:						
mg's used		control number		manufacturer		
HCl:						
ml's used		normality		control number		
				manufacturer		
H₂S GAS:						
cc's used		cylinder number		manufacturer		
NaOH:						
ml's used		normality		control number		
				manufacturer		
STERILIZATION:						
millipore size		μ. Prefilter		yes no manufacturer		
FINAL pH:						
ASSAY:						
mCi's/ml		time		total ml's		
				total mCi's % yield		
DISPENSING:						
Syringe Number	Scheduled		ml's	Assayed		Dispensed by
	mCi	Time		mCi	Time	
Month		Day		Year		Day of Week
Prepared by			control number			

solution. With continued stirring add 0.1 ml sodium thiosulfate solution. Place container in a boiling water bath. Add 0.1 ml 2 N HCl. Heat and stir for 15 min. Centrifuge. Remove supernatant through sterile needle. Wash with 5 ml sterile 0.1% Tween-80 solution. Suspend particles in 2 to 3 ml of 0.1% Tween-80 solution.

On completion of any preparation it is assayed for ^{99m}Tc . Patient doses are dispensed throughout the day according to the volumes taken from Table 1. Each syringe containing the patient dose is assayed before and after injection. A record is kept of each injection from each preparation as shown in figure 7. No patient dose is dispensed until the pharmacist has received the completed prescription form shown in figure 8. Each batch preparation is cultured on thioglycollate and Sabouraud's media. In no instance has bacterial contamination been demonstrated over a two-year period representing approximately 750 preparations a year.

System testing for pyrogens at infrequent intervals has proved adequate as no significant pyrogenic reaction occurred in any patient.

We attribute these favorable results to the use of strong chemical reagents which prevent the growth of bacteria and to careful handling of glassware which is routinely soaked in 2 N NaOH to destroy any possible adherent bacterial pyrogens. In addition, reusable glassware is kept to a minimum, i.e., for the handling of ketone. Otherwise, disposable, sterile, pyrogen-free equipment is used.

In developing the pharmaceutical preparations themselves, the basic philosophy has been to keep additives to a minimum and to use only what is absolutely essential. This simplifies the problem of assuring chemical purity of the preparations and minimizes any possibility of chemical toxicity.

REFERENCES

- [1] HARPER, P.V., ANDROS, G., LATHROP, K., Preliminary observations on the use of six-hour Tc^{99m} as a tracer in biology and medicine, Semiannual Report to the Atomic Energy Commission, Argonne Cancer Research Hospital, ACRH-18 (1962) 76-88.
- [2] RICHARDS, P., A survey of the production at Brookhaven National Laboratory of radioisotopes for medical research, V Congresso Nucleare, 2 (1960) 225-244.
- [3] HARPER, P.V., LATHROP, K.A., GOTTSCHALK, A., "Pharmacodynamics of some technetium- 99m preparations", in Radioactive Pharmaceuticals (Proc. of a Symposium held at the Oak Ridge Inst. of Nuclear Studies, 1-4 Nov., 1965) CONF-651111.
- [4] MATTHEWS, C.M.E., MALLARD, J.R., Distribution of ^{99m}Tc and tumour/brain concentrations in rats, J. Nucl. Med. 6 (1965) 404-408.
- [5] ANWAR, M., LATHROP, K., ROSSKELLY, D., HARPER, P.V., Pertechnetate production from ^{99}Mo by liquid-liquid extraction, J. Nucl. Med. 9 (1968) 298-299.

VOLUME INCREASE WITH TIME FOR ^{99m}Tc PREPARATIONS

1. Calculate the ml's required to give the requested mCi's for assay time of stock preparation.
2. Find this volume under the appropriate vertical time column.
3. Read the volume required for requested time on the same horizontal column.

7:00 7:30	8:00 8:30	9:00 9:30	10:00 10:30	11:00 11:30	12:00 12:30	1:00 1:30	2:00 2:30	3:00 3:30	4:00 4:30	5:00 5:30	6:00 6:30	7:00 7:30	8:00 8:30	9:00 9:30	10:00 10:30
1 1.06 .94 1	1.12 1.19 1.06 1.12	1.27 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16	3.55 3.76 3.35 3.55	4 4.22 3.76 4	4.47 4.74 4.22 4.47	5 5.32 4.74 5	5.63 6 5.32 5.63
.89 .94 .84 .89	1.1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16	3.55 3.76 3.35 3.55	4 4.22 3.76 4	4.47 4.74 4.22 4.47	5 5.32 4.74 5
.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16	3.55 3.76 3.35 3.55	4 4.22 3.76 4	4.47 4.74 4.22 4.47
.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16	3.55 3.76 3.35 3.55	4 4.22 3.76 4
.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16	3.55 3.76 3.35 3.55
.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82	3.16 3.35 3 3.16
.50 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51	2.82 3 2.66 2.82
.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24	2.51 2.66 2.37 2.51
.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2	2.24 2.37 2.11 2.24
.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78	2 2.11 1.88 2
.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59	1.78 1.88 1.68 1.78
.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41	1.59 1.68 1.50 1.59
.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26	1.41 1.50 1.33 1.41
.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12	1.26 1.33 1.19 1.26
.20 .21 .19 .20	.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1	1.12 1.19 1.06 1.12
.18 .19 .17 .18	.20 .21 .19 .20	.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89	1 1.06 .94 1
.16 .17 .15 .16	.18 .19 .17 .18	.20 .21 .19 .20	.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79	.89 .94 .84 .89
.14 .15 .13 .14	.16 .17 .15 .16	.18 .19 .17 .18	.20 .21 .19 .20	.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71	.79 .84 .75 .79
.125 .13 .12 .125	.14 .15 .13 .14	.16 .17 .15 .16	.18 .19 .17 .18	.20 .21 .19 .20	.22 .24 .21 .22	.25 .27 .24 .25	.28 .30 .27 .28	.32 .33 .30 .32	.35 .37 .33 .35	.40 .42 .37 .40	.45 .47 .42 .45	.5 .53 .47 .5	.56 .60 .53 .56	.63 .67 .60 .63	.71 .75 .67 .71

Figure 7

[illegible]

Figure 8

RADIOPHARMACY
PRESCRIPTION

Date _____

Radiopharmaceutical _____

Dose: _____ mCi Time _____

Type of Scan _____

Patient's Name _____

Unit Number _____

Perchlorate Yes No

- [6] TOREN, D.M., POWELL, M.R., Automatic production of technetium-99m for pharmaceutical use, J. Nucl. Med. 11: In press (1970).