MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
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NUCLEAR MEDICINE
Part I

HOW MUCH ANXIETY

"There is a common tendency in our day, both on the part of professional psychologists and laymen, to look upon anxiety as a negative, destructive, "abnormal" experience, one which must be fought and if possible annihilated...."

O. H. Mowrer[1]

Since 1950 the literature on anxiety, both professional and lay, has increased a thousandfold in the form of articles, symposia, reports and scientific exhibits. And virtually all of this output reflects a common presumption—that anxiety is a negative, nonproductive experience. This viewpoint leads naturally to a discussion of how to combat or eliminate anxiety.

But anxiety, as Mowrer implies, has its uses. It can play a positive and constructive role in human development. Without it neither an individual nor a society can grow.

Productive vs. nonproductive anxiety: a matter of degree

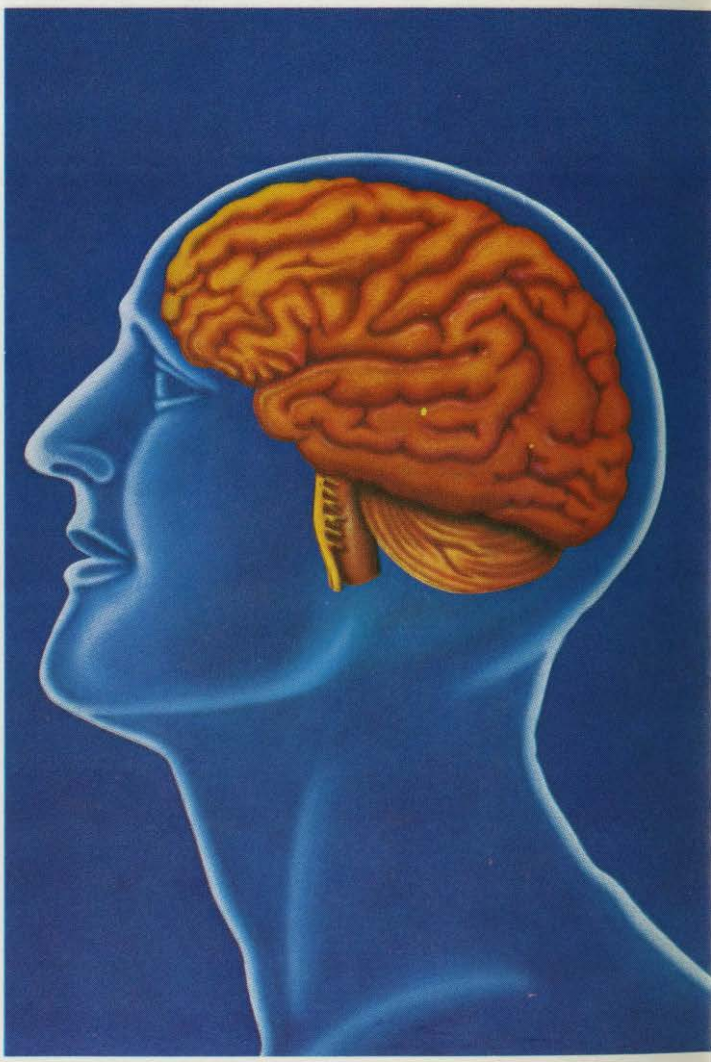
For the physician the difference is not an academic one. He *must* distinguish between productive and nonproductive anxiety. And the difference is often one of degree.

In low levels of anxiety, for example, the individual is alert and sensitive to threats and acquires an increased ability to cope. Performance is often improved.[2]

But at higher levels of anxiety the opposite is true.[2] The ability to distinguish between the dangerous and the trivial is reduced and often leads to inappropriate behavior. Apprehension becomes fear. And coping becomes difficult, if not impossible.

Crossing the anxiety threshold

The key question for the physician then becomes: Is the degree of anxiety experienced productive or nonproductive for the individual patient? And while some patients may require relatively large amounts of anxiety to perform optimally, for others lower levels of anxiety may prove unproductive.



Librium®(chlordiazepoxide HCl): to help lower the level of anxiety

When anxiety has reached levels that seriously

IS PRODUCTIVE?

impair performance, reassurance and counseling may be sufficient for the patient. If not, adjunctive antianxiety medication may be called for.

Librium (chlordiazepoxide HCl), by quickly and effectively calming the anxious patient, helps to lower the level of anxiety. When anxiety has been reduced to manageable levels, therapy with Librium should be discontinued.

Librium®(chlordiazepoxide HCl): an uncomplicated clinical course

To be truly effective, antianxiety medication must allay anxiety without complicating the clinical course. Librium meets this criterion. Librium, when used in proper dosage, rarely interferes with mental acuity. Side effects are seldom encountered. And Librium is used concomitantly with many primary medications.

For a more detailed discussion of the side effects, precautions and warnings, please consult the brief summary of product information on this page.

References: **1.** Mowrer OH, quoted in May R: *The Meaning of Anxiety*. New York, Ronald Press Co., 1950, pp. 108 ff. **2.** Basowitz H *et al*: *Anxiety and Stress*. New York, McGraw-Hill, 1955, pp. 12 ff.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

LIBRIUM®
chlordiazepoxide HCl/Roche®
5 mg, 10 mg, 25 mg capsules

BASIC IN CLINICAL ANXIETY

ROCHE

Roche Laboratories
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Nuclear Medicine

Part I

MCV/Q

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1975 • Volume Eleven • Number Two

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INTRODUCTION

During my residency at the University of Chicago twenty years ago, I performed the few diagnostic studies employing radioactive isotopes as a "sideline," spending a couple of hours each day in the laboratory. Nuclear Medicine since then has grown into a vast field incorporating in vitro studies, in vivo procedures, and treatment with radioactive isotopes.

The continued development of new isotopes is presenting us with new techniques. Some of these isotopes have such a short half-life that they have to be produced locally, and their purity and concentration have to be controlled by a radiopharmacist who has become a team member of all larger nuclear medicine divisions.

The equipment detecting the radiation emerging from these isotopes has become much more sophisticated, and the quality of the images produced during scanning procedures approaches that of radiographs. But imaging has changed from being a simple reflection of normal or pathological morphology to a method of dealing with abnormal physiology. Dynamic computer-assisted scanning of the heart, for example, can tell us today whether myocardial damage is irreversible, and multiple sequential scans can demonstrate an arteriovenous shunt of the brain.

It is not astonishing that in this rapidly progressing field even the expert might lose sight of the latest developments, and this is the reason why the Department of Radiology of the Medical College of Virginia felt it would be appropriate to present a program on Nuclear Medicine during our Annual Postgraduate Course Series in Williamsburg. We were fortunate in attracting an outstanding faculty which agreed to undergo the additional workload of editing selected papers presented in Williamsburg for publication in this and the forthcoming issue of the *MCV Quarterly*.

I would like to congratulate my colleagues for their superb contributions to the *Quarterly*. I would like to thank Drs. Ghahremani and Sharpe who so ably organized the Postgraduate Course and express my special appreciation to Ms. Mary-Parke Johnson, the Managing Editor of the *MCV Quarterly*, for her support and editorial assistance.

KLAUS RANNIGER, M.D.
Professor and Chairman
Department of Radiology

Radiopharmaceutical Production and Quality Control*

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With the development of shorter-lived, organ-specific radiopharmaceuticals, much of the manufacture and quality control of these products have shifted from commercial manufactures to individual nuclear medicine laboratories. Recognizing this fact, the Nuclear Regulatory Commission (NRC) is encouraging quality assurance by proposing that "an authorized physician may permit technicians and other paramedical personnel to perform the preparation and quality control testing of radiopharmaceuticals . . ." (1).

Cohen (2) has catagorized pharmaceutical controls into chemical, biological, and physical. Figure 1 is a diagram of these controls. In each control a degree of purity is implied and is often determined by comparison to a standard.

Chemical controls.

A. *Radiochemical purity.* May be defined as that portion of the stated radionuclide in the stated chemical form. This can be assessed in the nuclear medicine laboratory by several techniques. It is applicable to Tc^{99m}-pertechnetate compounds where the degree of tag to an organ-specific molecule must be evaluated.

Radiochemical impurities may be demonstrated in those images where organs other than the target organ are visualized due to a free (unbound) radioactive component of a labeled product. Visualization of thyroid on lung imaging (Fig. 2) or stomach with kidney (Fig. 3) and bone (Fig. 4) imaging are examples of these. Reagent "kits" labeled with radionuclides should be at least 90% bound for optimum organ visualization. The assessment of binding can be accomplished in the laboratory by the use of gel filtration and/or thin-layer chromatographic techniques. Labeled reagent kits may contain small molecules (free Tc^{99m}-pertechnetate), larger labeled molecules, and a reduced technetium fraction which is considered neither free nor bound to an organ-specific molecule. To determine the percentage of each component in this three-phase system by employing the gel filtration technique, 1-2 μl of the material is placed at the top of a gel column and eluted with a suitable solvent. Heavy molecules which do not enter the gel meshwork will be eluted first, after the void volume. Light molecules will follow several milliliters later. Reduced technetium, if present, will bind to the gel and can be removed by oxidation with 0.1% H_2O_2. This fraction can be subsequently collected with additional volumes of solvent. The fractionated volumes are counted and quantitation of each component may be determined.

Thin-layer chromatography employs the use of suitable media strips to which is spotted 5μl of the radioactive material 2.5 cm from the bottom of the strip. The strip is dried and placed in a developing tank containing a suitable solvent system (Fig. 5). The solvent is allowed to ascend the strip until the front is at approximately 14 cm. Solvent systems chosen provide for the bound material to remain approximately at the origin (point of application) while free activity migrates to the level of the solvent front. Using this method, Rf (reference factor) may be determined. These factors are ratios of distance

* Presented by Dr. Hirsch at the Postgraduate Course in Nuclear Medicine, February 25, 1975, in Williamsburg, Virginia.

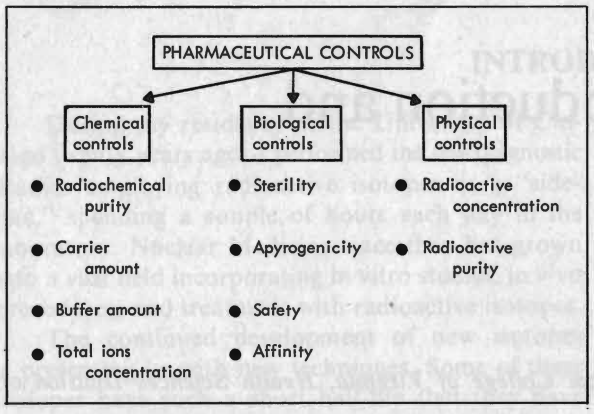


Fig. 1—Diagram of the radiopharmaceutical controls.

traveled by the radioactive entities to that traveled by the solvent front. Labeled molecule Rf are approximately 0–0.1 while that of free species 0.8–1.0. Solvent systems may be single or multiple components and provide for good separation of labeled molecules and free ionic species.

Strips are removed from developing tanks, air dried, and analyzed for quantitation of components in the sample. Strips may be cut into 1 cm widths and placed into gamma well counters to determine presence and, therefore, identity of activity on the strip. The origin (2.5–3.5 cm) of acceptable radiopharmaceuticals contains 90% of the counts. A radiochromatogram well adapter can be used and is less time consuming (3). Radioscanchromatographs can provide this information by producing a graph with peaks of activity demonstrating location and quantitation of radioactive components.

Figure 6 is a chromatograph of Tc^{99m}-Polyphosphate® (New England Nuclear) used as the bone scanning agent in Figure 4. The chromatograph demonstrates activity at the origin representing

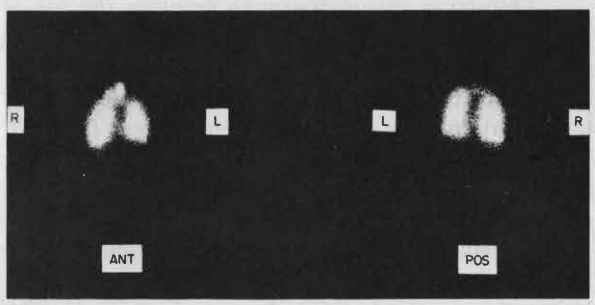


Fig. 2—I^{131}-macroaggregated albumin (Abbott) lung image demonstrating thyroid uptake of free radioiodine.

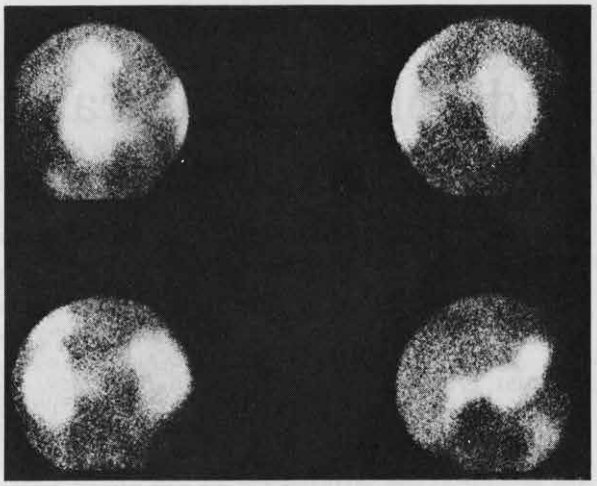


Fig. 3—Tc^{99m}-Renotec (Squibb) kidney image demonstrating stomach uptake of free Tc^{99m}-pertechnetate. (Image provided courtesy Dr. H. T. Haden, McGuire VA Hospital, Richmond, Va.)

Tc^{99m}-pertechnetate bound to phosphate complexes, activity between origin and solvent front demonstrating reduced pertechnetate and/or labeled metabolized phosphates, and a second but less prominent

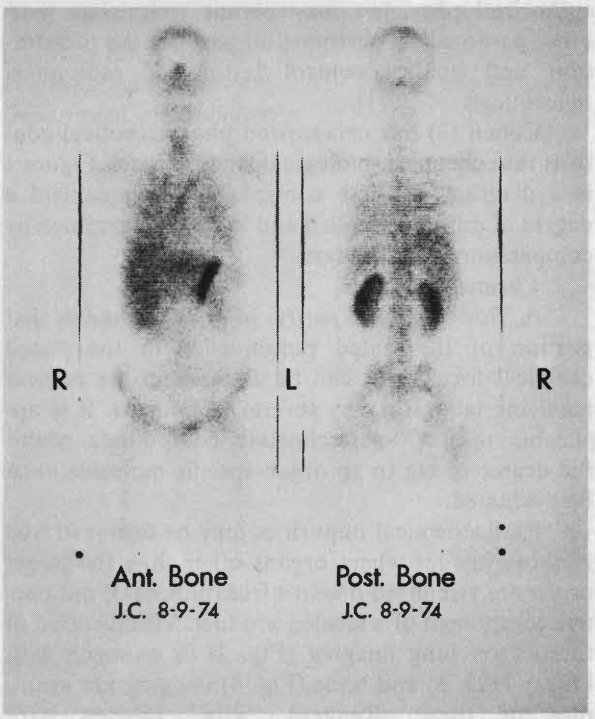


Fig. 4—Tc^{99m}-Polyphosphate® (New England Nuclear) bone image demonstrating stomach uptake of free Tc^{99m}-pertechnetate. Increased activity in liver probably associated with a reduced technetium species in blood pool.

Recommended Chromatography Solvents

Preparation	Solvent	Rf BTc	Rf FTc
Tc99m (Sn) DTPA	Acetone	0.0	1.0
	Butyl acetate	0.0	0.8
Tc99m (Sn) Gluco-heptonate	M.E.K.	0.0	1.0
Tc99m - HSA	Methanol, 85%	0.0	0.8
Tc99m - MAA	Methanol, 85%	0.0	0.8
Tc99m - Polyphosphate	Acetone	0.0	1.0
	Butyl acetate	0.0	0.8
Renotec*	Butanol: Ethanol: Water (2:2:1)	0.1	0.7
Tc99m - Sulfur Colloid	Methanol, 85%	0.1	1.0

*Eastman TLC Cellulose #6064 media; all others, Gelman ITLC Type SG

Fig. 5—Chromatography solvent systems recommended for the determination of bound (BTc) and free (FTc) components of technetium-99m kit preparations. Each system provides reproducible Rf values used in the identification and quantitation of each component.

peak at the solvent front demonstrating free pertechnetate.

Figure 7 compares the chromatographs of Tc^{99m}-Polyphosphate® (NEN) to that of Osteoscan® (Proctor and Gamble). Technetium-99m-pertechnetate obtained from a 400 millicuries fission Mo^{99}-Tc^{99m} generator was used to prepare each of the above bone imaging agents. The Tc^{99m}-Polyphosphate® chromatogram demonstrated 98.5% of the pertechnetate bound to the phosphate complex. With Osteoscan®, the chromatograph demonstrated a reduced and/or labeled metabolized phosphate component of approximately 40%. The manufacturer claimed that the nitrogen atmosphere in the vial was lost through the rubber closure with oxidation of the Sn(II) reducing agent. (Recently the manufacturer has adopted a butyl rubber closure which has resolved this problem.)

Figure 8 is a chromatograph of Tc^{99m}-Sn-Glucoheptonate® (NEN). With methyl ethyl ketone (MEK) solvent, peak activity was found at the origin corresponding to the bound component. No free pertechnetate was demonstrated. The manufacturer claimed the material may be subject to colloid formation with some resultant localization of activity in the liver. The material was chromatogramed in a physiologic saline solution demonstrating no colloid at the origin.

B. *Carrier amount.* May be defined as stable or long-lived isotopes of the nuclide present at the time of administration of the radiopharmaceutical. Carrier, if present in large quantities, alters the distribution of the nuclide in vivo or adds to radiation burden if it is radioactive. Manufacturers prepare compounds that are "carrier-free." This has come to mean that no other isotope of the nuclide has been intentionally added.

C. *Buffer amount.* The pH of radiopharmaceuticals should be adjusted to provide for stable complexes as well as physiologic suitability. Most radiopharmaceuticals are adjusted in the range of pH 4.0 to 8.8.

D. *Total ions concentrations.* Radiochemical solutions after production may contain various metals or metaloids as contaminants. These contaminants may be imparted from apparatus and reagent materials even if very pure. Complexation of the radiochemical with these traces give chemically unstable radioactive solutions. A standard of 80μg/ml of these ions has been set; however, the current state of the art is to prepare products with less than 1μg/ml.

Of the potential nonradioactive ionic impurities present in Tc^{99m}-pertechnetate eluent, aluminum [Al (III)] has produced the most concern. Toxicology of Al (III) of potential doses administered appears minimal (Fig. 9); however, it has been reported to cause flocculation of Tc^{99m}-sulfur colloid preparations as well as agglutination of red blood cells during the labeling process (4). Current NRC standards limit the presence of this ion to 10μg (fission Mo^{99}) and 20μg (activation Mo^{99}) per milliliter of generator

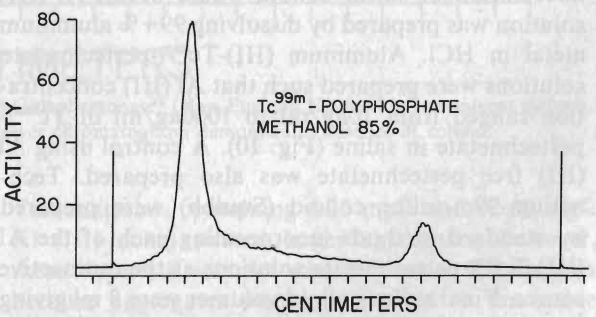


Fig. 6—Chromatograph of Tc^{99m}-Polyphosphate® used to produce bone image in Figure 4 demonstrates bound, reduced, and free components of the radiopharmaceutical.

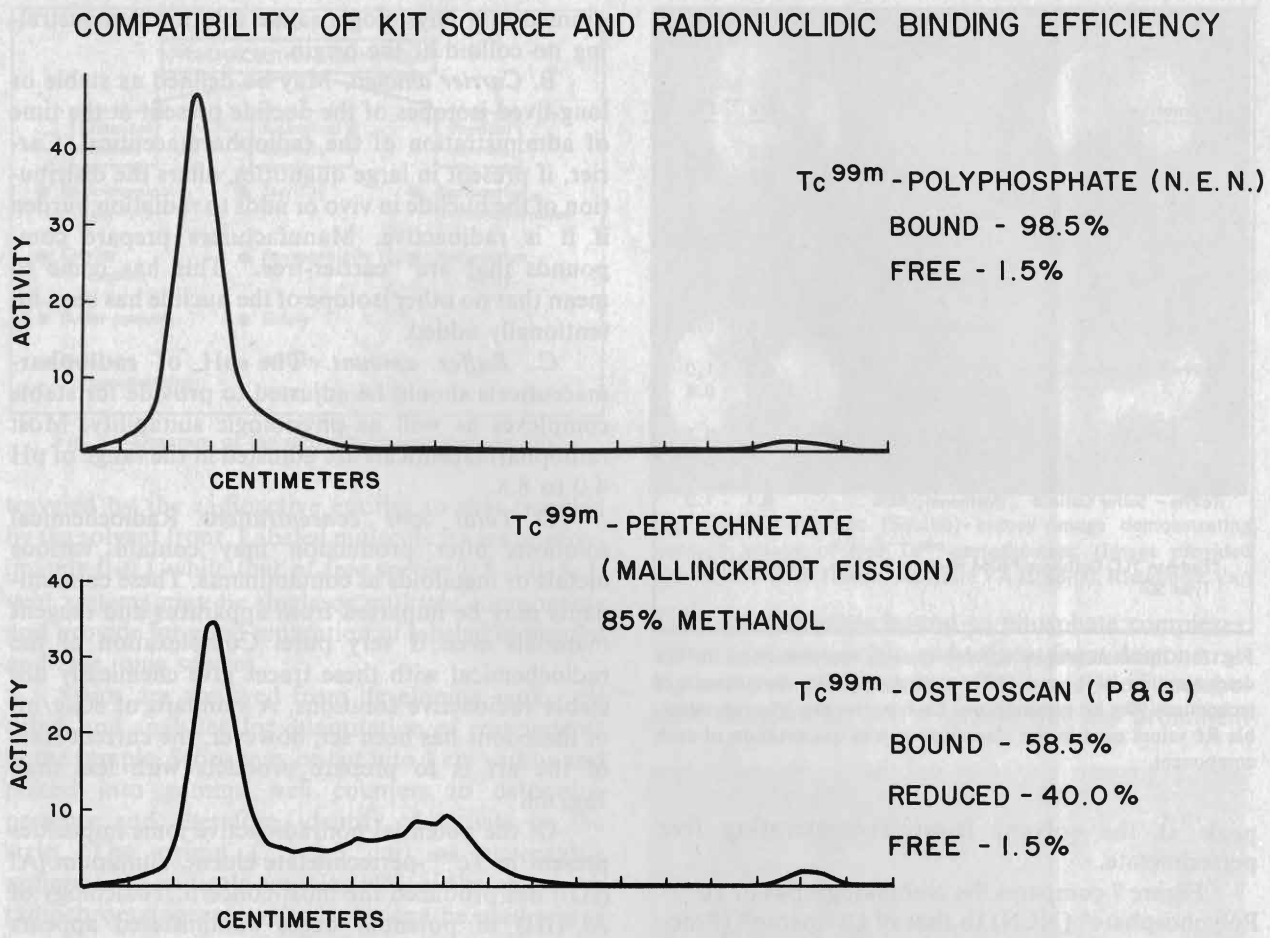


Fig. 7—Comparison of chromatographs obtained after preparation of two commercially available bone imaging agents; Tc^{99m}-Polyphosphate® (New England Nuclear), Tc^{99m}-Osteoscan® (Proctor and Gamble).

eluent. This represents a more stringent requirement from a previous 500μg Al (III)/10 millicuries Tc^{99m}-pertechnetate limitation.

To determine at what concentration of Al (III) flocculation of sulfur colloid would occur, Al (III) solution was prepared by dissolving 99+% aluminum metal in HCl. Aluminum (III)-Tc^{99m}-pertechnetate solutions were prepared such that Al (III) concentration ranged from 10μg/ml to 1000μg/ml of Tc^{99m}-pertechnetate in saline (Fig. 10). A control using Al (III) free pertechnetate was also prepared. Technetium-99m-sulfur colloid (Squibb) were prepared by standard methods incorporating each of the Al (III)-Tc^{99m}-pertechnetate solutions as the radioactive source. Final sulfur colloid volumes were 8 ml giving resultant Al (III) concentrations of 0 to 12.50 mg%. Aluminon reagent (aurin-tricarboxylic acid) test strips (NEN) were evaluated for suitability in the detection of Al (III) contamination at levels associated with sulfur colloid flocculation (Fig. 11). Colloid aggregation was determined by placing 0.1 ml of each sample on a standard hemocytometer chamber and observation under light microscopy (Fig. 12).

Two hundred microcuries (0.2 ml) of each of the sulfur colloid preparations were injected into 250 g female Sprague-Dawley rats via a femoral vein. Scintiphotos were obtained using the Searle Radiographics Pho-Gamma HP camera fitted with a pinhole collimator to demonstrate distribution of the radiocolloid (Fig. 13).

Preparations of sulfur colloid from 0 to 0.63 mg% Al (III) demonstrated no aggregation. Aluminon test papers demonstrated an increase in the presence of Al (III) with each increase in ion concentration. Scintiphotos of test animals demonstrated

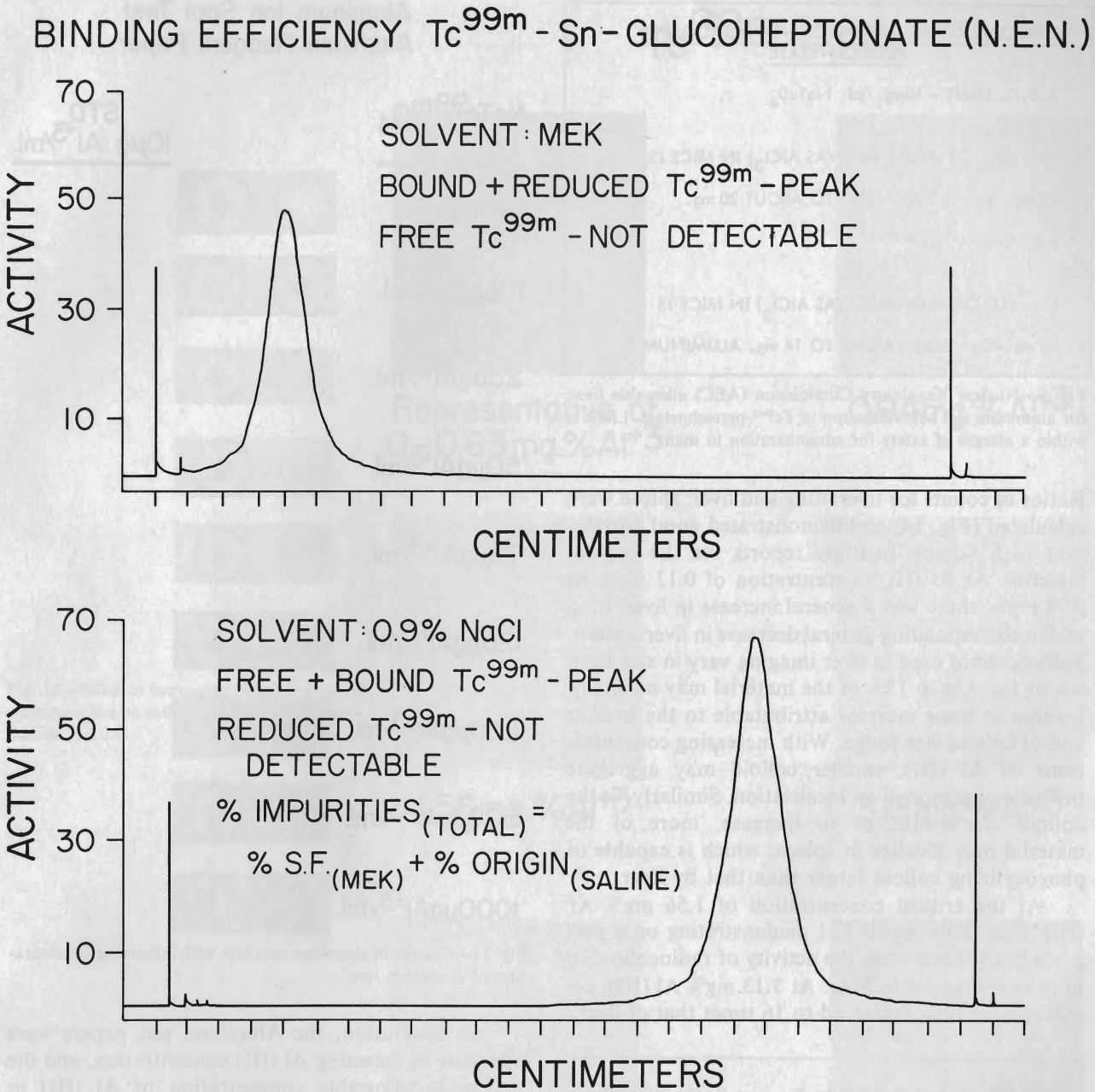


Fig. 8—Chromatographs obtained following development of TC^{99m}-Sn-Glucoheptonate® (New England Nuclear) in two solvent systems. Upper chromatograph demonstrates absence of free pertechnetate. Lower chromatograph demonstrates absence of colloid.

distribution of radiocolloid to liver with no uptake in lung. At 0.94 mg% Al (III), some colloid aggregation was present with minimum uptake of colloid in the lung of test animal. At 1.56 mg% Al (III), aggregate size became critical with scintiphotos demonstrating significant quantities of radiocolloid in lung. Lung uptake of radiocolloid increased at 3.13 mg% Al (III). Test materials containing 6.25 mg% and 12.50 mg% Al (III) demonstrated larger aggregates; however, these materials were not administered to test animals because aggregates would be limited to the inside diameter (254μ) of the 25 G needle.

Liver, lung, and spleen from each test animal were excized and counted using a Picker well counter.

TOXICOLOGY ALUMINUM CONTAMINATION IN PERTECHNETATE

A.E.C. LIMIT - 10μg./ml. $NaTcO_4$

I.V. LD_{50} OF ALUMINUM (AS $AlCl_3$) IN MICE IS 79 mg./Kg. (EQUIVALENT TO ABOUT 20 mg. ALUMINUM/Kg.)

I.V. LD_2 OF ALUMINUM (AS $AlCl_3$) IN MICE IS 55 mg./Kg. (EQUIVALENT TO 14 mg. ALUMINUM/Kg.)

Fig. 9—Nuclear Regulatory Commission (AEC) allowable limit for aluminum ion contamination in Tc^{99m}-pertechnetate. Limit is within a margin of safety for administration to man.

Ratios of counts for liver: lung and liver: spleen were calculated (Fig. 14) and demonstrated good correlation with Squibb Institute reports for the control material. At Al (III) concentration of 0.13 mg% to 0.94 mg%, there was a general increase in liver: lung with a corresponding general decrease in liver: spleen. Sulfur colloid used in liver imaging vary in size from mμ to 1 μ. Up to 15% of the material may normally localize in bone marrow attributable to the smaller end of colloid size range. With increasing concentrations of Al (III), smaller colloid may aggregate providing for more liver localization. Similarly, as the colloid size continues to increase, more of the material may localize in spleen, which is capable of phagocytizing colloid larger than that by liver.

At the critical concentration of 1.56 mg% Al (III), liver: lung was 0.32:1 demonstrating on a pergram basis three times the activity of radiocolloid in lung as compared to liver. At 3.13 mg% Al (III), activity in the lung increased to 16 times that of liver.

μg. Al + 3	μg. Al + 3/ml. Tc99m04 (mg. %)		μg. Al + 3/ml. Kit* (mg. %)	
10	10	(1.0)	1.25	(0.13)
25	25	(2.5)	3.13	(0.31)
50	50	(5.0)	6.25	(0.63)
75	75	(7.5)	9.38	(0.94)
125	125	(12.5)	15.63	(1.56)
250	250	(25.0)	31.25	(3.13)
500	500	(50.0)	62.50	(6.25)
1000	1000	(100.0)	125.00	(12.50)

* FINAL PREPARATION = 8 ml.

Fig. 10—Concentration of aluminum ion in radioactive solutions. Center panel expresses aluminum concentration present in Tc^{99m}-pertechnetate. Third panel expresses aluminum concentration present following preparation of sulfur colloid kit.

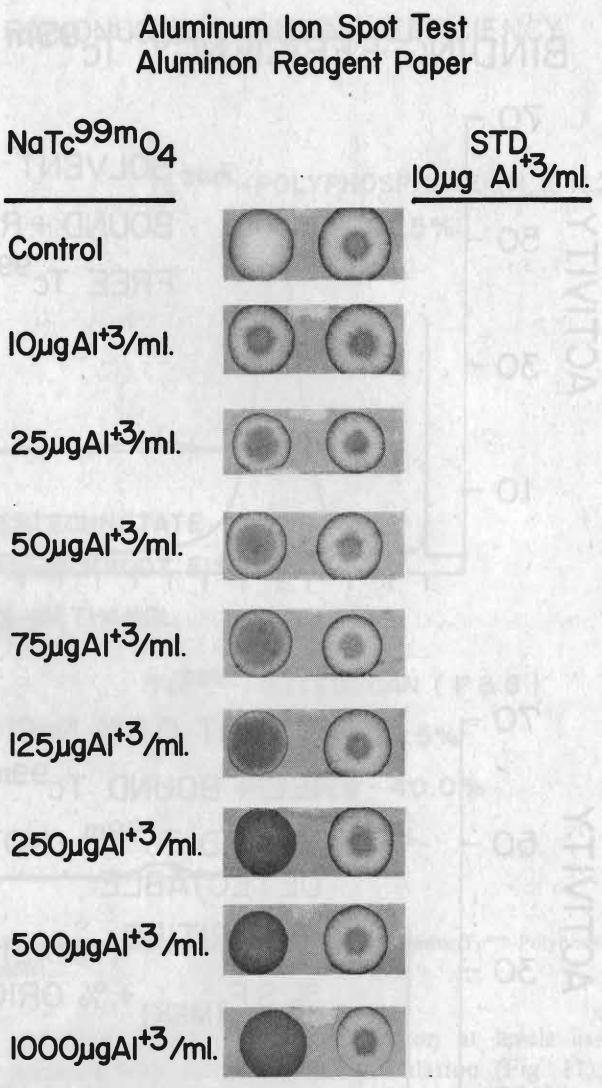


Fig. 11—Change in aluminon spot test with increasing concentration of aluminum ion.

In conclusion, the Aluminon test papers were adequate in detecting Al (III) concentration, and the maximum allowable concentration of Al (III) in Tc^{99m}-pertechnetate was found to be 75μg/ml. The current standard is well within this value.

Biological Controls. The United States Pharmacopeia (USP) specifications for all parenteral products includes the absence of viable forms of bacteria, viruses, yeast, and molds as well as pyrogenic substances. Therefore, radiopharmaceuticals administered parenterally must also be of this quality.

A. *Sterility.* Many of the radiopharmaceuticals

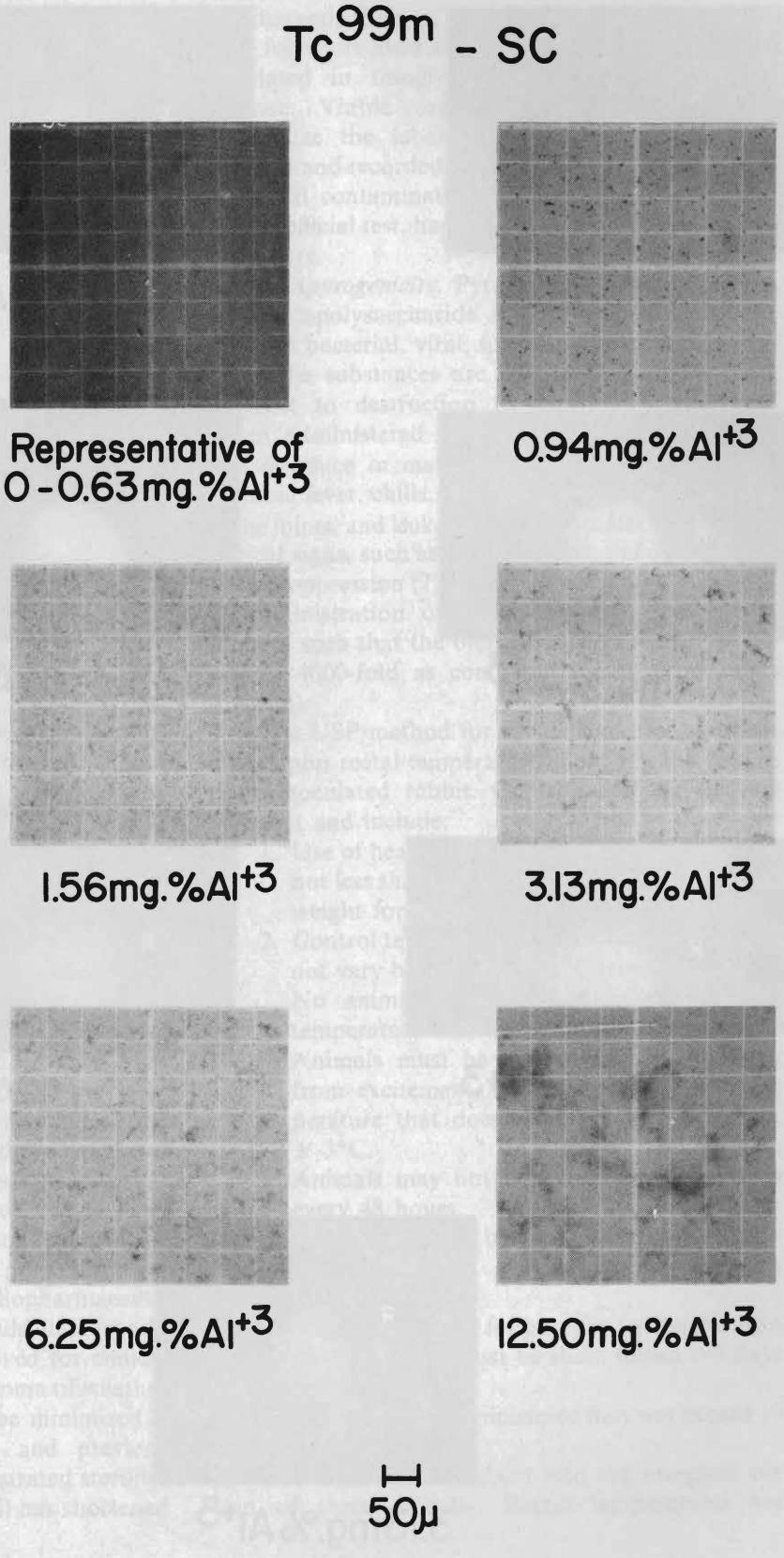
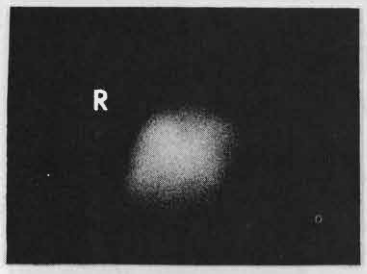
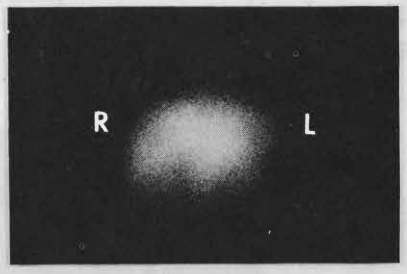


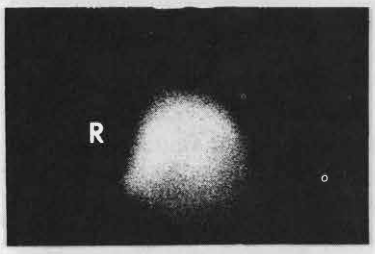
Fig. 12—Effect of increasing concentration of aluminum ion on colloid aggregation. Magnification is 10X.



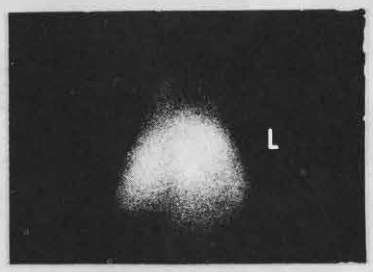
0mg.% Al^{+3}



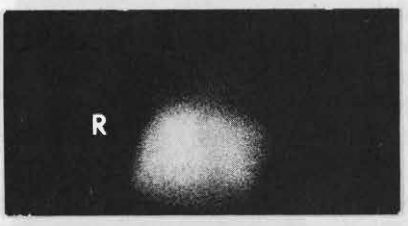
0.13mg.% Al^{+3}



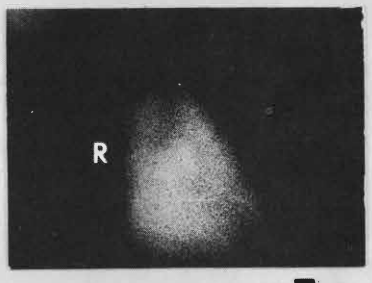
0.31mg.% Al^{+3}



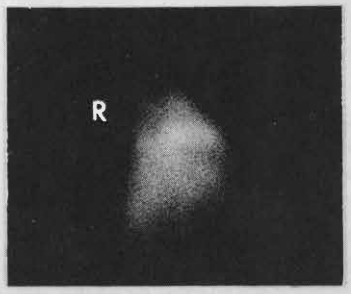
0.63mg.% Al^{+3}



0.94mg.% Al^{+3}



1.56mg.% Al^{+3}



3.13mg.% Al^{+3}

Fig. 13—Effect of increasing concentration of aluminum ion on radiocolloid distribution in rat. Anterior views obtained with Searle Radiographics-HP gamma camera fitted with a pin-hole collimator. Each image represents the accumulation of 100,000 counts.

Effect of Al^{+3} Content in Tc99m - Sulfur Colloid on Distribution Ratios* in Rat Organs (per gram wt.)

mg. % Al^{+3}	Liver:Lung	Liver:Spleen
0	4.73:1	1.23:1
0.13	6.73:1	6.43:1
0.31	5.23:1	4.77:1
0.63	3.46:1	1.83:1
0.94	4.81:1	1.59:1
1.56	0.32:1	1.16:1
3.13	0.06:1	0.37:1

* 20 min. post-injection (i.v.)

Fig. 14—Ratios of liver:lung and liver:spleen counts obtained from excized rat organs. Ratios are expressed per-gram weight of organ.

used as diagnostic agents in nuclear medicine are intended for parenteral administration. Pharmaceuticals of this type must meet USP requirements in that they are sterile, apyrogenic, and of acceptable pH (5).

Methods of sterilization vary and selection is dependant upon stability of the compound and its label. Terminal sterilization in an autoclave and membrane filtration are two of the more commonly used methods employed to sterilize radiopharmaceuticals. With each of the above methods, however, samples must be taken and tested to confirm sterility.

The USP method requires innoculation of the radiopharmaceutical into fluid thioglycolate and Soybean-Casein Digest medias. A 7-day incubation period at 30 to 35°C with fluid thioglycolate and 20 to 25°C with Soybean-Casein Digest without evidence of viable organisms indicates a sterile preparation. It becomes apparent that activity of radiopharmaceuticals with short physical half-lives would significantly decay before the product was approved for clinical use. Under this circumstance, the dilemma of whether to administer the preparation may be minimized if asceptic technique were employed and previous materials tested after-the-fact demonstrated sterility.

Work by Deland and Wagner (6) has shortened the determination of sterility to within acceptable time for short-lived nuclides. Test materials are innoculated in thioglycolate broth containing C^{14} glucose. Viable organisms, if present, would metabolize the labeled sugar to $C^{14}O_2$ which is detected and recorded, demonstrating the presence of microbial contamination. This procedure, although not an official test, has reduced lag time from days to 1–3 hours.

B. *Apyrogenicity.* Pyrogens of microbial origin, are mucopolysaccharide molecules present as the result of bacterial, viral, fungal, or yeast contamination. The substances are heat-stable and therefore resistant to destruction by terminal sterilization. When administered by some injection route, they may produce in man such symptoms as mono-or biphasic fever, chills, malaise, mild to moderate pain in the joints, and leukopenia, or other less well-defined clinical signs, such as apprehension, pallor, and substernal oppression (7). Sensitivity of the human body to administration of pyrogens by the intrathecal route is such that the biologic insult of this type increases 4000-fold as compared to the intravenous route (8).

The USP method for the detection of pyrogens relies upon rectal temperature change in the pre- to post-innoculated rabbit. Controls for the test are stringent and include:

1. Use of healthy, mature rabbits each weighing not less than 1.5 kg that have maintained this weight for one week.
2. Control temperature of each rabbit used does not vary by more than 1°C from each other. No animal may be used with a control temperature exceeding 39.8°C.
3. Animals must be housed individually, free from excitement, in an environmental temperature that does not vary by more than ± 3°C.
4. Animals may not be used more than once every 48 hours.
5. Animals may not be used before 2 weeks having been given a test sample that was pyrogenic.
6. Animals not used for pyrogen testing during a 14-day period must be sham tested 1–3 days before use.
7. Test material administered may not exceed 10 ml.

Test material is injected into the marginal ear vein of three animals. Rectal temperatures are

recorded at hourly intervals for three hours post injection. If none of the test animals show an individual temperature rise of 0.6°C or more above its control temperature and if the sum of the temperature rises in all three animals does not exceed 1.4°C, the test material meets the requirement of apyrogenicity. If the above criteria are not met, the test must be repeated with five rabbits. If not more than three of the eight rabbits show temperature rises of 0.6°C or more and if the sum of the eight temperature rises does not exceed 3.7°C, the product under test meets the requirement for apyrogenicity.

Pyrogen testing by the USP method is difficult, time consuming, and generally not amenable to small laboratories. Cooper et al (9), have introduced an in vitro test based on the detection of endotoxin through gelation of Limulus polyphemus lysate prepared from blood amebocytes. Test results may be obtained in 1 hour which represents time saved with respect to short-lived nuclides. This test is significantly more sensitive than the official test; however, it is subject to false positive results if the preparation to be tested contains Ca (II). The problems of adopting a more sensitive test must be justified in view of the fact that no documentation exists of pyrexia following administration of materials found apyrogenic by the USP test. The question of how sensitive pyrogen testing must be deserves further investigation.

C. *Safety.* With the administration of pharmaceuticals in radioactive form, safety includes radiation-absorbed doses received by target and nontarget organs that are within acceptable limits. The product must also be nontoxic in doses administered with respect to formed cells in blood as well as organs to which the material will be distributed.

D. *Affinity.* Radioactive compounds used in organ imaging localize by various physiological mechanisms. Control of the physiochemical characteristics of the radiopharmaceutical are needed to assure affinity of the product for target organs.

Soloway and Davis (10) reviewed radiopharmaceuticals currently used for organ imaging and have catagorized their biological basis for localization. In vitro quality control testing is essential to predetermine that organs of interest will be visualized. Poor affinity demonstrated by suboptimal images must frequently be repeated, therefore, necessitating subsequent dosing with radionuclides and increased radiation burden to patients.

Perfusion lung imaging is dependant upon blood flow to that organ with capillary and terminal arteriolar blockage by radiolabeled particles. Particles for this purpose must be larger than that of red blood cells (7μ) to prevent arterial distribution after intravenous administration. To avoid an unnecessarily long, effective half-life in lung, as well as optimum patient safety, particles should be limited in size to 50μ. Particle size determination can be easily accomplished in the laboratory using light microscopy as a routine check.

Images of liver and spleen are dependant upon blood flow to these organs with phagocytosis of radiocolloid by reticuloendothelial cells. Colloid of 0.6μ and 1.0μ are necessary for localization in liver and spleen respectively. Although colloid may not be visualized by light microscopy, the test serves as a negative check for aggregates so large that they might localize in lung.

Radioactive materials have been used to delineate special anatomic or biochemical compartments. Labeled serum albumin has been used in the past for cisternography and currently for blood pool imaging. Care must be taken not to denature the protein by excessive labeling or chemical manipulation.

Stannous chloride [Sn(II)] has become a useful reducing agent in the preparation of technetium-labeled radiopharmaceuticals. Yano et al (11), in studies with the bone imaging agent Tc^{99m}-Sn-EHDP, found optimum molar ratio of Sn (II):EHDP for greater bone localization and rapid soft tissue clearance. They reported the importance in the order of combination of EHDP, Sn (II) and Tc^{99m}-pertechnetate such that poor formulation resulted in radiocolloid formation with localization in liver. Poor localization of other technetium products with significant uptake in thyroid has been noted when stannic chloride [Sn(III)] forms on crystal surfaces of the reducing agent.

Physical Controls.

A. *Radioactive concentration.* Refers to the activity concentration of the product with respect to activity per unit volume. Activity concentration can be easily determined using a dose calibrator. This instrument has an overall accuracy of 5% and is designed to quantitate many of the more commonly used radionuclides.

B. *Radioactive purity.* This term should be discontinued in favor of the more accurate term "radionuclide purity." It may be defined as that proportion of the total activity that is present as the stated radionuclide.

The NRC limit for Mo^{99} contamination has been set at 1 microcurie Mo^{99} per millicuries Tc^{99m}-pertechnetate and 5 microcuries per dose of Tc^{99m}-pertechnetate. On a milligram basis the amount of Mo^{99} necessary for a lethal dose or LD_{50} dose in test animals is large as compared to what can be eluted from an intact generator system (Fig. 15). However, on an equal activity basis using the MIRD system (12, 13), radiation burden from Mo^{99} is 35 times greater as compared to Tc^{99m}. It has also been demonstrated that parent Mo^{99} produced by neutron activation of Mo^{98} results in Cs^{134} contamination.

Radioactive contaminants of Mo^{99}-Tc^{99m} generator systems may be detected radiometrically. Molybdenum-99 emits 740 and 780 kev gammas as well as other less energetic photons. A 4 mm lead shield adapter inserted in the ion chamber of the dose calibrator would absorb all but 0.0002% of Tc^{99m} gamma (140 kev) and 50% of Mo^{99} gamma (14). It is fortuitous that Mo^{99} activity can be read directly on the Tc^{99m} setting when the pertechnetate source is placed in the lead adapter. The method allows for quantitation of the Mo^{99} activity which should not exceed 0.1% of the Tc^{99m} activity. Cesium-134 emits 605 and 796 kev gammas which penetrate the 4 mm lead shield and will be quantitated with the Mo^{99} reading.

In-House Preparation of Radiopharmaceuticals.

Present day practice of nuclear medicine relies upon readily available organ-specific radiopharmaceuticals. Exhaustive research of natural and man-made radionuclides has resulted in a handful that demonstrate organ specificity with patient safety. As a result, research has been directed toward the labeling of molecules with radionuclides of near-ideal properties for organ selectivity. Technetium-99m having suitable physical, chemical, and biological properties enjoys an active role in organ imaging. Since 1961, many Tc^{99m}-labeled compounds have been introduced which have broadened the diagnostic capabilities of nuclear medicine and/or improved radiation burden as compared to previously used radionuclides.

Much of this research has resulted in the commercial availability of kit preparations where simple asceptic techniques are employed to produce the desired Tc^{99m} radiopharmaceutical. With the commercial availability of Mo^{99}-Tc^{99m} generators, daily delivery, or MEK extraction techniques, a continuous supply of Tc^{99m}-pertechnetate is at hand for the preparation of kits. The commercial availability of these tools has been a boon to many institutions which might not be able to provide this diagnostic service. This availability, however, is not without cost, and newer formulations with clinical merit may take months before they become commercially available, thereby limiting diagnostic studies to current available preparation.

Toxicology of Radionuclidic Impurities in Pertechnetate

Mo^{99}

NRC Limit - 1 μCi Mo^{99} /mCi Tc^{99m}

5 μCi Mo^{99} /dose Tc^{99m}

I.P. lethal dose of Mo (as Na_2MoO_4) in rate is about 114 - 117 mg. Mo/Kg.

I.V. LD_{50} of Mo (as Na_2MoO_4) in mice is about 248 mg./Kg. (equivalent to 116 mg. Mo/Kg.)

No effect dose in mice is about 28 mg./Kg.

Cs^{134}

NRC Limit - 20μCi (total body burden)

Fig. 15—Nuclear Regulatory Commission maximum allowable limits for radionuclidic impurities in Tc^{99m}-pertechnetate.

Radiopharmaceutical scientists (radiopharmacist, radiochemist) have paralleled the growth of nuclear medicine consultants by providing efficacious radiopharmaceutical diagnostic agents. In-house preparation of radiopharmaceuticals by these individuals have allowed for the availability of newer agents in nuclear medicine practice. Institutions preparing radiopharmaceuticals are increasing, and those without this technical capability may benefit under a cost-sharing program (15).

Several formulations are available for the preparation of the more routinely used imaging agents. The following are currently used at the Medical College of Virginia Hospitals. Drug-adverse reactions have not been reported for any of the products since clinical initiation.

PREPARATION OF TC99M-SULFUR COLLOID KIT (16)

Solution A:

To 100 ml of Sterile Distilled Water add:

1. 400 mg Sodium Thiosulfate
2. 750 mg Gelatin
3. 850 mg Potassium Monohydrogen Phosphate (Dibasic)
4. 200 mg Disodium Edetate

Stir and warm the mixture gently to dissolve the gelatin. After solution is complete, pipette exactly 3 ml of the solution into each 30 ml serum vials. Seal the vials with rubber closures and aluminum caps (twice boiled in sterile distilled water for not less than 30 minutes and autoclaved, wrapped in aluminum foil) and autoclave Solution A for 15 minutes at 20 PSIG pressure.

Solution B:
Sterilize 1-3 ml of exactly 0.5N HCl solution in serum vials by autoclaving for 15 minutes at 20 PSIG pressure.

Solution C:
To 100 ml Sterile Distilled Water add:
1. 1.20 g Sodium Hydroxide pellets
2. 2.8 g Sodium monohydrogen phosphate

Mix well until solution is complete. Do not autoclave. Sterilize by filtration using 0.22μ membrane filter.

Preparation of Tc99m MAA Kit (16)

A. Prepare Albumin Sodium Acetate solution in distilled water such that it contains 10 mg/ml of HSA, 100 mg/ml of Sodium Acetate. Sterilize by membrane filtration (0.22μ size).
B. Prepare Stannous Chloride solution in 1N HCl such that it contains 5 mg/ml of stannous chloride. Sterilize by membrane filtration (0.22μ size).
C. To an empty sterile serum vial containing a small magnetic stirrer mix 5 ml of Solution A with 19 ml of Sterile Water for Injection. Mix well. Add 1 ml of Solution B. The pH should be approximately 5.5.
D. Macroaggregate the Albumin in the above solution in a water bath at 80°C±1 for 12 minutes with stirring.
E. Cool and mix the aggregates well. Each ml of this preparation now contains:
   1. 2 mg HSA as aggregates (denatured)
   2. 200μg Stannous Chloride as hydroxide
   3. 20 mg Sodium Acetate as buffer
F. Transfer under aseptic conditions 1 ml each of this solution to presterilized empty serum vials and store under refrigeration.

Preparation of Tc99m-Labeled Human Serum Albumin (17)

Materials:

I. Kit (consists of 3 sterile pyrogen-free vials).
   Vial "A"—20 ml vial containing 0.85 ml of 1N HCL with two 1-inch lengths of Zr wire inserted through the diaphragm.
   Vial "B"—5 ml containing approximately 1 ml of HSA 25%.
   Vial "C"—5 ml vial containing approximately 2 ml of Sodium Bicarbonate 3.75% and Sodium Hydroxide 2.0% in sterile pyrogen-free water for injection.
II. Lead pig (for housing 200 ml vial during procedure).
III. D.C. power source with external leads adapted with alligator clips capable of providing 100 milliamps constant current at 3–5 volts.

Procedure:

I. Place vial "A" in lead pig; electrically insulate the top of the container by covering top of lead pig and aluminum band with masking tape. Rubber diaphragm is left exposed.
II. To vial "A" aseptically add 5.5 ml of pertechnetate in normal saline (oxident free). Remove 5.5 ml air.
III. To vial "A" aseptically add 0.1 ml of HSA from vial "B" using a 1 ml TB syringe adapted with a 21 G needle. Flush syringe several times and remove 0.1 ml of air.
IV. Immediately connect electrodes to power supply leads by means of alligator clips.
V. Invert vial allowing contents of vial to come in contact with both electrodes.
VI. Using circular motion gently agitate the inverted vial. Pass 100 milliamps of current for exactly 42 seconds; continue to agitate vial inverted position for an additional 15 seconds after electrolysis is completed.
VII. Remove leads from electrodes, reinvert vial to upright position and allow vial "A" to incubate at room temperature for at least 30 minutes.
VIII. Add to vial "A" 1.2 ml of vial "C". Remove an equivalent amount of air.
IX. Pass the product through a 0.22μ

membrane filter and collect in a sterile empty vial.

Radiopharmaceuticals, whether prepared in-house or obtained commercially, should be subjected to quality control testing. If the limitations of image interpretations are instrumentation, technique, adequate patient history, and radiopharmaceutical quality, equal attention must be payed to all.

REFERENCES

1. 10 CFR Part 35(35.32) Federal Register 38:46 (March 9) 1973.

2. COHEN Y: Chemical and radiochemical purity of radioactive pharmaceuticals related to their biological behavior, in Andrews GA, et al (eds): *Radioactive Pharmaceuticals.* U.S. Atomic Energy Commission publ. CONF-651111, Clearinghouse for Federal Scientific and Technical Information, Springfield, Va, 1966, p 67–91.

3. GUTKOWSKI RF, DWORKIN HJ: A simplified radiochromatographic purity check. *J Nucl Med* 12(pt 2):513–515, 1971.

4. STELMACH HA, QUINN JL III: Radiopharmaceutical quality control. *Semin Nucl Med* 4:295–303, 1974.

5. *The United States Pharmacopeia* (Rev. XIX) Mack Printing Co., Eastman, PA, 1975.

6. DELAND FH, WAGNER HN JR: Early detection of bacterial growth, with Carbon-14-labeled glucose. *Radiology* 92:154–155, 1969.

7. BRINER WH: Quality control, pyrogen testing and sterilization of radioactive pharmaceuticals, in Andrews GA, et al (eds): *Radioactive Pharmaceuticals,* U.S. Atomic Energy Commission publ. CONF-651111, Clearinghouse for Federal Scientific and Technical Information, Springfield, Va, 1966, p 93–111.

8. ATKINS E: Pathogenesis of fever. *Physiol Rev* 40:580–646, 1960.

9. COOPER JF, LEVIN J, WAGNER HN JR: New, rapid, in-vitro test for pyrogen in short-lived radiopharmaceuticals, abstracted. *J Nucl Med* 11:310, 1970.

10. SOLOWAY AH, DAVIS MA: Survey of radiopharmaceuticals and their current status, *J Pharm Sci* 63(pt 1):647–665, 1974.

11. YANO Y, MCRAE J, VAN DYKE DC, et al: Technetium-99m-labeled stannous ethane-1-hydroxy-1 1-diphosphonate: A new bone scanning agent. *J Nucl Med* 14(pt 1):73–78, 1973.

12. DILLMAN LT: Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. *J Nucl Med* 10 (MIRD suppl 2):7–32, 1969.

13. DILLMAN LT: Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation, part 2. *J Nucl Med* 10 (MIRD suppl 4):7–32, 1969.

14. RICHARDS P, O'BRIEN MJ: Rapid determination of ^{99}Mo in separated ^{99m}Tc, letter to the editor. *J Nucl Med* 10:517, 1969.

15. GNAU TR, MAYNARD CD: Reducing the cost of nuclear medicine: sharing radiopharmaceuticals. *Radiology* 108:641–645, 1973.

16. SUBRAMANIAN G: ^{99m}Tc labeled radiopharmaceuticals a compilation of procedures. Division of Nuclear Medicine, Department of Radiology, Upstate Medical Center, Syracuse, New York.

17. DWORKIN HJ, GUTKOWSKI RF: Rapid closed-system production of ^{99m}Tc-albumin using electrolysis. *J Nucl Med* 12:562–565, 1971.

Interpretation of Cerebral Dynamic Perfusion Studies*

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A review of the literature for the preceding 20 years reveals that by radionuclide static imaging there has been little improvement in the detection rate of cerebral lesions (1–5). The overall accuracy of brain scans has been reported from 81% to 84%. For glioblastoma multiforme and meningioma, the detection rate is 90%–95%; for low-grade astrocytoma, 55%; and for ischemic strokes, from 10% to 50% depending on the elapsed time from the onset of symptoms. An aneurysm must be at least 2.5 cm in diameter and an arteriovenous malformation 3–4 cm in diameter before the information content is adequate for detection. In patients with transient ischemic attacks, static imaging has been unrewarding (6, 7). Why has there been little improvement in the detection of cerebral lesions by static imaging in spite of improved instrumentation and techniques? Visualization of abnormalities depends on a concentration of radioactivity that is greater in the lesion than in the surrounding tissue, and the mechanisms for nuclide concentration are similar for nearly all of the agents that have been used during the past 20 years. With few exceptions the brain-imaging radiopharmaceuticals are not target specific but depend on the nonspecific changes in vascular wall integrity (for example, dedifferentiation or focal increased intravascular volume, or shunts).

There are a number of lesions that may not be apparent on static images, which include early cerebral infarctions, early subdural hematomas, concussion, arteriovenous malformations of less than critical size for visualization, and neoplasms that are not sufficiently vascular or the vascular component is not sufficiently dedifferentiated to contribute to a preferential concentration of radioactivity. If radioactivity does concentrate in a lesion, the dynamic vascular character of the pathology has not been revealed without the appropriate study. During the first passage of the radiopharmaceutical, rapid sequential radionuclide images provide valuable information on the dynamics of the vasculature. Rapid imaging increases the sensitivity of the total study because an increase, decrease, or no change in the blood flow as reflected by the radiopharmaceutical, has diagnostic meaning when correlated with the static images. Correlations are made with both abnormal and normal scans, and the normal scan may provide diagnostic information relative to the character of the dynamic flow studies.

Technique. In order to obtain radionuclide images that provide the required information, precise attention must be given to the technique used in the study. The radionuclide bolus, method of intravenous injection, route of administration, patient position, and shielding—each must be given consideration.

Since the radionuclide bolus must transverse more than a meter of vascular channels, mix with blood from the inferior vena cava in the right heart, pass through the pulmonary capillary bed, return to the heart, and then be transported to the brain, a "tight" bolus is required; that is, less than 1 one ml. Two administrative techniques of the radionuclide bolus are commonly used: the Oldendorf technique (8) and the saline flush (9). Details of these procedures can be found in the original articles.

Most commonly, intravenous materials are ad-

* Presented by Dr. DeLand at the Postgraduate Course in Nuclear Medicine, February 25, 1975, in Williamsburg, Virginia.

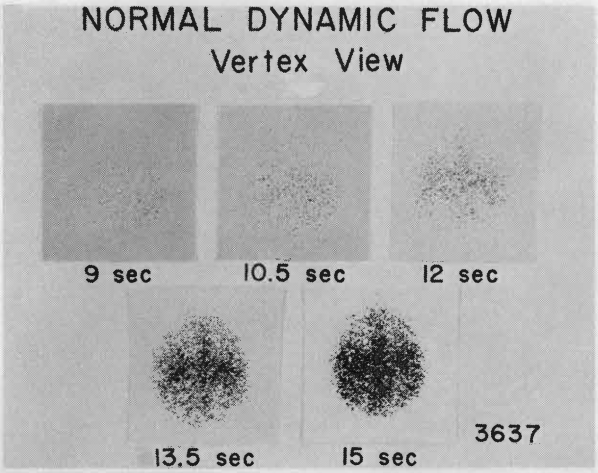

Fig. 1*A*—Early phases of normal dynamic flow (vertex).

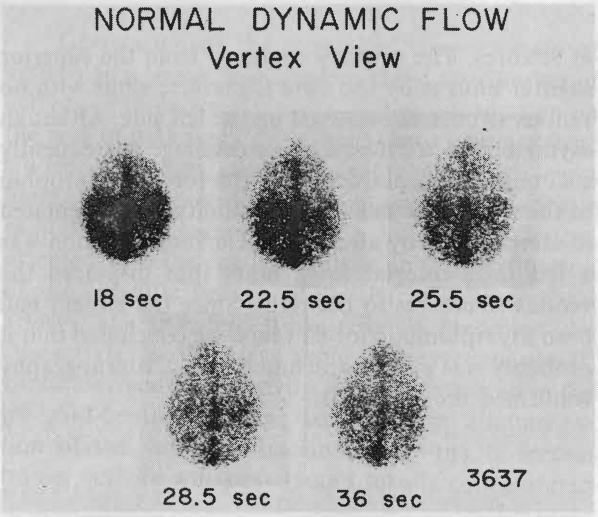

Fig. 1*B*—Venous and recirculatory phases of normal dynamic flow.

ministered in the veins of the antecubital fossa. It is imperative that the medial basilic vein be used whenever possible because this is the most direct route to the axillary vein. Injection into the lateral cephalic vein may result in: 1) delay and lengthening of the bolus because of the narrower caliber of the vessel and the right angle junction with the axillary vein, and 2) fractionation of the bolus because of anastamotic channels and the right angle junction (10). The Valsalva maneuver may also contribute to poor bolus characteristic.

Adequate shielding of the chest and shoulders with lead-impregnated drapes minimizes undesirable activity from the heart and great vessels. During the

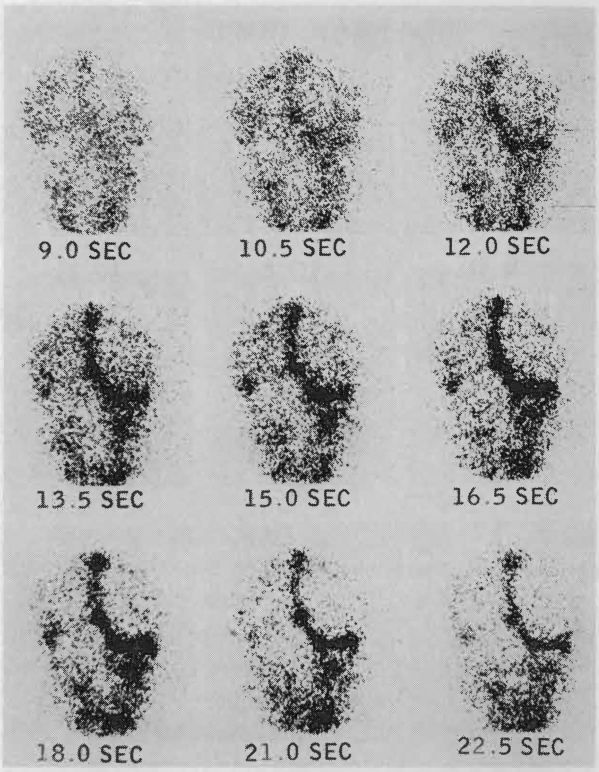

Fig. 2—Nuclear angiography on 65-year-old patient being evaluated for seizures.

first passage of the radionuclide bolus through the head, unwanted activity in the scalp can be eliminated by compression with a blood pressure cuff at the level of the external occipital protuberance and the forehead. When the cuff is inflated to above systolic pressure, the amount of radioactivity detected during the first transit is reduced about 15% to 30% (11).

We use the vertex projection as the position of choice for routine cerebral dynamic perfusion studies. This projection will provide data on the cortical distribution of most of the anterior cerebral artery, a portion of the posterior cerebral artery, and a splay of the middle cerebral artery. Not only is a greater area of cortex visualized, but a spread of the middle cerebral branches also provides greater sensitivity for the detection of partial decreases in blood flow. Other projections are used when the clinical information dictates, particularly in patients with suspected subdural hematomas.

Cases. Figure 1A illustrates the early phases of a normal dynamic flow (vertex). At 10.5 seconds after intravenous administration of $^{99m}TcO_4$, the activity is

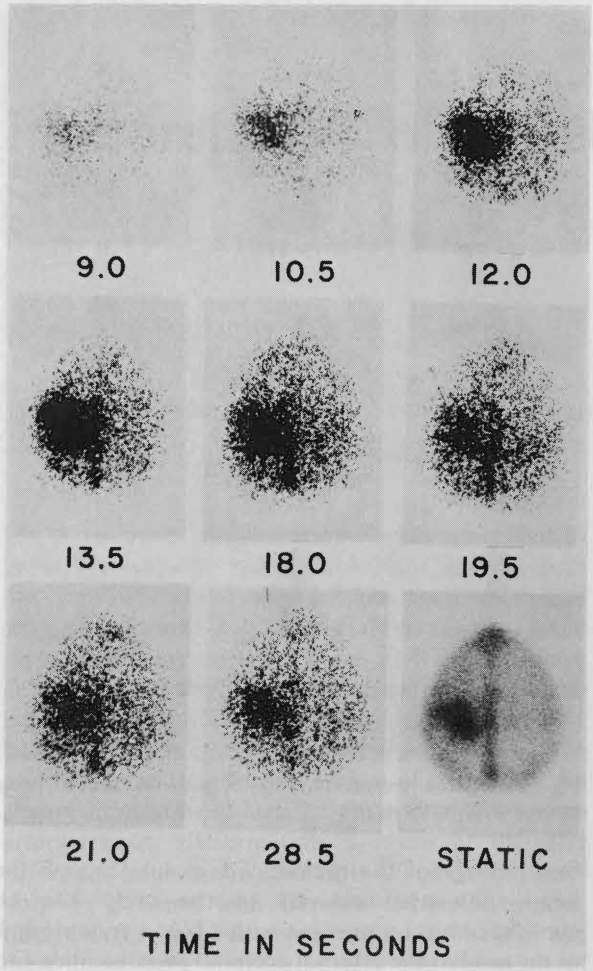

Fig. 3—Dynamic study on patient with left cortical lesion.

first noted in the head; at 12 seconds distribution can be observed in branches of the middle cerebral artery and early filling of the anterior and posterior cerebral arterial areas; further distribution in all three major cerebral arterial regions is demonstrated; and at the end of the early circulation, the cerebral cortex is perfused and activity is beginning to drain into the superior sagittal sinus. Figure 1B illustrates the "venous" and recirculatory phases. Venous drainage is noted throughout the sequence. Demarcated areas of persistent activity are found in the superior sagittal sinus, torcular Herophili, and the bilateral jugular bulbs (36-second frame).

Figure 2 illustrates the information that can be obtained from a dynamic study. The sequence was performed from the posterior projection. The patient, 65 years old, was being evaluated for the recent onset

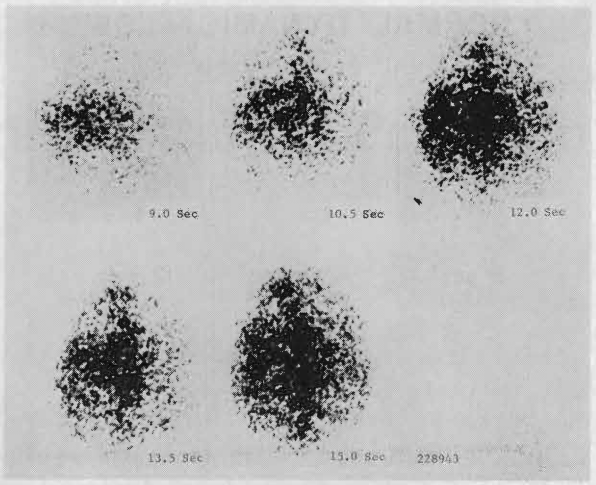

Fig. 4—Nuclear angiography on 14-year-old drowning victim.

of seizures. The primary drainage from the superior sagittal sinus is by the right transverse sinus with no venous structures observed on the left side. Although asymmetrical transverse sinus drainage is frequently encountered, displacement of the torcular Herophili to the right indicates an abnormality that originated in utero or shortly after birth. The interpretation was a left infratentorial fossa mass that displaced the venous structures to the right. Since the patient had been asymptomatic for 65 years, we concluded that it probably was a large arachnoid cyst. Cisternography confirmed the diagnosis.

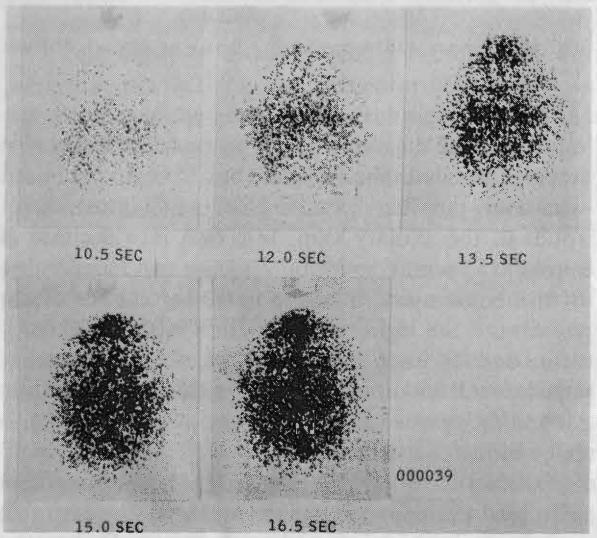

Fig. 5—Nuclear angiography on patient with head trauma.

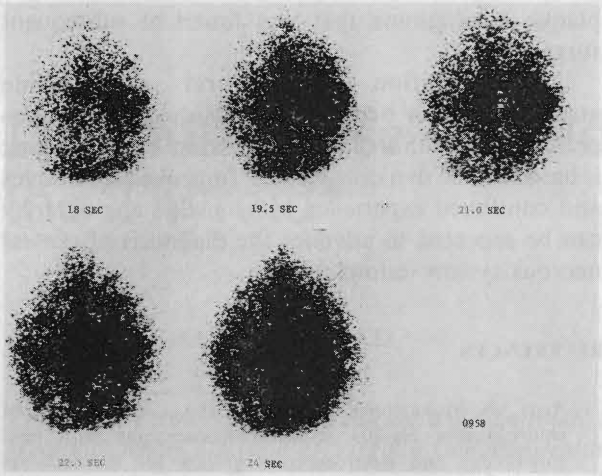

Fig. 6—Diminished flow of left middle cerebral artery in patient with right hemiparesis.

Correlation of the sequential concentration of activity in a lesion with the sequential distribution of activity in the normal brain provides information on the type of pathology. For eight years a young college student had had muscular twitching of the right hand, usually precipitated by physical stress. Static radionuclide images revealed a left cortical lesion, oriented with the rolandic sulcus, in the distribution of the rolandic branch of the left middle cerebral artery. The dynamic study (Fig 3) presented the characteristics of a large rapid arteriovenous shunt. Circumscribed radioactivity was first observed in the left mid-hemisphere nine seconds after administration of the radiopharmaceutical. By the 12-second frame, activity was heavily and focally concentrated

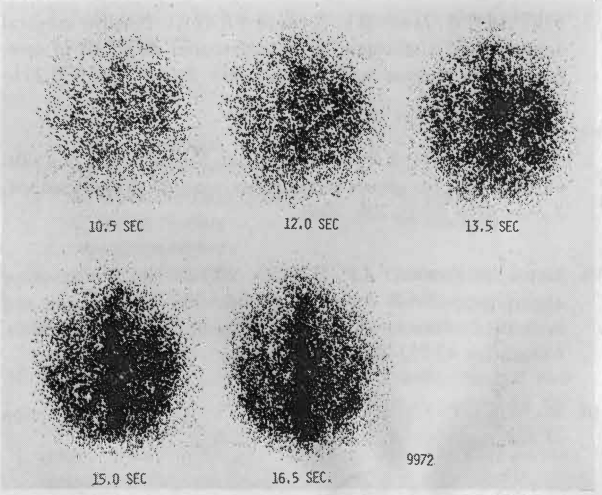

Fig. 7—Diminished flow to left hemisphere in patient with right hemiparesis.

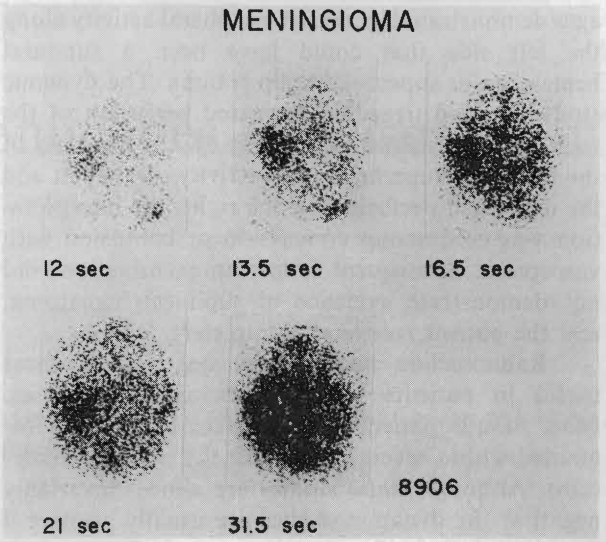

Fig. 8—Dynamic study on patient with suspected arteriovenous malformation.

in the left hemisphere, and early distribution to right cortical area was present.

Within 1½ seconds (13.5-second frame), there was venous drainage through the superior sagittal sinus. Since the 1.5-second interval was too short a period to attribute the venous drainage to the right hemispheric circulation, only a vascular shunt would produce this sequence of events. The diagnosis was a rapid arteriovenous malformation that originated from branches of the left middle cerebral artery and drained into the superior sagittal sinus. Contrast angiography demonstrated the arteriovenous malformation and also revealed that there was a "steal" from the right internal carotid blood supply by way of the anterior communicating artery.

A 14-year-old boy nearly drowned and subsequently developed pneumonia and pulmonary abscesses. He became somnolent, and an electroencephalogram demonstrated diffuse encephalopathy. In the radionuclide angiogram there was no perfusion through the right middle cerebral artery with little evidence of collateral circulation (Fig 4). Angiography revealed obstruction of the internal carotid at the base of the skull. The absence of flow and collateral circulation suggested cerebral edema which was demonstrated by autopsy examination.

Cerebral radionuclide angiography has been particularly helpful in the detection of concussion and contusion with associated vasospasm. For example, a 40-year-old man received head trauma with contusion of the scalp on the left side. The static im-

ages demonstrated increased peripheral activity along the left side that could have been a subdural hematoma or superficial scalp trauma. The dynamic study revealed irregular decreased perfusion of the right middle cerebral artery (Fig 5). On the basis of the increased superficial radioactivity on the left and the decreased perfusion on the right, the interpretation was contracoup concussion or contusion with vasospasm. Subsequent follow-up examinations did not demonstrate evidence of subdural hematoma, and the patient recovered completely.

Radionuclide angiography has proven most useful in patients with cerebrovascular diseases. Most of our patients with strokes usually are examined within several days after the onset of symptoms. Although static studies are almost invariably negative, the dynamic studies are usually positive if the site of the infarction is cortical. Figure 6 illustrates diminished flow of the left middle cerebral artery in a patient with a right hemiparesis. In addition to the localization of the decreased blood flow, collateral flow can frequently be evaluated and furnish prognostic information. In this patient there is little evidence of collateral blood flow to the left hemisphere. The probability of his regaining function from this hemisphere is poor, which was borne out by his subsequent course. In contrast, Figure 7 illustrates another patient with a right hemiparesis and decreased flow to the left hemisphere. In the sequential frames there is collateral blood flow to the left hemisphere, and this patient's prognosis is better. We have found a good correlation between the status of collateral blood flow (determined within a week after the stroke) and recovery of function in the affected side.

As stated earlier, increased, decreased, or no change in perfusion does contribute to the differential evidence in the diagnosis of cerebral lesions. For example, a 40-year-old man developed right-sided symptoms over a period of several months. The static images revealed an area of increased activity of the left cerebral hemisphere, limited to the cortex, and correlated with the configuration of the rolandic branch of the left-middle cerebral artery. From the static images the lesion was interpreted as a possible arteriovenous malformation, or as a lesser possibility, a progressive stroke. The dynamic study (Fig 8) demonstrated early concentration of radioactivity in the correct location that persisted through the dynamic sequence and did not "wash out." This evidence suggested a neoplasm, probably an en-plaque meningioma that was found at subsequent surgery.

The position of cerebral radionuclide angiography has been well established. In our experience, 75%–85% of diagnosis from brain imaging is based on the dynamic studies. Improved techniques and continued experience with nuclide angiography can be expected to advance the diagnosis of central nervous system lesions.

REFERENCES

1. AFIFI AK, MORRISON RR, SAHS AL, ET AL: A comparison of chlormerodrin Hg-203 scintiencephaloscanning with neuroradiology and electroencephalography for the localization of intracranial lesions. *Neurology* 15:56–63, 1965.

2. GOODRICH JK, TUTOR FT: The isotope encephalogram in brain tumor diagnosis. *J Nucl Med* 6:541–548, 1965.

3. OVERTON MC III, SNODGRASS SR, HAYNIE TP: Brain scans in neoplastic intracranial lesions; scanning with chlormerodrin Hg-203 and chlormerodrin Hg-197. *JAMA* 192:747–751, 1965.

4. WITCOFSKI RL, MAYNARD, CD, ROPER, TJ: A comparative analysis of the accuracy of the technetium-99m pertechnetate brain scan, follow-up of 1,000 patients. *J Nucl Med* 8:187–196, 1967.

5. O'MARA RE, MOZLEY JM: Current status of brain scanning. *Semin Nucl Med* 1:7–30, 1971.

6. MOSES DC, JAMES AE, STRAUSS HW, ET AL: Regional cerebral blood flow estimation in diagnosis of cerebrovascular disease. *J Nucl Med* 13(pt 1):135–141, 1972.

7. STRAUSS HW, JAMES AE, HURLEY PJ, ET AL: Nuclear cerebral angiography: Usefulness in the differential diagnosis of cerebrovascular disease and tumor. *Arch Intern Med* 131:211–216, 1973.

8. OLDENDORF WH, KITANO M, SHIMIZU S: Evaluation of a simple technique for abrupt intravenous injection of radioisotope. *J Nucl Med* 6:205–209, 1965.

9. KRISS JP, ENRIGHT LP, HAYDEN WG ET AL: Radioisotope angiography. Wide scope of applicability of diagnosis and evaluation of therapy in diseases of the heart and great vessels. *Circulation* 43:792–808, 1971.

10. WATSON DD, NELSON JP, GOTTLIEB S: Rapid bolus injection of radioisotopes. *Radiology* 106:347–352, 1973.

11. DELAND FH: Technique for improved visualization of cerebral blood flow, abstracted. *J Nucl Med* 12:428, 1971.

Diagnostic Use of Radionuclides in Diseases of the Thyroid*

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Since the introduction of radionuclides into clinical medicine, a number of specific tests have been designed to test thyroid function and to diagnose diseases of the thyroid gland.

These studies can be broadly grouped into in vivo and in vitro studies. Using ^{131}I and ^{125}I, tests have been designed to measure thyroid function at the hypothalamic, pituitary, or thyroid level and at the peripheral level by radioimmunoassay or radioassay of circulating thyroid hormones. The following schema of testing may be used to assess thyroid function:

I. *Hypothalamus.* Following the intramuscular administration of thyrotropic-releasing hormone, the following changes occur in plasma thyroid-stimulating hormone (TSH) level, which can be measured by radioimmunoassay using ^{125}I:

CONDITION	TSH
1. Normal	Increased
2. Hyperthyroidism	
A. Toxic Diffuse Goiter	No change
B. Toxic Nodular Goiter	No change
C. Toxic Nodule	No change
3. Hypothyroidism	
A. Hypothalamic	Increased
B. Pituitary	No change
C. Thyroid	Increased

II. Pituitary capability of secreting TSH under normal and abnormal conditions can be accurately measured by determination of peripheral level of TSH using ^{125}I radioimmunoassay techniques. The following are TSH values for various thyroid disorders:

CONDITION	TSH
1. Normal	1–10μU/ml†
2. Hyperthyroidism	
A. Toxic Diffuse Goiter	Normal
B. Toxic Nodular Goiter	Normal
C. Toxic Nodule	Normal
D. Hypothalamic	Increased (1)
E. Pituitary Tumor	Increased (1)
3. Hypothyroidism	
A. Hypothalamic	Low
B. Pituitary	Normal
C. Thyroid	Increased

III. Assessment of thyroid glandular function can be determined by measuring the concentration of ^{131}I using basal and dynamic studies following oral administration of ^{131}I.

1. BASAL STUDIES	PERCENT ^{131}I CONCENTRATION		
	3 hours	5 hours	24 hours
A. Normal Curve	†2.5–11.6%	†4.1–14.9%	†9.0–31.0%
B. Hyperthyroid Curve	>11.6%	14.9%	31.0%
C. Hypothyroid Curve	<2.5	4.1%	9.0%

2. DYNAMIC STUDIES	NORMAL RESPONSE
A. TSH Stimulation Test	>50% Increase
B. T-3 Suppression	>50% Decrease
C. $KClO_4$ Discharge	< 3% Decrease

Determination of the circulating thyroid hormones by radioassay and radioimmunoassay techniques using ^{125}I are readily available and offer accurate measurement of these hormones when properly performed. Normal values for the circulating hormones are as follows:

* Presented by Dr. Sharpe at the Postgraduate Course in Nuclear Medicine, February 27, 1975, in Williamsburg, Virginia.

† Normal values for the Medical College of Virginia.

1. Total thyroxine 5.6–13.1μg/dl†
2. Triiodothyronine 70–170 ng/dl†
3. Serum free thyroxine 1.2–3.5 ng/dl†

Discussion. Differential diagnosis of diseases of the thyroid can be made with a high degree of certainty using the previously mentioned tests employing radionuclides. The clinical applicability of the various tests is dependent upon a thorough knowledge of thyroid physiology and interrelationships of trophic hormones and carrier proteins. A review of the disease states and diagnosis using specific tests follows.

1. *Hyperthyroidism.* The vast majority of cases can be diagnosed on clinical grounds alone from the history and physical findings. Confirmation is easily obtained by employing the ^{131}I uptake at 3, 5, and 24 hours. This will be elevated in the majority of hyperthyroid patients. The above-mentioned test in conjunction with the T-4 and serum free thyroxine (SFT)-4, which are usually elevated, will establish the diagnosis in both Graves' disease and hyperthyroidism due to a nodular goiter. If the diagnosis is suspected on clinical grounds and the above tests are normal, one can then perform the T-3 suppression study. This is done by obtaining a baseline uptake at 3, 5, and 24 hours and then placing the patient on L-triiodothyronine, 150μg daily for seven days. The uptake in the normal person is suppressed after T-3 administration by at least 50% and is usually below 20% at 24 hours. Hyperthyroid patients seldom suppress below 20% and never below 50% of original uptake. The usual hyperthyroid patient has little or no change in 24-hour uptake following T-3. Data from our laboratory on T-4 and SFT-4 also reveal less than 50% suppression in the hyperthyroid patient with the average change being 1μg/dl or less. In rare cases, thyrotoxicosis may be due to elevated T-3 levels. Under these circumstances, the T-4 and SFT-4 and uptake are normal but the latter is nonsuppressible.

2. *Hypothyroidism.* In contrast to hyperthyroidism, hypothyroidism is not always easy to diagnose. This disease has protean manifestations and may be insidious in onset.

Diagnosis when hypothyroidism is suspected clinically is best confirmed by a 24-hour ^{131}I uptake of less than 9% in 24 hours and a low total and free thyroxine of less than 5.6μg/dl and 1.2 ng/dl, respectively.

Differentiation between pituitary or thyroid failure can now be made by measuring serum TSH by ^{125}I radioimmunoassay following intramuscular or intravenous injection of thyrotropin-releasing hormone (TRF). A rise in the serum TSH will occur within approximately 15 to 30 minutes after intravenous injection (2) and 2 to 3 hours after intramuscular TRF (3) injection if the pituitary is intact. Failure to detect a significant rise in TSH after TRF administration implies pituitary failure and hence, establishing the diagnosis of secondary hypothyroidism.

3. *Subacute thyroiditis.* Diagnosis of subacute thyroiditis is usually suggested by the clinical picture of anterior neck pain with exacerbation on swallowing or coughing, radiation of pain to the ears, hoarseness, and signs and symptoms of hypermetabolism. The thyroid is usually enlarged and especially tender.

Laboratory confirmation is established by the presence of a low ^{131}I uptake at 3, 5, and 24 hours and an elevated T-4 and SFT-4.

4. *Enzymatic defects.* These are usually characterized by the presence of a goiter dating from early childhood or the development of thyroid enlargement following ingestion of certain drugs or foods.

Laboratory studies usually demonstrate an elevated ^{131}I uptake value, low total T-4 and SFT-4 and discharge of ^{131}I from the thyroid gland of greater than 3% following oral administration of potassium perchlorate or potassium thiocyanate.

5. *Nodules.* Adequate assessment of both single and multiple nodules in the thyroid gland require that a scan be performed after the administration of ^{131}I (4), ^{125}I (5) if available, or ^{99m}Tc (6). The former is performed in our laboratory. Evaluation of nonfunctioning nodules subsequently removed surgically at our institution over a ten-year period reveals that single nonfunctioning nodules were malignant in 12.5% of cases, multiple nodules in 16.5%, with the total overall incidence of malignancy being 13.0% in nonfunctioning nodules. (These findings have been noted in a study by J. M. Harrison, MD, R. H. Kirkland, MD, and the author, unpublished data). Or 24 malignant nodules out of 184 nonfunctioning nodules by scan.

The incidence of malignancy in hot nodules in the same study was 1 out of 74, or 1.3%. Reexamination of the scan in the one case revealed that, in retrospect, this most likely was a cold nodule. A functioning nodule is thus strong evidence against malignancy, although some reports of this occurring have appeared in the literature (7).

The autonomous nodule with or without

hyperthyroidism is characterized by uptake in the nodule only and suppression of the remaining thyroid tissue. The nodule fails to suppress following the administration of L-triiodothyronine as previously discussed and there is no significant change in the T-4 or SFT-4 by ^{125}I radioassay. Thyroid-stimulating hormone and long-acting thyroid stimulator (LATS) values are characteristically low for the former and undetectable for the latter. Autonomy can be confirmed by repeating the scan after administration of 10 units of TSH.

Conclusion. Correct assessment of thyroid function and evaluation of nodules can be obtained by the proper application of the appropriate in vivo or in vitro tests as previously discussed. Thyroid function can now be evaluated at the hypothalamic, pituitary, and thyroid level using both ^{131}I and ^{125}I and at the peripheral level using ^{125}I radioassay or radioimmunoassay procedures. Using these procedures as described, quantitative evaluation of thyroid function can be made, and in most instances the disease process can be defined in a specific manner.

REFERENCES

1. EMERSON CH, UTIGER RD: Hyperthyroidism and excessive thyrotropin secretion. *N Engl J Med* 287:328–333, 1972.
2. HERSHMANN JM: Clinical application of thyrotropin-releasing hormone. *N Engl J Med* 290:886–890, 1974.
3. AZIZI F, VAGENAKIS AG, PORTNAY GI, ET AL: Pituitary-thyroid responsiveness to intramuscular thyrotropin-releasing hormone based on analyses of serum thyroxine, tri-iodythyronine and thyrotropin concentrations. *N Engl J Med* 292:273–277, 1975.
4. KING ER, SHARPE AR JR: Visualization of internal organs and tumors by radioisotope photoscanning. *Postgrad Med* 34:Sept, 1963, adv p 47–57.
5. LÖTTER MG, VAN DER MERWE EJ, VAN HEERDEN PDR, ET AL: The use of ^{123}I in thyroid diagnosis. *S Afr Med J* 46:186–189, 1972.
6. SHARPE AR JR, GARDNER CT JR, CASSIDA WA JR, ET AL: Thyroid uptake and scan using technetium-99m pertechnetate, abstracted. *J Nucl Med* 8:337, 1967.
7. MOLNAR GD, CHILDS DS, WOOLNER LB: Histologic evidence of malignancy in a thyroid gland bearing a hot nodule. *J Clin Endocrinol Metab* 18:1132–1134, 1958.

Evaluation of Thyroid Nodules—Hot and Cold*

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Thyroid nodules occur frequently, are more common in women, and the incidence increases with age for both sexes. Clinically normal thyroid glands commonly contain nodules in autopsy series. In 20- to 50-year-old females, as high as 50% of the thyroid glands are nodular, whereas in males the incidence approaches 30% (1). When the prevalence of clinically palpable thyroid nodules was the objective of the Framingham population researchers, Vander et al (2) detected nodules in 6.4% of females and 1.5% of males aged 30–50 years. Even with diligent, thorough examination of the neck, only about one tenth of pathologically nodular thyroid glands can be detected. However, the number of palpable nodules is significant, and determination of the pathology of the nodule or goiter, once found, rests with the patient's physician. Unfortunately, a detailed history and physical examination frequently does not provide all the necessary information needed to make a definite etiologic or pathologic diagnosis. Knowledge of the type of goiter is mandatory for proper treatment of the various disorders of the thyroid gland.

The various types or causes of goiters are shown in Table 1. Goiters may be divided clinically into diffuse or nodular; hyperthyroid, euthyroid, or hypothyroid. It is readily apparent that several pathologic entities may be diffuse or nodular in addition to altering thyroid function. Hyperthyroid patients may have a diffuse goiter, solitary nodule, or a multinodular gland. Graves' disease usually presents no diagnostic problems, but, rarely, a toxic diffuse goiter may be caused by excessive pituitary thyroid-stimulating hormone (TSH) from hypothalamic thyrotropin-releasing hormone (TRH) stimulation or pituitary tumor. Subacute nonsuppurative thyroiditis may be focal or diffuse and cause transitory hyperthyroidism. The hyperthyroid phase of this disease is associated with a low or blocked radioactive iodine uptake (RAIU) and usually a painful, hard gland. The hyperthyroid adenomatous goiter produces the usual findings of thyrotoxicosis and, clinically, a multinodular goiter. Evaluation of a toxic adenoma will be discussed later.

Euthyroid diffuse goiters, with the exception of thyroiditis, represent compensatory enlargement of the gland in an attempt to maintain normal hormone production. Patients with dietary iodine deficiency have an elevated RAIU that is suppressible with supraphysiologic doses of thyroid hormone (our standard procedure is to give 150μg daily of triiodothyronine for seven days). Excessive iodine intake is associated with a suppressed or blocked RAIU. Diffuse goiter from congenital thyroidal enzyme deficiency, that is, peroxidase deficiency, results in an initially elevated RAIU with discharge of radioiodine from the gland following potassium perchlorate administration. The early adenomatous goiter often feels diffuse rather than nodular. The RAIU usually is normal, but the scan often shows nonuniform distribution of radioactivity within the gland. Subacute thyroiditis may diffusely involve the gland, and the patient may be euthyroid when seen. Chronic thyroiditis (Hashimoto's thyroiditis) is a painless, firm goiter frequently with high titers of antithyroid antibodies present in the serum. Any of the diffuse goiters may be accompanied by hypothyroidism, but low thyroid function is more com-

* Presented by Dr. Fratkin at the Postgraduate Course in Nuclear Medicine, February 27, 1975, in Williamsburg, Virginia.

TABLE 1
Types of Goiters

DIFFUSE	NODULAR
HYPERTHYROID	
Graves' Disease	Adenomatous
Excess TSH	Adenoma
Thyroiditis	Thyroiditis
EUTHYROID	
Iodine Deficiency	Carcinoma
Iodine Excess	Adenoma
Enzymatic Defects*	Colloid Cyst
Adenomatous	Adenomatous
Thyroiditis*	Thyroiditis

* May be associated with hypothyroidism

monly seen with congenital enzymatic deficiency goiters and Hashimoto's thyroiditis.

Patients with nodular goiter (as mentioned earlier) may be hyperthyroid or, rarely, hypothyroid, but are usually euthyroid. The euthyroid patients with nodular goiter, and especially those with a solitary nodule, represent the greatest diagnostic problem, for thyroid carcinoma must always be considered and excluded. Since one cannot differentiate a benign from a malignant tumor with certainty by palpation alone, further diagnostic tests are indicated (Fig. 1). The thyroid scan will determine whether the nodule is functioning (Fig. 2) or nonfunctioning (Fig. 3). The pathology of functioning (hot) and nonfunctioning (cold) nodules is shown in Table 2. The demonstration of a hot nodule with scanning essentially excludes the probability that the lesion is a carcinoma. However, if the nodule is cold, one can only make a statistical guess concerning the pathology. Further diagnostic work-up can be pursued prior to surgical exploration (Fig. 1). Nonfunctioning, solitary nodules may be separated into cystic and solid with ultrasonography, and recent reports (3, 4) suggest that cystic thyroid nodules represent 20% of cold nodules and are benign. Additional procedures have been performed in an attempt to non-invasively exclude thyroid carcinoma. Sonography (5), in addition to distinguishing cystic from solid lesions, demonstrates a characteristic echo pattern in malignancy that may prove to be diagnostic if substantiated by additional reports. Thyroid scanning of cold nodules with other radiopharmaceuticals such as ^{67}Ga-citrate (6) and ^{75}Selenomethionine (7, 8) may be positive in cases of thyroid cancer, but false negatives (^{67}Ga) and false positives (^{75}Se) are frequent. Thermography (9) has been tried, but the number of lesions studied are too few to reach any conclusions. According to an oral communication from J. Frable, MD, in January, 1975, thin-bore needle aspiration can yield a positive diagnosis of papillary adenocarcinoma, but cannot differentiate follicular adenoma from adenocarcinoma. I might sum up by saying that the solitary, nonfunctioning and especially the solid thyroid nodule is malignant until proven otherwise by surgical exploration. The results of sonography are exciting and promising, but further studies are indicated before the role of ultrasound can be established in the evaluation of thyroid nodules (Fig. 4).

The thyroid nodule that concentrates radioiodine may be a follicular adenoma, adenomatous nodule, normal thyroid tissue such as a lingual thyroid, or residual hyperplastic thyroid tissue following a subtotal thyroidectomy. The triiodothyronine suppression test will differentiate the autonomously functioning thyroid nodule from other types of functioning nodules (Fig. 5). Treatment of suppressible functioning thyroid nodules with thyroid hormone results usually in no further enlargement and frequently in disappearance clinically of the nodule.

The typical autonomously functioning thyroid nodule is illustrated in Figure 2. Although the patient is euthyroid, the nodule has suppressed the function of the normal thyroid tissue and is not suppressible with administration of triiodothyronine (Cytomel®). Administration of thyroid-stimulating hormone, 10 units daily for three days, may be used to demonstrate the presence of normal but suppressed thyroid tissue. Treatment with 25 millicuries of radioactive iodine resulted in ablation of the nodule, appearance of the previously suppressed normal thyroid gland, and continuation of a euthyroid state.

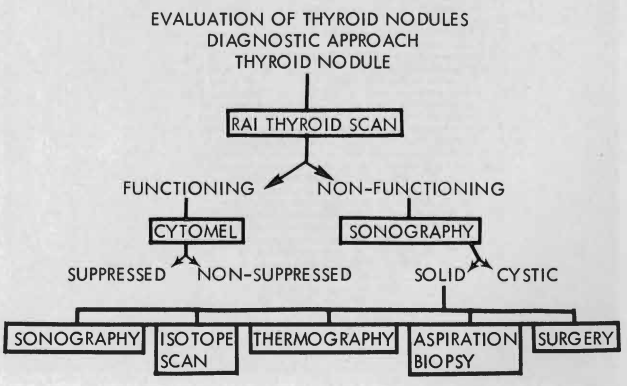


Fig. 1—Sequential diagnostic approach in evaluation of thyroid nodules.

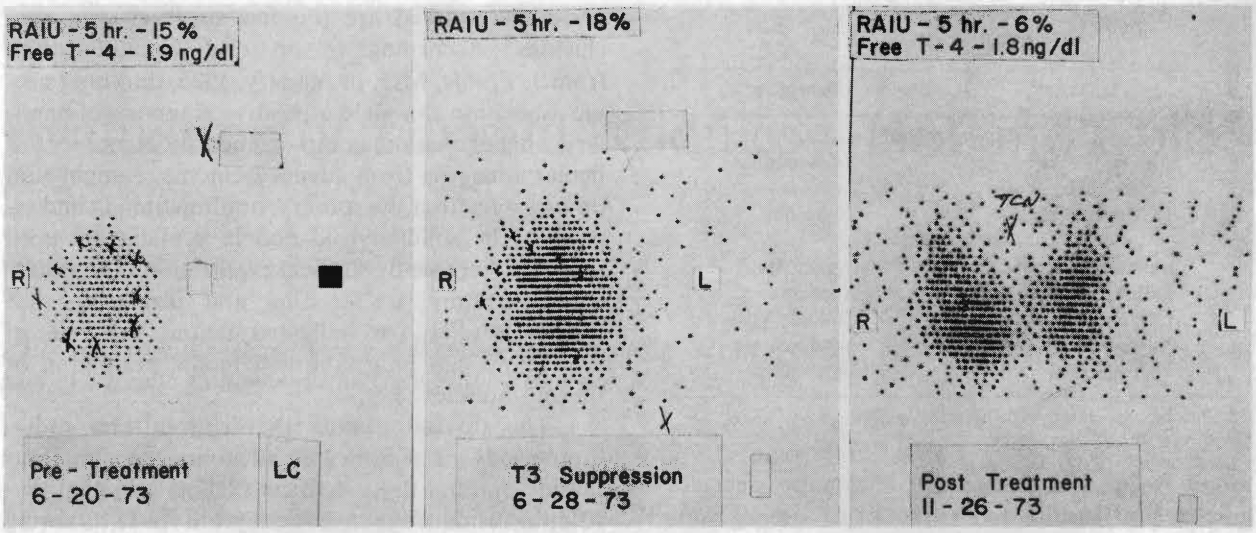


Fig. 2—*Left.* Functioning 4 × 3 cm right thyroid nodule with normal RAIU and serum free thyroxine concentration; no radioiodine uptake in area of left lobe. *Center.* Triiodothyronine (T-3) administration produced no decrease in RAIU or nodule uptake. *Right.* Following radioiodine treatment, nodule has been ablated; right and left lobes concentrate radioiodine; overall thyroid function remains normal.

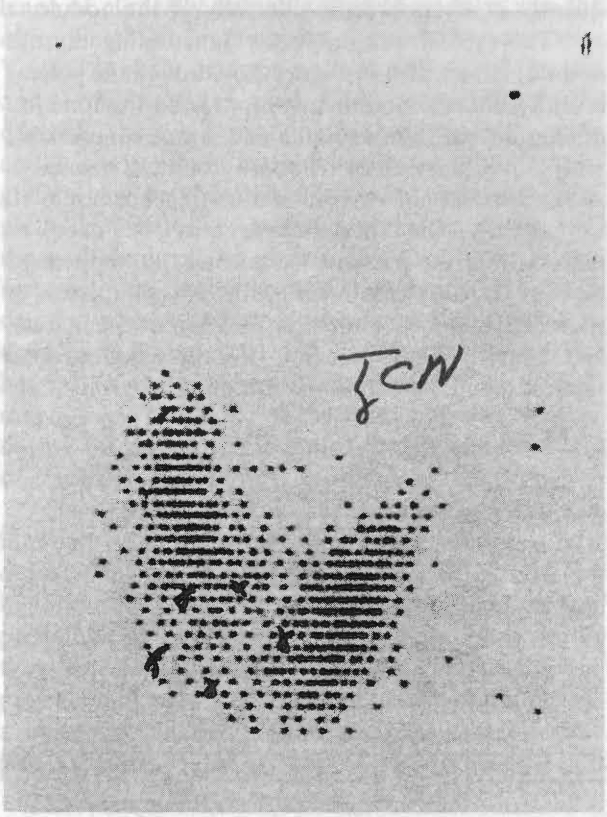
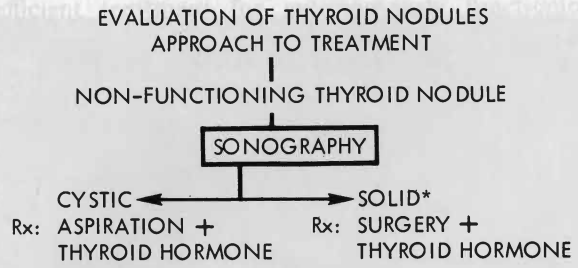


Fig. 3—Nonfunctioning thyroid nodule in lower pole of right lobe. Pathologic diagnosis was follicular adenoma.

The question arises, though, should a nontoxic, autonomously functioning nodule be treated at all? What is the natural history of a functioning follicular adenoma? There are case reports of nontoxic nodules progressing to toxic nodules which then require treatment because of the development of clinical hyperthyroidism. Such a course of events is shown in Figure 6. Patient W. W. first noted a goiter 15 years ago, but was advised that no treatment was necessary. In 1969, his protein-bound iodine (PBI) was normal, and his nodule had gradually increased in size. When seen in 1973, he was hyperthyroid. Treatment with radioiodine achieved a euthyroid state but little to no reduction in the size of the nodule. It can be assumed that he had an autonomously functioning nodule from the onset that progressed in size over the years, achieving a sufficient mass to produce excessive amounts of thyroid hormone and hyperthyroidism.

TABLE 2
Pathology of Thyroid Nodules

Histologic Diagnosis	Functioning No.	Functioning Percent	Nonfunctioning No.	Nonfunctioning Percent
Adenomatous	53	70	107	58
Adenoma	11	15	31	17
Carcinoma	0	0	24	13
Hyperplasia	5	7	0	0
Thyroiditis, Chronic	0	0	7	4
Unclassified	6	8	15	8
Total	75		184	



*FURTHER EVALUATION OF NON-FUNCTIONING, SOLID THYROID NODULE IS INVESTIGATIONAL (1975)

Fig. 4—Role of sonography in therapeutic approach to nonfunctioning thyroid nodules.

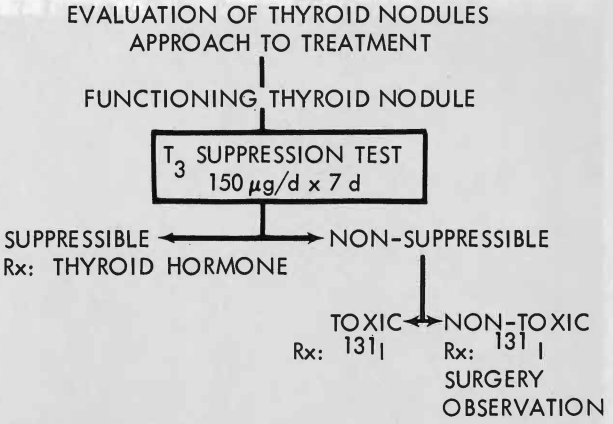


Fig. 5—Diagnostic and therapeutic approach to functioning thyroid nodule.

Is this case the exception or the rule? Horst and associates (10) and later Ferraz et al (11) suggest that the natural history of a nontoxic but autonomously functioning thyroid nodule is one of progression to hyperthyroidism. They based their conclusions on data demonstrating toxic nodules being larger than nontoxic ones, and the rather continuous spectrum of functional activity from euthyroidism to overt hyperthyroidism. Similarly, Hamburger and Meier (12) noted that those patients who were hyperthyroid were older and had larger nodules than euthyroid patients with nonsuppressible functioning nodules. In their prospective study of 28 nontoxic patients with autonomously functioning nodules followed one to ten years (majority followed less than six years), none became hyperthyroid, but four glands increased in size. A retrospective study by McCormack and Sheline (13) revealed 1 out of 14 nontoxic untreated

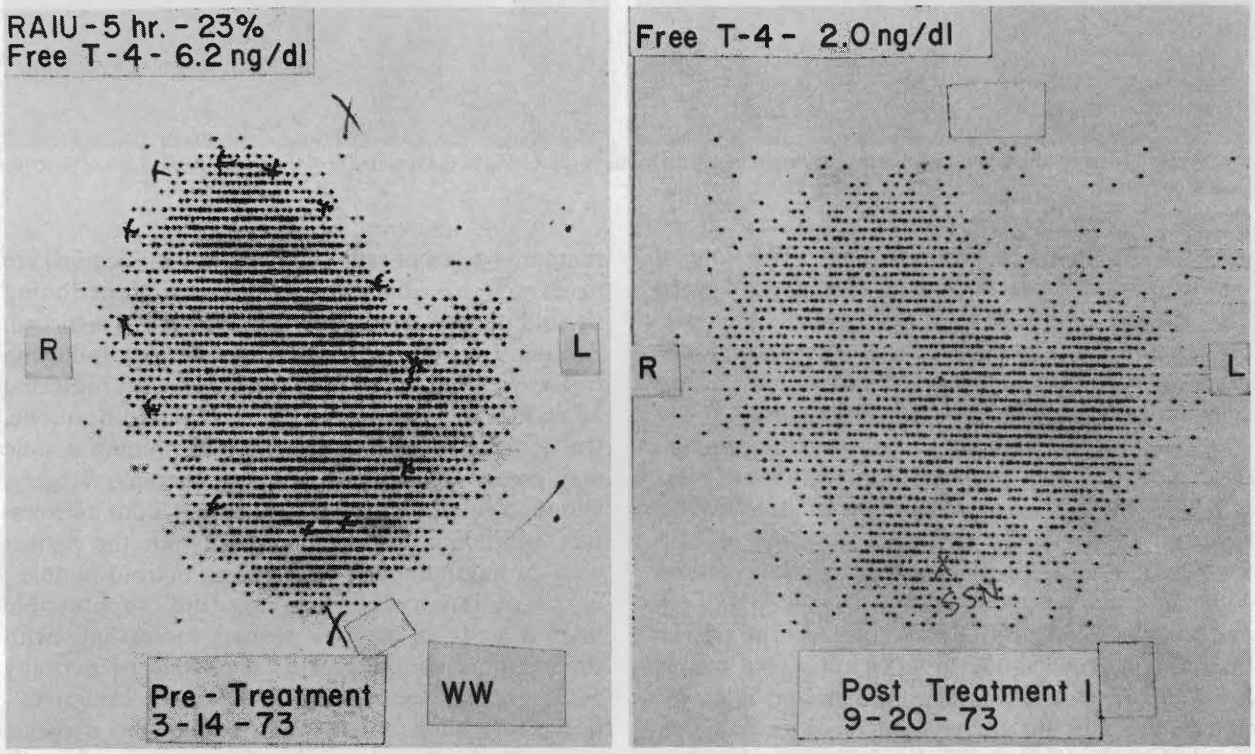


Fig. 6—*Left.* Large 9 × 6 cm toxic nodule with high RAIU and serum free thyroxine concentration. *Right.* Establishment of normal function, but persistence of nodule following radioiodine treatment.

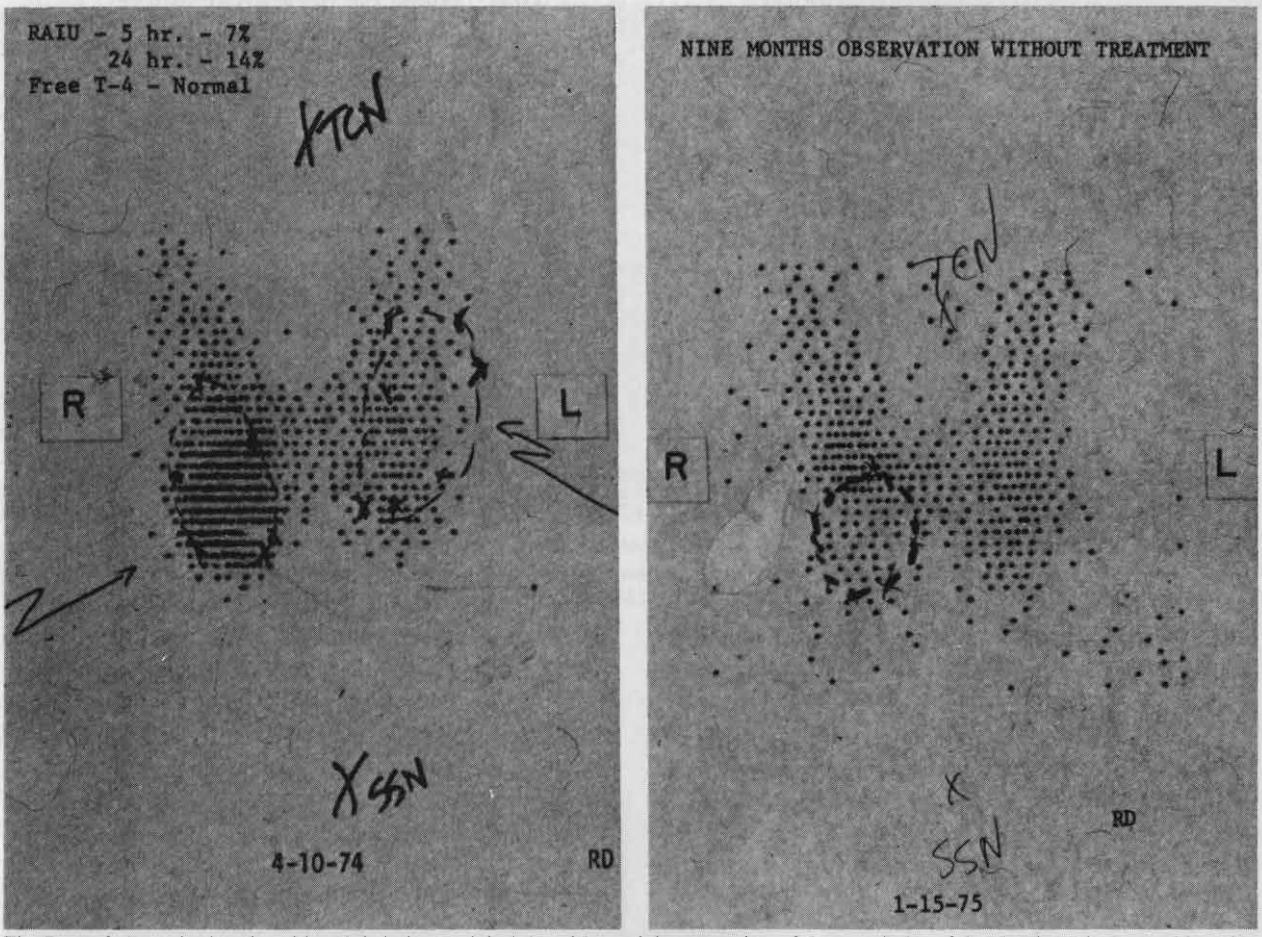


Fig. 7—*Left.* Functioning thyroid nodule in lower right lobe with partial suppression of the remainder of the gland. *Right.* Loss of function in outlined nodule.

patients developed hyperthyroidism. The longest follow-up was 8½ years with a mean of about 4 years. The available data suggest circumstantially that nontoxic, autonomously functioning thyroid nodules progress to toxicity, but usually not within the first eight to ten years from the initial diagnosis.

The next case (Fig. 7) illustrates the opposite natural history—spontaneous disappearance of function from a hot nodule. The initial scan shows a functioning nodule with partial suppression of the remaining gland. Treatment with triiodothyronine, 150μg daily for seven days, resulted in a RAIU of 1%, and no specific therapy was instituted. The patient became concerned about the small but visible mass in her neck. When she returned nine months later, the nodule had lost its ability to take up radioiodine. Surgical exploration revealed a follicular adenoma.

Our experience and that of others (10, 13) reveal that large doses of radioiodine (20–40 millicuries) are necessary to ablate autonomously functioning thyroid nodules, that euthyroid function is achieved, and that hypothyroidism does not develop following treatment when the normal thyroid tissue is protected by endogenous and/or exogenous thyroid hormone. On occasion, a residual but nonfunctioning nodule may persist following radioiodine therapy. Surgery, although equally effective therapy (13), adds unnecessary additional cost and morbidity for the patient with an autonomously functioning thyroid nodule.

In summary, functioning but suppressible thyroid nodules may be treated successfully with thyroid hormone (Fig. 5). Completely or partially autonomously functioning nodules are benign follicular adenomas. This type of nodule may progress in size to produce hyperthyroidism or may lose its ability to concentrate iodine. Radioiodine is a safe,

efficient treatment for autonomously functioning thyroid nodules and should be considered the treatment of choice.

REFERENCES

1. MORTENSEN JD, WOOLNER LB, BENNETT WA: Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab* 15:1270–1280, 1955.

2. VANDER JB, GASTON EA, DAWBER TR: The significance of nontoxic thyroid nodules. *Ann Intern Med* 69:537–540, 1968.

3. BLUM M, GOLDMAN AB, HERSKOVIC A, ET AL: Clinical applications of thyroid echography. *N Engl J Med* 287:1164–1169, 1972.

4. MISKIN M, ROSEN IB, WALFISH PG: B-mode ultrasonography in assessment of thyroid gland lesions. *Ann Intern Med* 79:505–510, 1973.

5. CROCKER EF, MCLAUGHLIN AF, KOSSOFF G, ET AL: The gray scale echographic appearance of thyroid malignancy. *J Clin Ultrasound* 2:305–306, 1974.

6. KAPLAN WD, HOLMAN BL, SELENKOW, H. A., ET AL: ^{67}Ga-citrate and the nonfunctioning thyroid nodule. *J Nucl Med* 15(pt 1):424–427, 1974.

7. THOMAS CG JR, PEPPER FD, OWEN J: Differentiation of malignant from benign lesions of the thyroid gland using complementary scanning with ^{75}selenomethionine and radioiodide. *Ann Surg* 170:396–408, 1969.

8. WEINSTEIN MB, ASHKAR FS, CARON CD: ^{75}Se Selenomethionine as a scanning agent for the differential diagnosis of the cold thyroid nodule. *Semin Nucl Med* 1:390–396, 1971.

9. SAMUELS BI: Thermography: a valuable tool in the detection of thyroid disease. *Radiology* 102:59–62, 1972.

10. HORST W, RÖSLER H, SCHNEIDER C, ET AL: 306 cases of toxic adenoma: clinical aspects, findings in radioiodine diagnostics, radiochromotography and histology; results of ^{131}I and surgical treatment. *J Nucl Med* 8:515–528, 1967.

11. FERRAZ A, MEDEIROS-NETO GA, TOLEDO AC, ET AL: Autonomous thyroid nodules: I. A Clinical classification and the use of a diagnostic index. *J Nucl Med* 13(pt 2):733–737, 1972.

12. HAMBURGER JI, MEIER DA: Nontoxic autonomously functioning thyroid adenomata-therapeutic considerations, abstracted. *J Nucl Med* 14:404, 1973.

13. MCCORMACK KR, SHELINE GE: Long-term studies of solitary autonomous thyroid nodules. *J Nucl Med* 8:701–708, 1967.

The Diagnosis and Treatment of Carcinoma of the Thyroid*

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Before going into a discussion of the diagnosis and treatment of carcinoma of the thyroid, I would like to make a few observations on the means of detection.

Thyroid scanning, in my opinion, is useful only in the study of nodules. We see many patients who have had scans for diffuse thyroid enlargement, and I feel that in this instance, scans are useless. The basic reason for the scan is to discover which pieces of thyroid tissue have to be removed because of possible malignancy. I would like to emphasize, that the physician has to do the scan himself. He has to localize the nodule, properly mark it on the scan, and remain during the scan, as the patient may move his neck, thus moving the position of the nodule in reference to the marks. We have seen scans in the early days of isotope scanning where the technician, who was not taught to palpate the thyroid, marked the scan. This system is inadequate, as errors can occur.

Using the T-3 suppression test, the criteria for suppression is a fall in uptake below 20% in 24 hours after a week on T-3, 150μ daily. However, the normal uptake is often below 20%, and hyperthyroid patients may also have less than 20% uptake, so the test is losing some of its specificity. I think the criteria for the suppression test should be changed, or the interpretation of it, to indicate that there is *"no significant"* fall in uptake after T-3 for a week. It is very difficult to establish such criteria, because I do not know what normal figures to give. We recently saw a patient with a nodule who had 8% uptake in 24 hours prior to T-3. We went ahead with T-3 suppression, and he had 7% after T-3. We did not know what to do or how to interpret this. We treated the patient with radioactive iodine, thinking that the nodule was not suppressible, and the other lobe did reappear on later scanning. This patient had an autonomous nodule with an 8.0% uptake.

In my opinion, 3- and 5-hour uptakes are absolutely essential. I would not want an uptake run only at 24-hour intervals, because we do see patients who have taken iodides or, unknown to us, antithyroid drugs and who have normal 24-hour uptakes but who have blocked thyroid function and are not making thyroid hormone at the moment. Therefore, it is necessary to run 3- and 5-hour uptakes to identify this blocked type of function and, if diagnosis is not clear at that time, at a later 24-hour point.

In the hot nodule with low radioiodine uptake where the T-3 suppression test may not be of great value, one can give TSH and do a scan afterward to see if the other lobe reappears. If it does reappear, indications are that the nodule is an autonomous one which was suppressing TSH.

I now want to discuss the diagnosis and treatment of carcinoma of the thyroid. Carcinoma of the thyroid gland is both rare and common. It is a frequent diagnosis on pathological sections, but clinically it is a rare disease. Very few patients die from carcinoma of the thyroid. Each of us has seen so few thyroid carcinomas of clinical significance that it is difficult to gather a series sufficiently large to determine what treatment techniques are best. As some

* The following is an edited transcription of a lecture presented by Dr. Kirkland at the Postgraduate Course in Nuclear Medicine, February 27, 1975, in Williamsburg, Virginia.

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evidence of the incidence, Dr. Fratkin showed that in one hundred cases of thyroid nodules 70% were cold. Of the 70% that were cold, he said 15% were carcinomatous. That is a high incidence of carcinoma of the thyroid. Recently, a student and I went around on the wards at the Medical College of Virginia and felt every patient's thyroid regardless of what the patient had been admitted for. Thirty-three percent of the women incidentally had palpable nodular thyroid disease. If we take these female patients with nodules—70% of them cold and 15% of them with carcinoma—3.48% of women in the Medical College of Virginia should have carcinoma of the thyroid. Obviously these figures are not true clinically. Even the pathologist has problems in diagnosing thyroid malignancy. Thyroid-stimulating hormone stimulation of the thyroid makes it so hypertrophic that sometimes the thyroid looks malignant although it doesn't behave that way.

In patients with carcinoma of the thyroid, the natural course of the disease is variable, so that a long-term follow-up is necessary to determine what happens to them. One cell type, such as papillary carcinoma of the thyroid, might change to follicular, or the metastases may show at the same time different pathological types. Any treatment I propose, therefore, would have to be very arbitrary.

I would like to mention something about the etiology of the carcinoma of the thyroid. Two Australians, Purves and Geishbach, in 1948, gave rats thiourea for two of their three-year life spans and found that 100% of the rats developed carcinoma of the thyroid. (This fact does not stop us from giving propylthiouracil to patients, and some clinics advocate this as the best treatment for hyperthyroidism). They stated in their article, "We think that the administration of thyroid extract to these rats would have prevented this." They gave thiourea to rats after hypophysectomies and none of these animals developed carcinoma of the thyroid. This suggests to me that the etiology for the carcinoma, or an etiological factor, was the TSH level which rose in the thiourea-treated rats and stimulated a blocked gland. That was the first finding that led me to think that carcinoma might be produced by long-term TSH stimulation of a blocked or damaged thyroid gland. There is also an increased incidence of carcinoma of the thyroid in patients who have congenital enzyme blocks. One type of congenital enzyme block is followed by nearly 100% incidence of carcinoma of the thyroid—another fact that makes me think that TSH stimulation might lead to carcinoma. There is a higher incidence of carcinoma of the thyroid in thyroiditis where the gland may be injured. The TSH may rise and the same circumstances occur. Irradiation of the neck in childhood is another etiologic factor. There are also cases of thyroid carcinoma which are TSH dependent. These tumors tend to grow more rapidly if the TSH levels are high. We should, therefore, keep the TSH low in patients who have carcinoma of the thyroid. This concept has been an important influence in my treatment of thyroid patients. Once hyperthyroidism is eliminated, I think anyone with thyroid disease should be on long-term suppressive thyroid hormones.

These factors led me to review the histories of patients with carcinoma of the thyroid at the Medical College of Virginia in order to see if I could find a thyroid-damaging factor. Fifty percent of the patients had had some thyroid destructive disease, such as thyroiditis or colloid goiter, or treatment for thyroid suppression, such as surgery. None of them had had radioiodine therapy, but I think the incidence of carcinoma of the thyroid might increase after radioiodine if we live long enough to observe this course.

How do we diagnose the carcinoma of the thyroid? Most cases are not diagnosed by symptoms, although there are some symptoms, such as hoarseness or a tracheal narrowing shown on AP and lateral x-rays. Hoarseness suggests that the recurrent laryngeal nerves might be invaded, and this might indicate the possibility of carcinoma, especially if it is accompanied by a mass in the thyroid area. Dysphagia is suspicious. X-ray studies of the esophagus showing real obstruction are helpful and do suggest that there is true disease present and not just an anxiety globus hystericus. We recently noted a bruit over the thyroid gland in the absence of hyperthyroidism. This indicated that there was high vascularity and suggested the possibility of

Thyroid	
Pathology found in "hot" nodules	
Nodular colloid goiter	70%
Hyperplastic goiter	7%
Adenoma	15%
Carcinoma	0%
Unclassified	8%

Fig. 1—Pathology in "hot" nodules at MCV.

Pathology found in cold nodules (184)	
Nodular colloid goiter	58%
Chronic thyroiditis	4%
Adenoma	17%
Carcinoma	13%
Unclassified	8%

Fig. 2—Pathology is 184 cold nodules at MCV.

malignancy. A distant metastasis might be a hint of carcinoma of the thyroid. If there are nodules, we want to do scans. If the scan shows a cold nodule, carcinoma is a prime possibility. Figure 1 shows the pathology we have seen in our "hot" nodules. Nodular colloid goiter was found in 70% of cases, hyperplastic goiter (we are not sure what the pathologist meant by this as these were supposedly nontoxic patients) in 15%, adenoma in 15%, but no carcinoma. Figure 2 shows the pathology in 184 cold nodules which were removed. Thirteen percent were carcinomas of the thyroid.

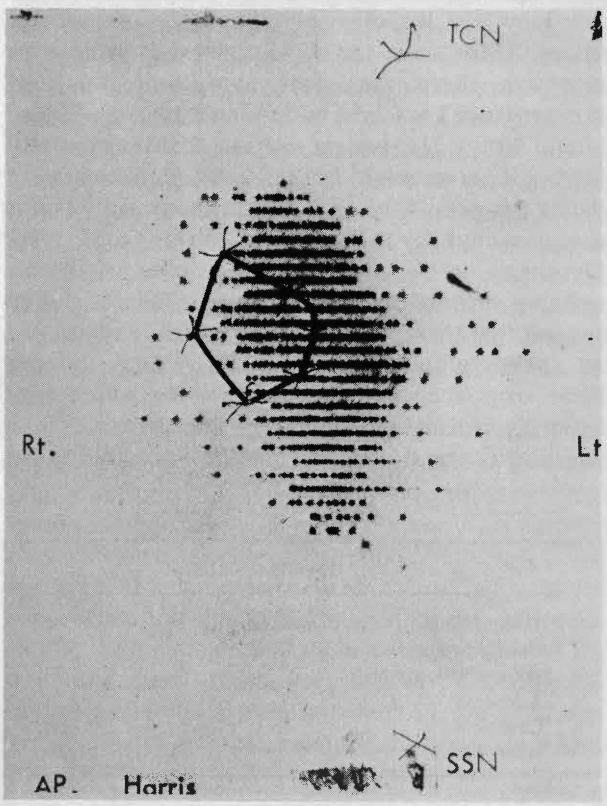

Fig. 3—AP scan of patient with suspect nodule.

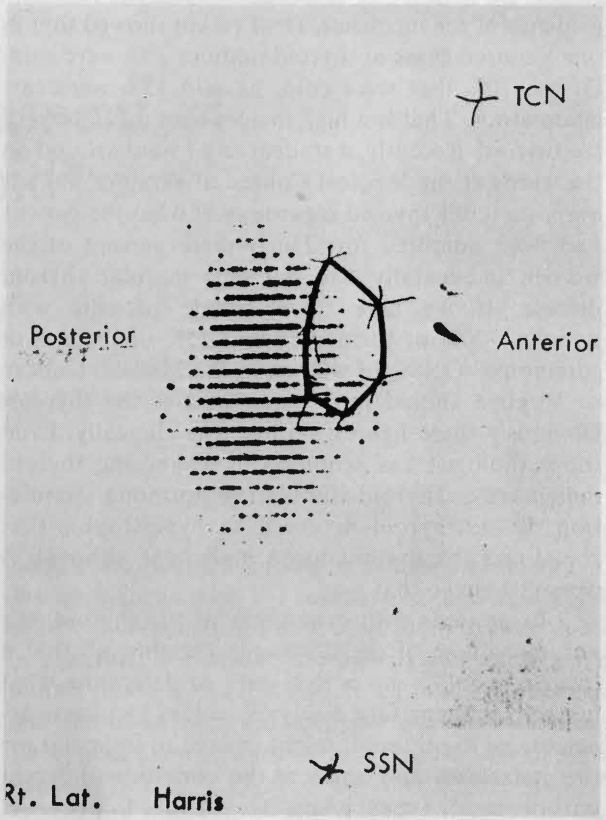

Fig. 4—Oblique scan of same patient, revealing cold nodule.

I want to emphasize the importance of lateral scans. Figure 3 is an AP scan of a patient who had had a nodule. One might think that this was a functional nodule and not malignant. But on the lateral or oblique scan (Fig. 4), a cold nodule is seen in front of the radioactivity. Figure 5 shows a nodule that might be interpreted as a hot nodule. There is suspicion that it might not be a hot nodule, however, for the center of the gland is thicker, and one would think it would have a higher radioactivity. On the lateral scan, it is confirmed as a cold nodule.

The treatment of carcinoma of the thyroid varies with the cell type, and Figure 6 shows the main types of the disease. The first approach to treatment of carcinoma of the thyroid is surgery. The extent of the surgery depends on the type of lesion. A biopsy with a frozen section will indicate what type of malignancy one is dealing with. The nodule should be removed along with any suspect tissue, and if it is carcinoma on a frozen section, a total thyroidectomy is indicated. The only exception would be that I would ask the surgeon not to take the parathyroid glands.

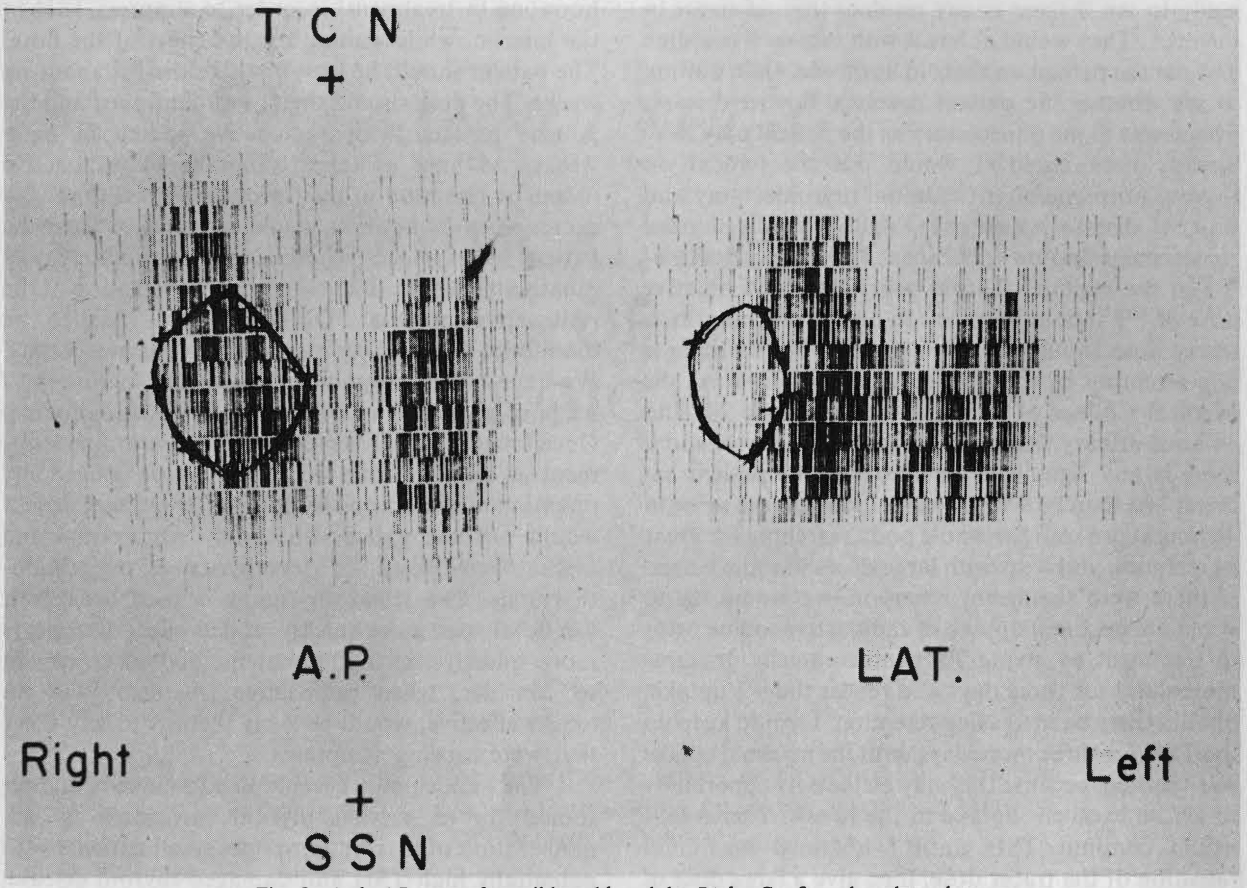

Fig. 5—*Left.* AP scan of possible cold nodule; *Right.* Confirmed on lateral scan.

As this might be difficult, he would perform a nearly total thyroidectomy. Myxedema as a result of surgery is of no concern because the patient will be placed on thyroid extract. All patients with carcinoma of the thyroid should be on thyroid extract for the rest of their lives in the hope that hormonal suppression of the tumor will be achieved, just as one might treat carcinoma of the breast with appropriate hormonal treatment. Radical neck dissection is not often my choice. The surgeon usually decides this. If he feels that the nodes are within the range of surgical resection, he should try to get them out, but in my opinion, severely disfiguring, radical neck dissection is of no great value. The prognosis for carcinoma of the thyroid is so good that, other than for anaplastic types, I would not urge extensive neck dissection. In a medullary carcinoma, there is one follow-up technique and that is to check on calcitonin levels, because this offers a marker for continuing disease. If the calcitonin levels were high before removal and afterwards fell to normal, it would be very reassuring that the malignancy had been completely removed. If calcitonin levels rose in the future, they would indicate that the carcinoma had recurred and that further treatment should be considered.

There is a difference of opinion regarding the surgical follow-up schedule. Some authors would wait a month and do a radioactive iodine uptake

Classification of Thyroid Neoplasms

A. Adenoma
B. Carcinoma
   1. Adenoma malignum
   2. Papillary
   3. Follicular
   4. Medullary
   5. Anaplastic

Fig. 6—Main types of thyroid disease.

study to see if there is any residual thyroid tissue in the neck. They would ablate it with radioactive iodine and put the patient on thyroid hormone while waiting to see whether the patient develops further disease. This seems to me unnecessary as the patient may have already been cured. I would put the patient on thyroid hormone after the initial thyroidectomy and wait. If disease appears, I would stop the thyroid replacement and do a ^{131}I scan. If there is uptake of ^{131}I in the residual thyroid area, a thyroid ablative dose of ^{131}I should be given. In one to two months, a tracer dose should be given to see whether there is any retention of the isotope after 48 hours. At the Medical College of Virginia, we determine 24- and 48-hour urinary excretions of ^{131}I at that stage, and if there is any significant retention (if the patient excretes less than 90% of the radioiodine in the urine in 48 hours), we scan the whole body searching for areas of retention and treat with large doses of radioiodine. If there were significant retention, we would try to stimulate maximal uptake of radioactive iodine prior to treatment by giving TSH intravenously or intramuscularly for three days and repeat the ^{131}I uptake. Should there be increasing retention, I would keep up the TSH for three more days until the maximal uptake was reached, because this may be the only opportunity to get an excellent uptake in the tumor. Therefore, I would continue TSH until I obtained maximum retention of the tracer dose, then give a large dose of radioactive iodine (150 millicuries of radioiodine), hoping to obtain the maximum uptake in the tumor. After radioiodine had had a chance to accumulate in the gland, I would put the patient on triiodothyronine (one of the few clinical uses for this hormone in treatment) in order to suppress TSH in the interim, while waiting for the effect of the dose. The patient should be kept on that dose for about six weeks. The dose should then be discontinued and the patient retested with radioactive iodine in eight weeks. As long as there is uptake of radioactive iodine or retention of the isotope with less than 90% excretion in 24 hours, I would continue to treat the patient with radioactive iodine at approximately two-month intervals until I had no further retention of the radioactive material. Of course, this has to be monitored by blood counts, primarily platelet counts. We have not seen significant platelet reduction until we have given 300 to 400 millicuries of radioiodine. Once I had achieved as much radioactive iodine treatment as possible, that is, there was no longer any retention of the isotope 48 hours after a tracer dose, I would put the patient on totally suppressive and replacement doses of levothyroxine or triiodothyronine. The triiodothyronine is used because it can be stopped more quickly, and its effect disappears more quickly. An additional method of treatment to consider, when radioactive treatment was no longer effective, would be x-ray therapy to any areas that were causing symptoms.

The major point I would like to make is that we should try to prevent thyroid carcinoma by administration of thyroid hormones to all patients with potentially high TSH and damaged-thyroid disease, using suppressive doses of levothyroxine. In my opinion, all patients who have thyroid disease should be treated with thyroid hormone indefinitely, once hyperthyroidism has been eliminated.

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Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severely limited respiratory reserve, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations* under **WARNINGS**); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Hematologic:* rarely depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia. *Other:* rarely respiratory depression, urinary retention, toxic epidermal necrolysis.

Dosage and Administration: *Adults.* The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.

Children Under 12 Years of Age. Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

Duration of Therapy. Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see WARNINGS). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

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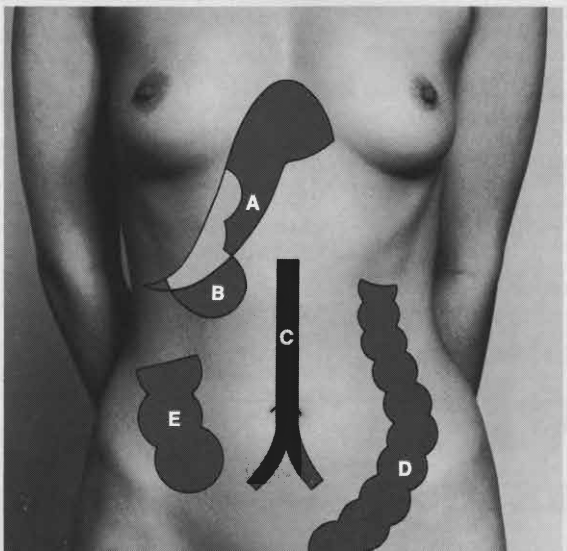
Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.



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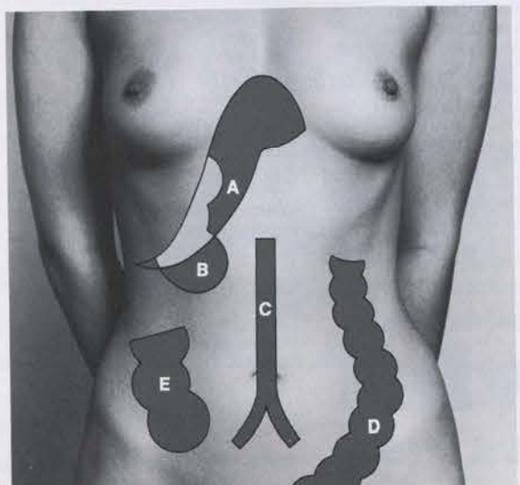
Normally palpable organs: the edge of the liver descending, on inspiration, below the costal margin (A); the lower pole of the right kidney (B); the abdominal aorta (C); the descending colon and the sigmoid (D); the ascending colon (E); and occasionally the bladder (though rising of this organ beyond the pubis does not necessarily indicate disease).

Impossible to outline, unless diseased, distended or enlarged: the gallbladder, pancreas, stomach, small intestine, transverse colon and spleen.



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hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg.
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hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(1/4 gr.) 16.2 mg.	(1/2 gr.) 32.4 mg.	(3/4 gr.) 48.6 mg.
(warning: may be habit forming)			

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

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hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg.	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg.

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Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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