Radioactive Drugs in Clinical Medicine

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Radioactive drugs, or radiopharmaceuticals, are used clinically for the diagnosis, investigation and occasionally for the therapy, of many human illnesses.

The first radiopharmaceutical to be widely used was the fission product, iodine-131, in the form of the simple salt, sodium iodide, the use of which was established in the late forties as a diagnostic test for certain thyroid disorders. Because the drug could be administered orally, in solution, it was referred to in the press as the "Atomic Cocktail".

Since those pioneering days, the practice of nuclear medicine has soared in most developed countries. Approximately 10,000,000 people in the United States are tested diagnostically each year with a radioactive drug, either *in vivo* or *in vitro*.

The total value of the radiopharmaceuticals used throughout the world is approaching $(US) 100,000,000 per year, with over two-thirds of the total being produced by private companies. The world-wide use of these drugs is growing at a rate of 15 - 20% per year.

IN VITRO APPLICATION

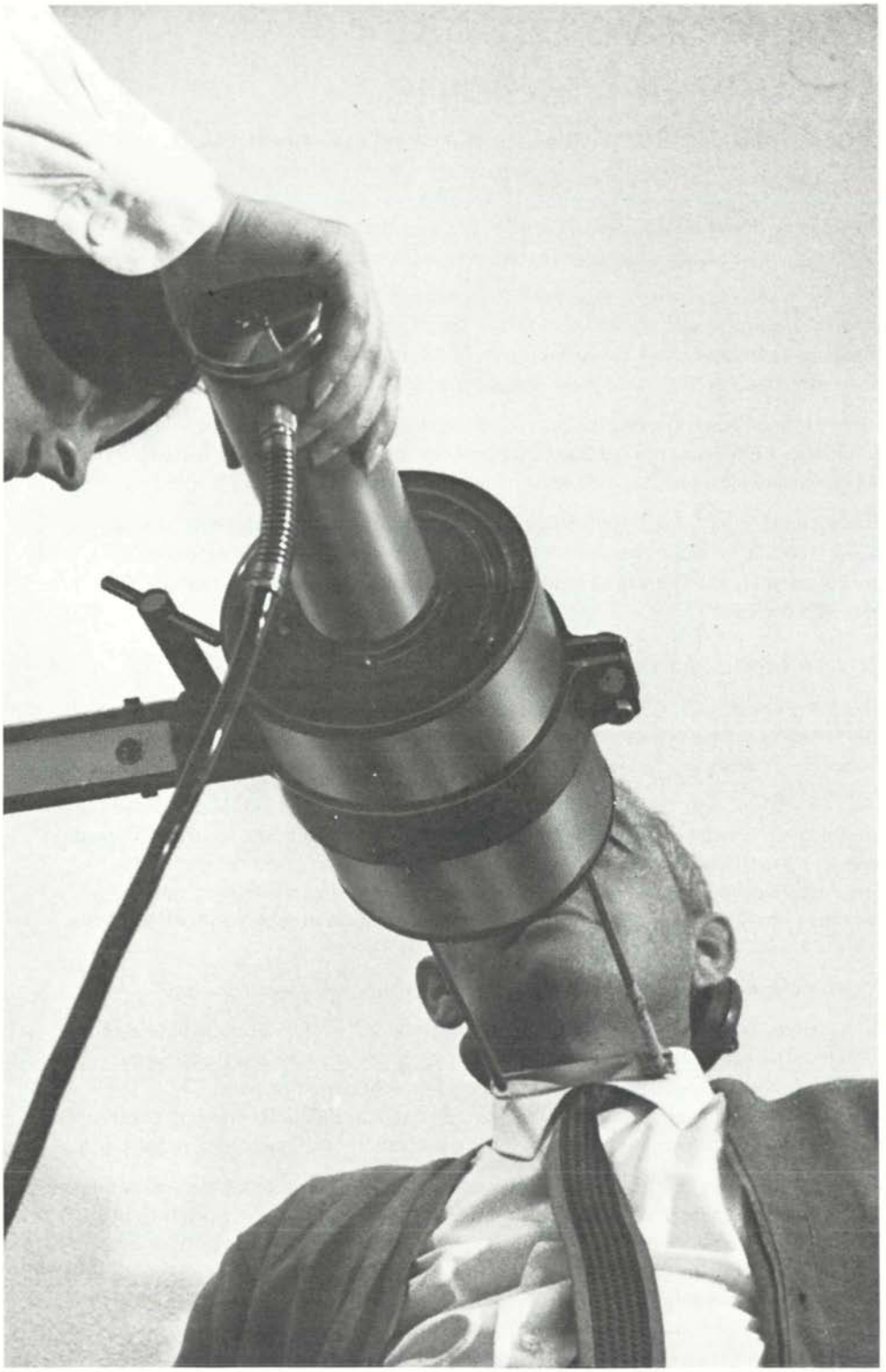
There are a number of *in vitro* clinical tests which employ radioactive reagents, but the most important one in present use is the radioimmunoassay for body hormones. Although a number of variations of this test have been developed, the essential features common to all are:

1. A protein which selectively interacts with the hormone (binding agent). This protein may be naturally-occurring, e.g. a globulin, or a non-naturally occurring antibody. The latter is produced by a crossed-species reaction, e.g. the injection of human (or pork) insulin into a rabbit, which causes the formation of rabbit antibodies to the human insulin.

2. A hormone preparation which has been labelled with a radioactive atom.

3. An effective method to separate the free hormone from the hormone bound to the protein. The total amount of the labelled hormone preparation and the binding protein, followed by separation of the bound from unbound hormone. By measuring the radioactivity in each fraction, one obtains a bound: unbound ratio which is referred to a standard curve to obtain the concentration of the hormone in the plasma.

Radioimmunoassay is an exceedingly sensitive method which is capable of measuring most hormones at the nanogram to picogram level. It is also very specific since the antibody binds its specific hormone very selectively. A surprisingly wide range of hormones and other antigens can be assayed by this method. A few examples are assays for insulin, thyroxine, prostaglandins, digitoxin, human growth hormone, and the "hepatitis-associated" antigen, the test for which can minimize hepatitis injection through blood transfusions by pre-testing donors.



IN VIVO APPLICATIONS

Radiopharmaceuticals are used *in-vivo* to obtain clinical information by measuring the spatial distribution of the drug in an organ (scintigraphy), or by measuring the uptake or throughput of the drug within the organ (uptake or organ-function test). A scintigraphic measurement produces a two dimensional "picture" or scan (or three dimensional if a tomographic device is used) which shows whether or not the radiopharmaceutical is distributed over the organ in a "normal" manner. If the radioactivity scan shows abnormal areas, these can indicate the presence of a tumour or the reduced viability of that portion of the organ (see Figure 1).

The uptake test is best typified by the thyroid radioiodine uptake measurement. The rate at which the thyroid removes radioactive iodide from the blood stream furnishes important information regarding the physiological state of this gland. Similarly, kidney function can be evaluated by measuring the rate of accumulation of a radiopharmaceutical, such as 197 Hg chlormerodrin, in both kidneys at the same time.

TABLE I

Radiopharmaceutical	**Application**
^{131}I (also ^{125}I)* - Sodium iodide	Thyroid uptake
^{131}I - Rose Bengal	Liver scan
^{131}I - Hippuran	Kidney scan
^{131}I - Human serum albumin	Blood volume, circulatory studies
^{131}I - Iodinated oils	Fat absorption studies
^{51}Cr - Sodium chromate	Spleen scanning (by tagging red blood cells)
^{57}Co - Vitamin B-12	Pernicious anemia diagnosis
^{198}Au - Gold colloid (less than 1 micron diameter particle)	Liver scan
^{197}Hg - Chlormerodrin	Brain and kidney scans
^{75}Se - Selenomethionine	Pancreas scan
^{131}I or ^{99m}Tc - Macroaggregated serum albumin (30 - 50 micron diameter particles)	Lung scan
^{18}F - Sodium fluoride	Bone scan

* The use of ^{125}I reduces the radiation dose to the patient, and is therefore gradually displacing ^{131}I in many applications.

◀ Radio-iodine uptake measurement test for thyroid in the Research Institute for Nuclear Medicine, Heidelberg, FRG – WHO

There are less than 50 radiopharmaceuticals for *in vivo* administration which are in common use. Many of them are used for identical diagnostic tests, the choice of a particular one frequently depending on the personal preferences of the practitioner. The development of more effective radiopharmaceuticals is being intensively investigated in several score laboratories all over the world and it is likely that the drugs used in nuclear medicine will be altered considerably during the next 10 to 20 years. A representative list of established radiopharmaceuticals may be found in Table I.

ISOTOPE GENERATORS

One of the major developments of the past ten years has been the commercial introduction of the isotope generator into nuclear medicine. This device is based on a mother-daughter isotope decay scheme, the former being relatively long-lived and the latter short-lived. The long-lived mother isotope is shipped to the hospital. By simple manipulations, it is possible to obtain the desired daughter isotope from the generator in sterile apyrogenic solution.

The impetus for the rapid acceptance of generators has been the awareness that the radiation dose to the patient should not be above acceptable levels, and should also be minimized. The simplest way to do this is to employ a radioisotope with a convenient short half-life, so that after the medical information is obtained, the isotope rapidly decays away. Other incidental desirable properties are the absence of beta ray emission, which causes unnecessary radiations exposure, and a high degree of localization of the radio-pharmaceutical in the target organ or region of body (high target to non-target ratio of incorporation), followed by rapid biological clearance from the body.

The technicium-99^m generator is employed in over 2000 hospitals at the present time. The parent isotope, molybdenum 99 (half life 67 hours), absorbed on an alumina column, is shipped weekly. The technetium-99^m (half-life 6 hours) can be eluted once or twice daily, and in this chemical form, the pertechnetate ion, it can be used directly for brain and thyroid scanning. Various commercial kits have been developed which permit the conversion under sterile conditions of the pertechnetate into other useful radio-pharmaceuticals, e.g. technetium-sulfur colloid (liver scanning), technetium labelled serum albumin (blood pool studies) and macroaggregated serum albumin (lung scanning).

Some useful isotope generators of radiopharmaceutical interest are shown in Table II.

TABLE II: NUCLIDE GENERATORS

	System	Half Lives		Principal Daughter		
		Parent	Daughter	Gamma Ray	Column	Eluant
(r)	$^{99}Mo/^{99m}Tc$	2.7 d	6 h	140 KeV	Alumina	Saline
(r)	$^{113}Sn/^{113m}In$	118 d	1.67 h	393 KeV	ZrO	0.05N HCl
(c)	$^{87}Y/^{87m}Sr$	3.3 d	2.8 h	388 KeV	DOWEX-1	0.15M $NaHCO_3$
(c)	$^{68}Ge/^{68}Ga$	280 d	1.1 h	β^+ 150 KeV	Alumina	0.005M EDTA

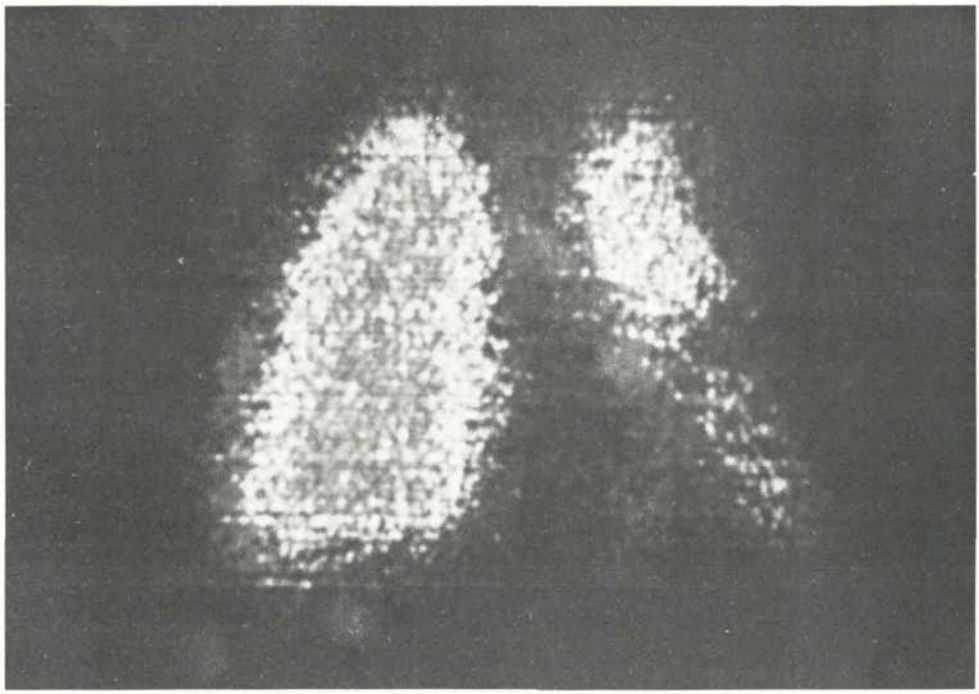
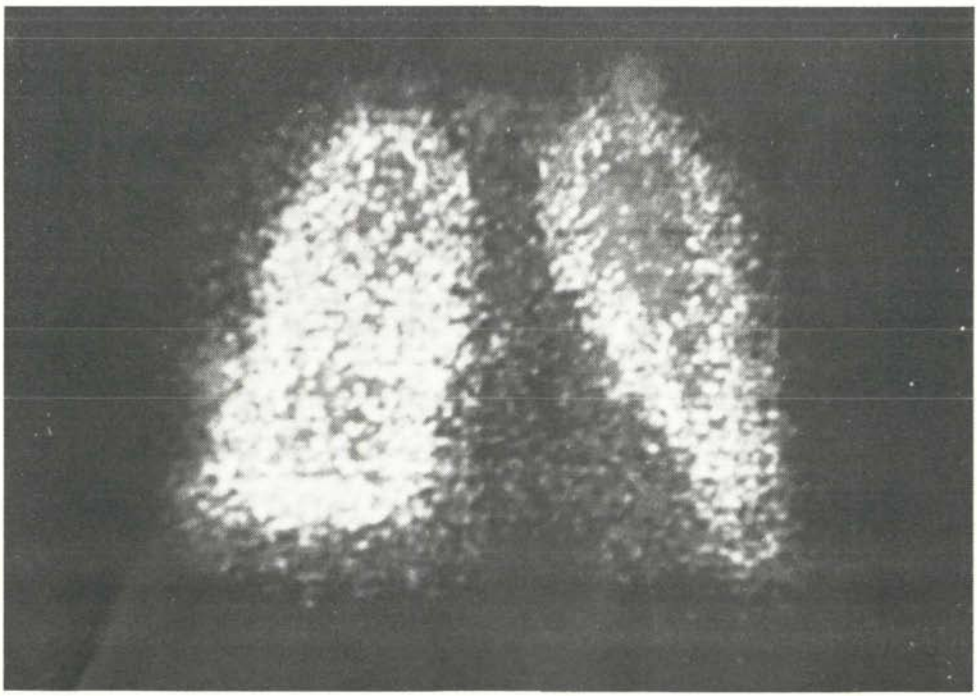


Figure 1: Lung scan of patient J.S., anterior view, using ^{99m}Tc MAA, showing pulmonary emboli in the left lung, October 1970. ▲

Same patient, anterior view, using ^{113m}In SMA, showing improvement in the left lung, July 1971. ▼



The control desk for a scintillation camera for viewing concentration of radioactivity — WHO

MEDICAL CYCLOTRONS

Another effort to produce short-lived isotopes and isotopes not otherwise accessible by reactor irradiation has been the installation of ' compact" or "medical" cyclotrons adjacent to nuclear medicine clinics. At the present time, there are about 30 such installations, which are producing such isotopes as ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{52}Fe, ^{67}Ga, and ^{123}I, each of which offers desirable characteristics for use in a radiopharmaceutical.

THERAPEUTIC APPLICATIONS

Todate, there have been relatively few therapeutic applications of radiopharmaceuticals. The early successes in treating certain thyroid diseases with radioactive iodine have been followed by a few other major breakthroughs. Certain leukemic diseases have responded to therapeutic doses. Radiopharmaceutical therapy is still a frontier in nuclear medicine.

During the past twenty-five years, nuclear medicine has developed into a widely accepted medical discipline and has been one of the major positive contributions to human welfare to arise out of the atomic era. The Agency is playing an active role in transmitting these techniques to developing nations for the betterment of health throughout the world.

This composite of a series of photos (figure left) shows isotopes revealing the inner geography of the body. These photographs were taken by a scintillation camera - WHO.

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