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PRODUCTION OF CYCLOTRON RADIOISOTOPES AND RADIOPHARMACEUTICALS FOR MEDICAL USE.

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Abstract : Positron emission tomography in conjunction with radiopharmaceuticals labeled with positron emitting radionuclides opens the possibility of visualizing in vivo in an atraumatic way fundamental parameters of metabolism in man. The main positron emitting radioisotopes carbon-11, oxygen-15, nitrogen-13 and fluorine-18 used for labeling radiopharmaceuticals (sugars, aminoacids, fatty acids and drugs) are produced by nuclear reaction involving charged particles accelerated with cyclotrons. Small cyclotrons producing 8 MeV deuterons and 15 MeV protons seem optimal for the routine production of these radionuclides. Some specific medical examples are given illustrating the potency of this new tool.

Gamma emitting radioisotopes were proved very early to give unique biochemical or physiological information when injected in a living organism in a suitable chemical form. The possibility of external detection offers a non invasive way to follow changes in the distribution of the tagged species.

Using adequate detectors, regional distribution as well as quantitative kinetic parameters may be obtained in such a way that abnormalities of metabolism may be observed with great accuracy.

However the radioisotopes used for this purpose must fulfil a number of physical and chemical criteria.

According to the size, and density of the human body, the turnover and sensitivity to radiation damage of living biological matter, the disintegration scheme and the half-life of the useful radioisotopes should be kept within narrow limits.

For most applications the half-lives of the radioisotopes used to date fall between a few seconds and a few days. Beta/gamma or pure gamma emitters with gamma ray energy ranging from a few tenths to a few hundred keV are the most commonly used with an ideal energy around 150 to 200 keV to insure a minimum loss of information from absorption in the biological matter and a maximum sensitivity of the detection devices. Alpha emitting radioisotopes are avoided because of the high ionization of these particles which would deliver a radiation damage to the target organ incompatible with a diagnostic test.

According to the chemical criteria a good radionuclide has to be an isotope of the component elements entering in the composition of biological matter in order to reliably trace a biological or physiological event.

With few exceptions (radioiodine in endocrinology, radio-iron or cobalt in hematology) the radioisotopes used so far do not entirely meet these criteria.

Technecium 99 m which is used for more than 80 % of the diagnostic tests in Nuclear Medicine has ideal physical characteristics but is not a good biochemical

tracer since its presence can modify the chemical structure and thus the metabolism of a labeled organic substrate.

In the last ten years there have been a considerable effort to make new radionuclides available to better respond to the needs of modern Nuclear Medicine.

Positron emitting radioisotopes are ideal in this respect since their mode of disintegration allows them to be detected quantitatively and located with accuracy by tomographic devices. In addition, those which are of interest for following biological phenomena such as carbon 11, nitrogen 13, oxygen 15, fluorine 18 and a few others, are short lived radionuclides and thus can be injected to humans without giving rise to high radiation doses.

However, it must be kept in mind that some drawbacks are the consequence of these short half-lives. Some are methodological : the need of having at the same site the means of producing and incorporating them in radiopharmaceuticals and of in vivo measurement for achieving the medical studies, others are directly concerned with the type of physiopathological parameters which will be obtainable. Only short term studies will be possible eliminating the possibility of observing slow metabolic pathways.

Many reviews have already been published on this subject (1,2) and the scope of this paper will be focussed on a few specific points in relation to the production of the short-lived positron emitting radioisotopes, their incorporation in radiopharmaceuticals and some medical applications under development in a few medical centers.

I) Production of short lived positron emitting radioisotopes and radiopharmaceuticals.

The short half-life of the radioisotopes under consideration necessitates that the means to make and to use them be available at the same site. This means that the accelerator for isotope production, usually a cyclotron, the chemistry laboratory for radiopharmaceutical synthesis, and the detection device with other facilities for the medical study should all be located in or adjacent to the hospital.

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A) Cyclotrons

Although any accelerator able to produce charged particles with an energy higher than a few MeV would be suitable to produce ^{15}O , ^{11}C , ^{13}N and ^{18}F , cyclotrons are the most widely used machine and considerable effort has been given by their manufacturers to optimize them for radioisotope production.

In fact, the medical cyclotron needs no longer be considered as a particle accelerator but as a radioisotope generator capable of producing enough radioactivity to service a nuclear medicine unit.

Whereas in the recent past, medium energy, (20 to 40 MeV protons), four particle machines were found to be necessary because of their versatility to make several isotopes with potential for medical use, the trends is now toward cyclotrons specialized for a specific use. Thus it has been shown that for the four short radionuclides precited a 8 MeV deuterons, 15 MeV protons cyclotron would be sufficient.

Four manufacturers : CCR-MeV Sumitomo, Scanditronix, Japan Steel Works and the Cyclotron Corporation, have designed "baby" cyclotrons on this basis having external beam currents of 50 μA . These small machines, some of them being partly self-shielded, need minimum operator intervention and can be located in an area as small as 40 m^2 (including power supplies and control room). In addition to the cyclotron targetry and remote systems for production of radioisotopes and a limited number of radioactive precursors can be provided.

of each can be obtained using the nuclear reactions indicated in table I. However if the production yield approaches the theoretical values for carbon-11, oxygen-15 and nitrogen-13, fluorine-18 still suffers from a difficulty in quantitative recovery. When produced in the form of elemental fluorine carrier F_2 must be added to the target gas in order to facilitate the extraction of the radioactive isotope from the target holder. With ^{18}F production higher yields seem to be possible without adding carrier.

Since at this writing, no "baby cyclotrons" are working routinely, it is still difficult to ensure that the amount of fluorine 18 to be made available by these machines will be sufficient for routine medical applications. Other nuclear reactions involving the use of enriched isotopes are under study which might overcome this difficulty. For fluorine 18 it is thought that the reaction $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ will give rise to high yields.

Also in table I is indicated the theoretical specific radioactivity of these radioisotopes. The importance of this parameter is that for a given radioactivity corresponding to a tracer dose (a few millicuries) the amount of material given to the patient will be very small. Thus, the possibility exists to study highly toxic molecules without observing any physiological or pharmacological effects.

B) On line production of positron emitting short lived radioisotopes and simple precursors.

The need for rapid manipulation of high radioactivi-

TABLE I

Radionuclide	Nuclear Reaction	Half life	Theoretical specific activity (Ci/ μmole)
Oxygen-15	$^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$	2.05 min	$0.15 \cdot 10^6$
Carbon-11	$^{10}\text{B}(\text{d},\text{n})^{11}\text{C}$ $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$	20.4 min	10^4
Nitrogen-13	$^{12}\text{C}(\text{d},\text{n})^{13}\text{N}$ $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$	10 min	$0.38 \cdot 10^5$
Fluorine-18	$^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ $^{20}\text{Ne}(\text{}^3\text{He},\alpha\text{n})^{18}\text{Ne}$ $\rightarrow ^{18}\text{F}(1)$ $(1) ^{16}\text{O}(\alpha,\text{p})^{18}\text{F}$	112 min	$0.3 \cdot 10^4$

(1) not possible with "baby cyclotrons"

Theoretical calculations of the yield for producing ^{15}O , ^{13}N , ^{11}C and ^{18}F based on published cross section and maximum beam currents available and allowing irradiation time of the target near saturation for the shortest lived radio-nuclides and of two hours for fluorine 18 indicate that a minimum of one curie

ties governs the strategy for the production of the radiopharmaceuticals. In some cases the very small amount of material involved (due to the high specific activity) introduces another difficulty. The first step of the strategy consists of the on-line production of simple molecules or precursors which will then be used for labeling more complicated radiophar-

maceuticals.

Figures 1, 2, and 3 give some schemes routinely used in many laboratories for such a production.

As can be seen from figure 1 four different molecules labelled with ^{15}O can be obtained continuously

mical steps used for trapping impurities or converting the radioisotope into the desired molecule, labeled molecular oxygen, carbon dioxide, carbon monoxide or water may be directly obtained for medical use. It is worth noting that they all contain large amounts of carrier which is not a drawback, however, since they are all physiologic molecules with the exception of

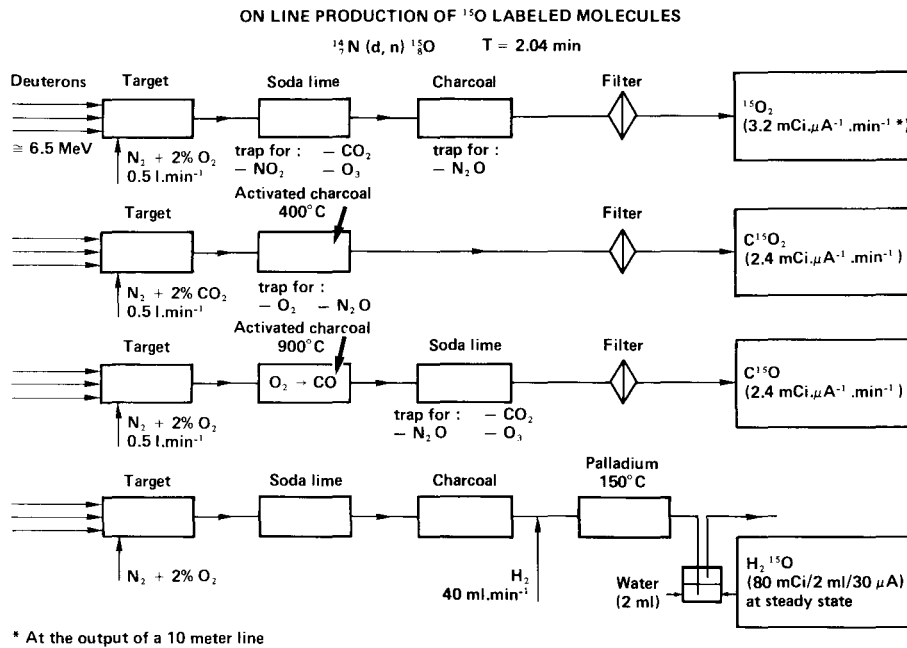


FIGURE 1

in large amounts using 6.5 MeV deuterons and nitrogen as the target gas. According to the chemical identity of the carrier gas added to the nitrogen and the che-

carbon monoxide. For the latter gas toxicity problems might arise if the specific activity is too low.

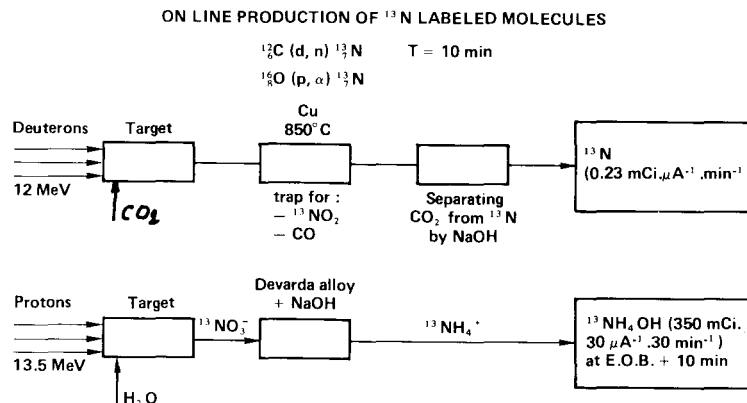


FIGURE 2

Figure 2 gives two reactions for making nitrogen-13 either as molecular nitrogen or as ammonia. The latter after millipore sterilisation, may be used as a radio-pharmaceutical for perfusion studies of the brain or heart and also serve as a starting material for the labeling of amino acids.

Carbon-11, in spite of its short half-life, is perhaps the most interesting radioisotope for labeling because it can be introduced in any kind of biomolecule or in drugs of various classes without modifying their structure. Figure 3 indicates how labeled carbon dioxide, carbon monoxide and cyanide, three important precursors for organic synthesis, are obtained on line and in high yields.

into account the biological phenomenon which is to be observed. It is generally considered that the time of synthesis including purification and sterilization must not be longer than two to three times the half life of the radioisotope used for labeling. On this basis the number of radiopharmaceuticals labeled with ^{15}O and ^{13}N will be limited to very simple products.

However ^{13}N as ammonia- ^{13}N has been used for enzymatic labeling of the amino group of various aminoacids on the amino group such as alanine, glutamic acid, glutamine or phenylalanine (4,5).

A considerable number of ^{11}C labeled molecules have been synthesized in the last few years for which large amounts of simple precursors are available.

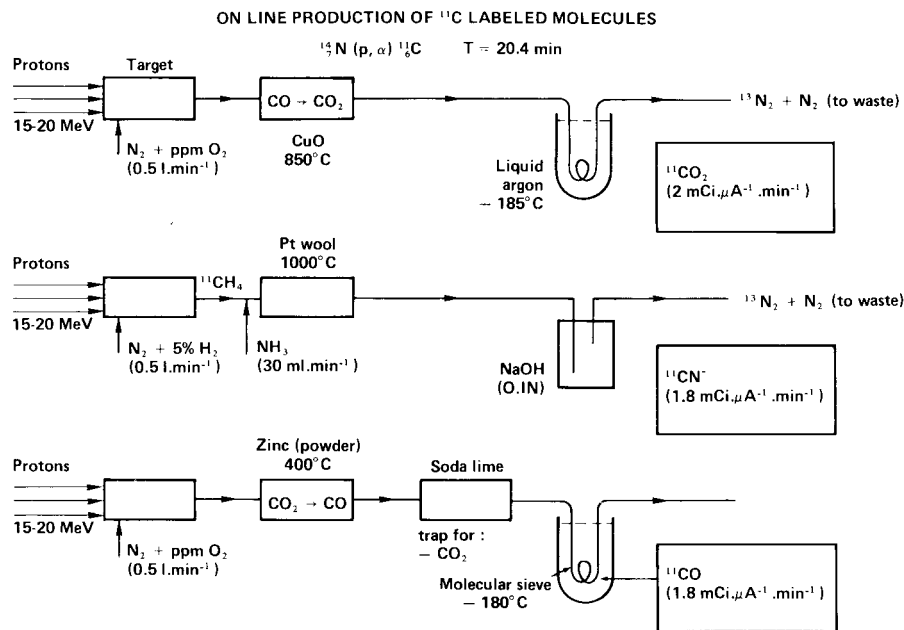


FIGURE 3

More specific details on the production of these three radionuclides may be found in the book of Buckingham and Clark (3).

Fluorine-18 in spite of the difficulties already mentioned for its production in the chemical forms necessary for organic synthesis is also a major radioisotope for the labeling of biomolecules. Since it has a longer half life than the other positron emitters more time is available for chemistry and for following its fate in biological systems. However most of the biologically active molecules, with the exception of a few drugs, do not normally contain a fluorine atom and it must be considered that replacing a hydrogen with fluorine could alter the behavior of the thus altered labeled molecule in the biological system in which it is introduced.

C) Radiopharmaceuticals.

The synthesis of radiopharmaceuticals labeled with these short lived radionuclides is particularly difficult because of short half life. In other respects the choice of the molecule to be labeled must take

Starting with $^{11}\text{CO}_2$ fatty acids such as palmitic acid have been produced labeled on the carboxyl group from Grignard reagent (6) and used for heart metabolic studies (7).

$^{11}\text{CO}_2$ was also introduced in glucose by biological synthesis (8,9). ^{11}CO as label of carboxyhemoglobin is a good marker of the blood pool (10). Converted into phosgen ($^{11}\text{COCl}_2$) this precursor has a great potential for labeling various drugs: Pimozide, a neuroleptic pharmaceutical known to have a high and specific affinity for dopamine receptors (11), diphenylhydantoin one of the major drugs for the treatment of epilepsy (12), dimethylxazolidinedione (DMO) an in vivo pH marker (13).

$^{11}\text{CO}_2$ is easily transformed into formaldehyde and methyl iodide and used for attaching a labeled methyl group to amines and hydroxyl groups: drugs used for in vivo binding studies at the level of dopamine, opiate, cholinergic and benzodiazepine receptors, (14,15), sugars (16), proteins (17), and aminoacids

(18) were labeled at high specific activities using this approach.

$H^{11}CN$ another important precursor has been used for labeling the carboxyl group of many amino acids by the Bucherer Strecker synthesis (19). However only a racemic mixture can be obtained. Resolution of the optical isomers is currently under development since only the L-amino acids are normally metabolized by the organism. (20). $H^{11}CN$ is also used for labeling sugars such as deoxyglucose (21) and various amines (22, 23).

This list is not limitative and many other radiopharmaceuticals are currently labeled with carbon-11. (24).

From the technical point of view, efforts were made to obtain these molecules in the shortest time possible with a high radiochemical purity. Rapid high performance liquid chromatography (HPLC) is now generally used for purification step (25) and semi automated or remote control apparatus set up in lead shielded cells are available in many laboratories (26). With these techniques, and starting with Curie amounts of carbon 11, 200 to 300 mCi of the radiopharmaceutical can be obtained routinely in sterile and pure form in thirty to forty minutes with minimal radiation exposure to the operator. In spite of special care taken to avoid contamination with stable carbon the specific activity of these molecules is far less than the theoretical.

The best obtained to date is in the range of 1 to 2 Ci/ μ mole at time of injection. The low mass of the carbon-11 labeled precursor involved in a radiochemical synthesis may however give rise to low yields or important secondary reactions as well (27).

The incorporation of fluorine-18 in an organic skeleton has also been the object of considerable work. Since fluorine is much less common in environment than carbon less contamination of the radioisotope by stable fluorine will occur than is the case for carbon-11. Due to this advantage, nearly carrier-free fluorine-18 labeled radiopharmaceuticals can be obtained.

However, when ^{18}F as F_2 is needed for labelling the only way of recovering it from the cyclotron target in which the nuclear reaction takes place, is to add carrier fluorine. This leads to a considerable decrease in specific activity which may limit its use.

In spite of this limitation fluorine-18 as F_2 is currently used to label a sugar : (^{18}F)-fluoro-2-deoxyglucose (28,29). This compound in combination with a sugar metabolism model developed by Sokoloff (30) is used for the measurement of regional sugar consumption in the brain and in the heart in various physiological and pathological situations (31, 32,33).

Fluorine 18 as $H^{18}F$ has recently been produced in a carrier free state and has been used for labeling neuroleptic drugs having affinity for dopamine receptors in the brain.

Many other fluorine-18 labeled molecules such as amino acids, fatty acids and drugs have also been made and their syntheses can be found in the literature (34).

2) Examples of the use of radiopharmaceuticals labeled

with short lived radioisotopes for medical research.

The development of positron emission tomography has been one of the most important recent events allowing the quantitative regional in vivo measurement of radiopharmaceuticals labeled with positron emitters. (36, 36). This technique is based on the detection in coincidence of the gamma rays emitted following positron annihilation and allows transverse section tomographic pictures of the body to be obtained.

Positron emission tomography in conjunction with the radiopharmaceuticals described earlier is used for the measurement of fundamental medical parameters such as :

- The distribution and movement of fluids (cerebral blood flow and volume for example),
- The metabolism of natural substrates (sugar or oxygen consumption in various organs , amino acid incorporation into proteins).
- The fate and pharmacokinetics of drugs (regional distribution of drugs, specific receptor binding studies).

Three examples will illustrate physiopathological and pharmacological parameters of which measurements are under study at the present time.

A) Cerebral blood flow and oxygen metabolism

These measurements are based on a model developed by T. Jones (37) which consists in the continuous inhalation by the patient of $C^{15}O_2$ or $^{15}O_2$. $C^{15}O_2$ is a marker of water since a rapid exchange occurs in the lung capillaries between the oxygen of carbon dioxide and oxygen of blood water.

This radioactive water is distributed to the different structures of the brain according to regional blood flow. The inhalation of molecular radioactive oxygen will lead to the labeling of blood oxyhemoglobin which is also distributed to the brain according to its blood flow. But in contrast radioactive oxygen is extracted by the brain cell proportionally to its metabolic rate. Because of the short half life of oxygen 15 a continuous inhalation will lead to a steady state in a few minutes and the tomographic images registered at this time at the level of the brain will represent both the cerebral blood flow ($C^{15}O_2$ picture) and the oxygen metabolism ($^{15}O_2$ picture).

This method has been used for studying brain metabolism in various brain ischemic diseases (38). Figure 4 shows an example of the recovery of brain oxygen consumption as demonstrated in a patient suffering transient ischemic attacks, after restoration of the regional blood flow by anastomosis of the temporal artery with the cerebral artery. The first three pictures of figure 4 represent blood flow, oxygen metabolism and brain oxygen extraction fraction before operation.

The arrows indicate the regions of the brain with a decreased blood flow. No abnormalities can be seen on the $^{15}O_2$ picture indicating that in spite of the low perfusion, oxygen metabolism is still efficient.

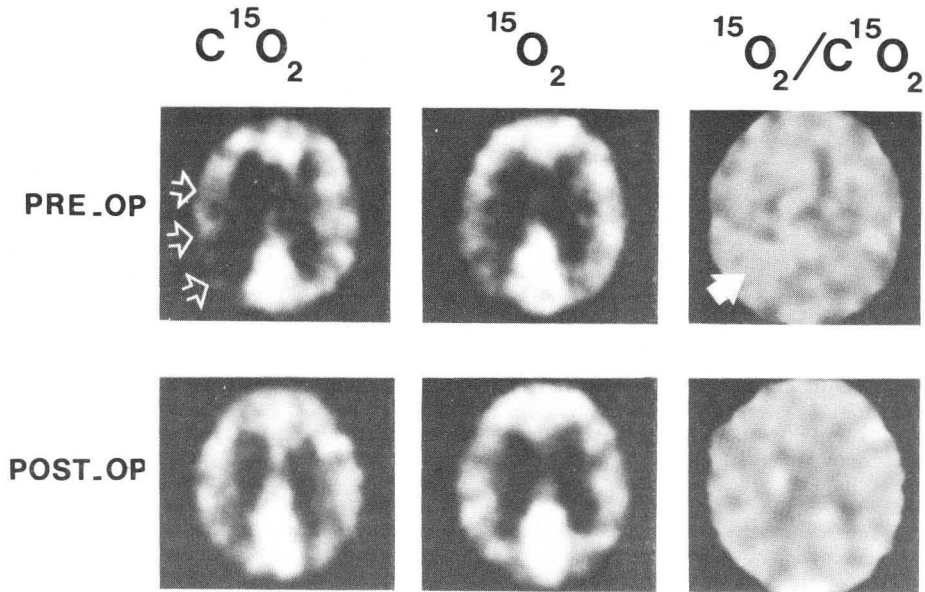


FIGURE 4 : Oxygen PET Scans in a patient suffering transient ischemic episodes.

But the brain cells in the affected region are obliged to extract a greater than normal percentage of oxygen as seen on the third picture. After the operation of revascularization of the diseased brain region, (second line of figure 4) cerebral blood flow as well as oxygen metabolism returned to normal. This example shows how this approach may help the surgeon to determine the outcome of the treatment.

B) Specific binding of drugs in the heart. (39).

Specific binding of drugs to tissular receptors is one of the mechanisms which explains their pharmacological effect. This specific binding may be visualized in vivo by positron emission tomography as shown in figure 5.

In this experiment ^{11}C -methylquinclidinyl benzylate (MQNB), a specific ligand of cholinergic receptors which are present in high concentration in the heart, was injected into a baboon. The distribution of this labeled drug in the heart (horseshoe shape of the left ventricular wall) and in the liver is shown in the 2 cm thick transaxial slice presented as images 1 and 3 obtained 10 and 13 minutes after the injection of the drug. To confirm the specific binding at the level of the heart, a pharmacological dose of atropine, a drug known to act on the cholinergic receptors, was injected. The competition of atropine and the labeled MQNB for the same receptor is exemplified by the displacement of the radioactivity in the heart (image 2) but not in the liver (image 4) where no receptors are known to be present.

Other experiments of the same type were performed with observation of the brain using labeled psychoactive drugs which bind to various specific receptors for neurotransmitters (40,41).

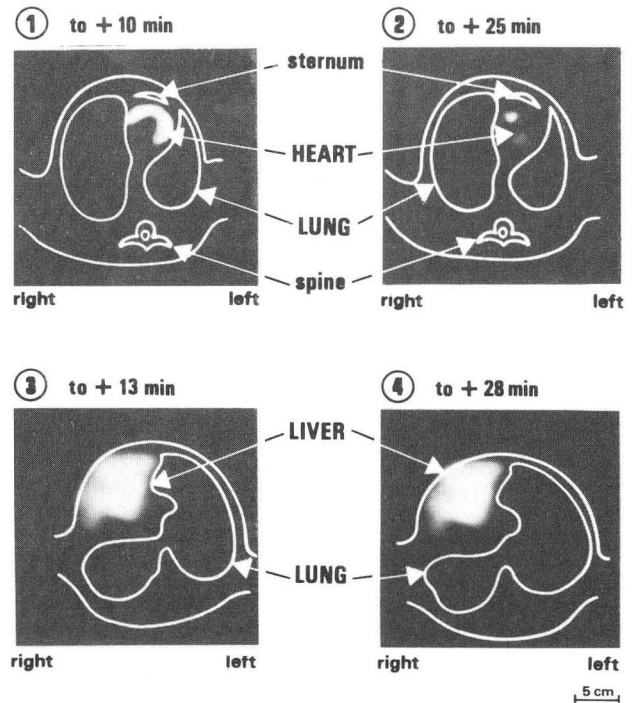


FIGURE 5 : in vivo study of the binding of ^{11}C -MQNB to the heart of the baboon.

C) Detection of pancreatic disease. (42)

The difficulty of evaluating the condition of the pancreas has led to the development in the past few years of further tools of investigation such as ultrasound, transmission computed body tomography and others.

More recently positron emission tomography has begun to be used for evaluating the normal and abnormal pancreas. Imaging of this organ has been accomplished by labeling natural aminoacids such as ^{11}C -methionine. When injected, this aminoacid is readily extracted from the blood. The duration of the process of its incorporation into protein and secretion is approximately the same as the carbon-11 physical half life.

phy when used in conjunction with positron emitting radiopharmaceuticals is a new and efficient means for study of metabolic pathways *in vivo* in an atraumatic way. However, the wide spread of this methodology will be possible only with further efforts to optimize the different techniques involved and decrease original investment and operational expenses.

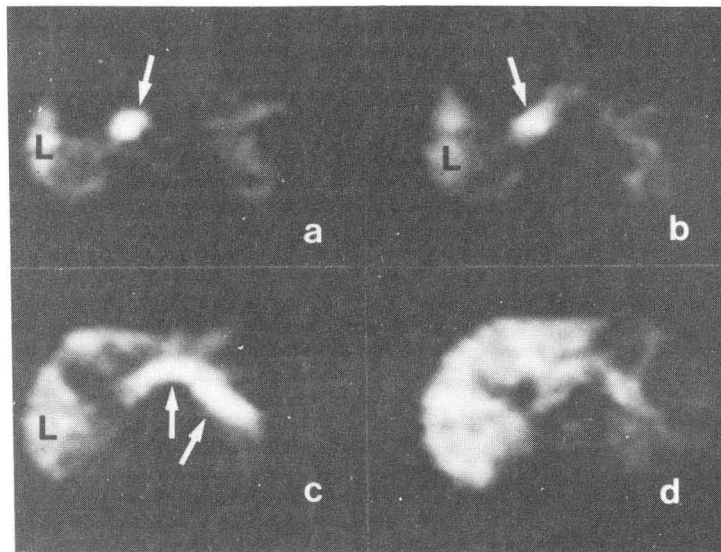


FIGURE 6 : PET Scans of a normal pancreas obtained with ^{11}C - methionine

Figure 6 shows a ^{11}C -methionine scan in a normal patient. 4 slices were made at 6, 8, 10 and 12 cms above the umbilicus. The arrow shows the head (a and b), the body and the tail (c) of the pancreas.

Carbon-11 activity is also seen in the liver (L). Low or no uptake of the radiopharmaceutical is observed in chronic pancreatitis and cancer. This study performed on 100 patients confirms that positron emission tomography has, compared to other diagnostic methods, the highest overall diagnostic efficiency in detecting pancreatic disease. However the price of such an examination is still too high to be used routinely.

Conclusion.

It is now obvious that positron emission tomogra-

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