INIS-mf--10952

INTERNATIONAL ATOMIC ENERGY AGENCY

# SUMMARY REPORT

## CONSULTANTS' MEETING

## on

## REACTOR PRODUCTION AND UTILIZATION OF FLUORINE-18

International Atomic Energy Agency
Heidelberg, Federal Republic of Germany
German Cancer Research Centre
26 to 29 August 1986

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# I. INTRODUCTION

Nuclear research reactors are increasingly being used for the production of radionuclides of medical importance such as $^{99}Mo$-$^{99m}Tc$ and $^{131}I$. The demand for these and other radionuclides and their labelled compounds is also increasing continuously with the organization of more nuclear medicine centers.

During the past few years, the trend in modern diagnostic nuclear medicine has been towards the utilization of short-lived positron-emitting radionuclides. In this regard, cyclotrons and other accelerators are playing an important role in the production of radioisotopes of "organic" elements such as $^{11}C$, $^{13}N$, $^{15}O$ as well as of $^{18}F$ as an analogue tracer. These radionuclides are particularly well suited for probing regional human biochemistry in a quantitative way with a Positron Emission Tomograph (PET).

Though fluorine-18 was produced in nuclear reactors in moderate quantities in the early days of nuclear medicine for bone scanning, attempts to label organic compounds were not initially satisfactory owing to the difficulties of introducing fluorine into organic molecules with acceptable yields. These difficulties are now easily overcome due to the many studies utilizing accelerator-produced $^{18}F$ in the form of gaseous $^{18}F_2$, $H^{18}F$ and other precursors. However, there are some disadvantages inherent in the chemistry of gaseous reactive species such as $F_2$, and in the fact that fluorine carrier gas has to be added in order to improve the recovery yield of $^{18}F$, which results in a non-carrier free product. There also remains a more serious difficulty, particularly for developing countries, of having access to a cyclotron or accelerator facility. More recently, however, new and efficient synthesis techniques have become available for preparing fluorine-18 compounds via nucleophilic substitution with no-carrier-added $^{18}F^-$ fluoride.

Because $^{18}F$ organic radiopharmaceuticals, e.g. 2-[$^{18}F$]-fluoro-2-desoxy-D-glucose ($^{18}F$-2FDG), have already been successfully used in clinical research and practice, it is of interest to explore further the potential and associated problems of producing $^{18}F$ with nuclear reactors in quantities of practical importance for nuclear medicine studies. This interest stems from the fact that there are several countries which do not have an accelerator but operate nuclear research reactors and maintain extensive programmes of radionuclide and radiopharmaceutical production, and do have active nuclear medicine communities eager and able to have access to organic radiopharmaceuticals labelled with a positron emitter such as $^{18}F$.

From the above considerations, it was felt that it was high time for the Agency to take an active role by facilitating closer contact among scientists to discuss problems relevant to the reactor production of fluorine-18 and its utilization in nuclear medicine. In order to accomplish this goal, the consultants were asked specifically to address the following aspects:

(a) to review the reactor production techniques of $^{18}F$ and to discuss the associated problems with a view to improving $^{18}F$ production and recovery yield;

(b) to review and assess synthetic methods of preparing $^{18}F$ organic radiopharmaceuticals from fluoride;

(c) to assess the potential, from the view-point of the clinical information obtained, of utilizing existing instrumentation other than a PET to measure biological functions with organic radiopharmaceuticals labelled with a positron emitter such as $^{18}F$. It is assumed that, if a country or institute does not have a cyclotron, it is most likely that it does not have a PET system either; and

(d) to identify and issue recommendations on future activities for which the Agency's efforts would have the greatest impact and significance.

## II. REACTOR PRODUCTION OF $^{18}F$

### 2.1. Survey

- Radiopharmaceutical synthesis with $^{18}F$ requires reliable production of no-carrier-added (n.c.a.) $^{18}F$ as the $F^-$-ion in 10-100 mCi quantities. A nuclear reactor can meet these requirements if a thermal neutron flux of $\geq 5.10^{12}$ $cm^{-2}$ $s^{-1}$ is available.

- The specific activity of the $^{18}F$ obtained from a reactor has been estimated as ~500 Ci $mmol^{-1}$, which is sufficient for high specific activity $^{18}F$-tracers.

- The reactor production of $^{18}F$ is based on the irradiation of a lithium compound containing oxygen with thermal neutrons, utilizing the consecutive reactions: $^{6}Li(n,\alpha)^{3}H$ followed by $^{16}O(t,n)^{18}F$. Other reactor-neutron-induced reactions which lead to $^{18}F$ are not useful.

- Lithium salts enriched in $^{6}Li$ are preferred as target materials. The most common choices are $Li_2CO_3$ and $LiOH.H_2O$.

### 2.2. Principles of $^{18}F$-production in a nuclear reactor

#### 2.2.1. The reaction $^{6}Li\ (n,\alpha)^{3}H$

- Thermal neutrons induce this exothermic reaction with a net energy production (Q-value of 4.8 MeV). The cross section for thermal neutrons is $\simeq$ 950 barn.

- The initial energy of the tritons is 2.74 MeV; the triton range is $\simeq$ 100 µm in $Li_2CO_3$. Most of the energy is dissipated in the first 50 µm. The total heat production in natural $Li_2CO_3$ is, at the usual density of 0.7 $g.cm^{-3}$, in the order of 7 $W.g^{-1}$ at an in-target flux of $10^{13}$ $cm^{-2}s^{-1}$.

The heat production is proportional to the amount of $^{6}Li$ in the target material and is in practice the limiting factor.

- At natural abundances of $^{6}Li$, the triton flux in $Li_2CO_3$ is $\sim 7 \times 10^{-3}$ times the thermal neutron flux; this ratio increases somewhat with the $^{6}Li$-enrichment.

2.2.2. The reaction $^{16}O(t,n)\ ^{18}F$

- The exothermic reaction (Q = 1.26 MeV) has a coulomb barrier around 0.6 MeV.

- The effective triton range over which $^{18}F$ is produced is $\simeq$ 70 µm, the average cross-section over the total range is 87 mb.

2.2.3. The production of $^{18}F$

The produced $^{18}F$-activity per gram $Li_2CO_3$ can be calculated from the following expression:

$$^{18}F\text{-act.} = \frac{6 \cdot a \cdot \overline{\sigma_T} \cdot \sigma_N \cdot \delta \cdot N_{Av}^2 \cdot R \cdot \phi_N (1 - e^{\lambda t_1})}{3.7 \times 10^7 \cdot M^2} \quad \text{mCi.g}^{-1} \qquad \ldots (1)$$

where

a = fractional abundance of $^{6}Li$.

$\sigma_T$ = average cross-section for the $^{16}O(t,n)^{18}F$ reaction ($87 \times 10^{-27}$ cm$^2$)

$\sigma_N$ = cross-section for the $^{6}Li(n,\alpha)^{3}H$ reaction; ($950 \times 10^{-24}$ cm$^2$)

$\delta$ = density of the Li-compound in g.cm$^{-3}$. For $Li_2CO_3$ $\delta = 0.7$ g cm$^{-3}$

$N_{Av}$ = Avogadro's number; $6.02 \times 10^{23}$

R = total range of the tritons. For $Li_2CO_3$
R = $10^{-2}$ cm (100 μm).

$\Phi_N$ = average thermal neutron flux over the target, including flux depression, in $cm^{-2}.s^{-1}$.

$\lambda$ = decay constant of $^{18}F$; $6.3 \times 10^{-3} min^{-1}$

$t_1$ = irradiation time in min.

M = molecular weight in g; for $Li_2CO_3$
M = 73 g.

The average thermal neutron flux is the product of the original flux, $\Phi_N^o$, and the flux depression factor, F.

2.2.4. The flux-depression factor (F)

- The value of F can be estimated as

$$F = \exp [-2.4. V.\Sigma a/s] \quad \ldots (2)$$

where V = volume of the target in $cm^3$
s = surface area of the target in $cm^2$.

$\Sigma a$ = macroscopic absorption cross section in $cm^{-1}$.

The value of $\Sigma a$ is proportional to the $^6Li$ abundance in the target material and to its density:

$$\Sigma a = \frac{2\ a\ \delta\ \sigma_N\ N_A}{M} \quad \ldots (3)$$

The specific activity (mCi $^{18}F.g^{-1}$) can be calculated as a function of layer thickness and density of the target material for various simple shapes. It appears that an annulus is the most advantageous target shape.

The corresponding maximum specific activity for highly enriched $Li_2CO_3$ and a thermal neutron flux of $10^{13}$ $cm^{-2}s^{-1}$ is $\simeq$ 35 $mCi.g^{-1}$ of target for an irradiation time of ~6 h. About 1-2 mm is a practical value for the target thickness.

2.2.5. Target design

Due to the large heat production the target must provide good heat transfer from the lithium salts. Annular 1 or 2 mm layers of lithium salts have been found useful over the years. Lithium carbonate is preferred because of its high thermal stability (m.p. 612°C).

For low flux reactors (< 1 x $10^{13}$ n $cm^{-2}sec^{-1}$) encapsulation in quartz ampoules is sufficient. For neutron fluxes up to 5x$10^{13}$ n $cm^{-2}sec^{-1}$, encapsulation in standard aluminium irradiation cans with a graphite insert provides sufficient heat transfer. For fluxes > 5x$10^{13}$ n $cm^{-2}sec^{-1}$ the heat production in the target may be so great that only natural lithium carbonate can be used as target material.

The most convenient design consists of pellets or annuli, combined with graphite spacers, inside standard aluminium irradiation capsules which are closed by welding.

The use of a standard aluminium irradiation can has the additional advantage that handling facilities for canning and re-opening are usually available. Also, its use needs no additional regulatory approval.

2.2.6. Length of irradiation

For practical reasons an irradiation time of 2 to 4 hours is recommended. When standard aluminium cans are used the build-up of co-produced activity in the can limits the irradiation time to about 3 hours.

2.2.7. Tritium contamination

At the end of irradiation the tritium activity is about 7 times higher than that of fluorine-18. Complete removal of $^{3}H$ is possible by an additional chromatographic separation step. For example, [$^{18}F$]fluoride could be adsorbed on an alumina column and Li as well as $^{3}H$ could be washed out. [$^{18}F$]fluoride, free of $^{3}H$, could then be eluted with basic solution. However, these solutions are not directly useful for the preparation of organic $^{18}F$ compounds.

2.3. Separation of $^{18}F$ from target materials

Various methods have been described for the separation of $^{18}F$ from irradiated lithium salts. They include

(i) Distillation of $H^{18}F/H_2O$ from the aqueous sulfuric acid solution of the lithium salt.

(ii) Chromatographic separation on ion exchange resins.

(iii) Solvent extraction.

(iv) Co-precipitation.

(v) Silylation of [$^{18}F$]fluoride in aqueous sulfuric acid and liberation of gaseous [$^{18}F$]trimethylsilyl fluoride.

Method (i) was used widely in the past when [$^{18}F$]fluoride in aqueous solution was required.

The use of nucleophilic substitution reactions for the introduction of fluorine into organic compounds requires [$^{18}$F]fluoride to be dissolved in a polar, aprotic solvent (e.g. acetonitrile, DMSO). This requirement is best met by method (v). In this procedure the irradiated lithium salt is dissolved in dilute sulfuric acid. Then, a silylating agent (such as trimethylsilyl chloride, hexamethyldisilazane or hexamethyl- disiloxane) is added and the gaseous [$^{18}$F]trimethylsilyl fluoride is removed from the solution by a stream of an inert gas. The gas stream is first passed through water to remove traces of sulfuric acid, silylating agent and possibly lithium. Secondly, it is passed through a solution of tetraethylammonium hydroxide in acetonitrile which hydrolyses [$^{18}$F]trimethyl silylfluoride to form [$^{18}$F]tetraethyl ammonium fluoride. Traces of water are removed azeotropically by repeated evaporations with dry acetonitrile. Solutions of n.c.a. [$^{18}$F]tetraethyl ammonium fluoride in acetonitrile prepared in this way, have been found to be an excellent source of nucleophilic fluorine for a variety of nucleophilic reactions.

The silylation procedure is efficient, since it converts >95% of the original $^{18}$F into nucleophilically reactive [$^{18}$F]fluoride within 30 minutes after the end of the irradiation. Most importantly for routine use, the procedure has been found to perform reliably as part of the routine synthesis of $^{18}$F-2 FDG. The procedure has an additional advantage in that the final [$^{18}$F]fluoride solution contains only < 0.1% of the original tritium without a specific step being used to remove tritium.

## 2.4. Radiochemical facilities

### 2.4.1. Staff

It is assumed that appropriate general technical staff are already available at the reactor facility and the nuclear medicine facility.

Persons with experience in radiochemistry and in synthetic organic chemistry are needed for production of $^{18}F$ labelled compounds.

2.4.2. Laboratory

A type B level laboratory is required for handling more than 10 μCi of $^{18}F$. Production of useful activities for imaging purposes (5-10 mCi) requires facilities for radioisotope handling of the order of 50-100 mCi. In addition, handling of tritium activities in the order of several hundreds of mCi is also required.

Regular surveys of the laboratory are required for tritium contamination. Health physics support is necessary to monitor the exposure of personnel to both $^{18}F$ and tritium. Access to a liquid scintillation counter for regular monitoring of tritium in urine is important.

2.4.3. Equipment

Classical hot cells with manipulators are not ideal for producing $^{18}F$ compounds. Lead enclosures (5 cm thick) should be used with facilities for remote operation, including addition and transfer of reagents.

Shielded equipment is also necessary for safely opening the aluminium irradiation capsules and transferring the $^{6}Li$ target material to the apparatus used for preparation of the reactive solution of nucleophilic $^{18}F$. It may be most convenient to transfer this solution to a separate lead box for preparation of $^{18}F$-2FDG or other organic $^{18}F$ labelled compound.

Work-up of reactor $^{18}F$ involves aqueous steps and it is convenient to remove acetonitrile-water with a rotary evaporator equipped with a mechanical pump and suitable cold-traps. A separate rotary evaporator should be available for the labelling step.

Analytical equipment is necessary for determining the purity of both organic starting materials and of final $^{18}F$ labelled products. High-performance liquid chromatography (HPLC) should be available for final quality control of $^{18}F$ radiotracers with detection of both $^{18}F$ radioactivity and mass, e.g. by ultra-violet absorption. Facilities for thin layer chromatography (TLC) and vapour phase chromatography (VPC) are also necessary for some syntheses.

Visible/ultra-violet, and infra-red spectrophotometers are minimum analytical requirements for preparation of starting materials. Local access to H-1 and F-19 NMR instruments and mass spectrometry is highly desirable.

## III. PREPARATION OF $^{18}F$ LABELLED COMPOUNDS

A wide range of organic $^{18}F$ compounds can now be prepared for biological experiments. The pathways to these compounds can be divided up into electrophilic and nucleophilic. Production of electrophilic $^{18}F$ fluorinating agents, such as fluorine, from reactors in useful yields has not yet been reported. At present, therefore, the preparation of $^{18}F$ tracers from reactors is restricted to nucleophilic labelling methods.

The early literature contains several reports of synthesis based on thermal decomposition of diazonium tetrafluoroborates. Synthesis of $^{18}F$ compounds from reactors could also be based on intermediates such as bromine fluoride or diethylamino sulfur trifluoride. However, most of the recently published work involves substitution of good leaving groups such as triflate or iodide in appropriate organic starting materials by near-anhydrous fluoride dissolved in polar aprotic solvents. A large cation without an extensive hydration sphere is used to support the fluoride. There are no essential differences between accelerator production and reactor production for this class of reactions, after initial work-up of irradiated targets.

Both aromatic and aliphatic substitution reactions can be made to occur rapidly (in terms of the half-life of $^{18}F$). The literature contains many examples of both direct incorporation of $^{18}F$ into the skeleton of the target compound, and of syntheses involving reactive $^{18}F$ precursors such as fluoroethyl bromide and fluorophenyl cyanide. Appropriate protective groups must be considered for direct incorporation routes, to avoid side reactions due to the strong basic properties of fluoride under aprotic conditions.

Some desired tracers, such as 6-FDOPA, may be more easily approachable by electrophilic methods. An alternative to developing new nucleophilic routes to these compounds would be to develop a method of production of difluorine etc. from reactors. However, the current consensus is that it will probably be possible to design techniques for synthesis of any desired $^{18}F$ compounds using aliphatic or aromatic nucleophilic substitution reactions.

Several groups have recently published their experience with nucleophilic substitution reactions of $^{18}F$ fluoride. Their detailed methodology has varied in terms of the following: source of $^{18}F$; type of vessel used; solvent; method of rendering near-anhydrous; concentration of substrates; leaving groups; temperature; and cation present.

Rapid reaction rates and high (>80%) yields can be obtained with tetralkylammonium or APE-potassium as the cation. Acetonitrile is probably the most commonly used solvent, and DMSO is generally used when a higher temperature is needed.

Apart from nearly quantitative yields, another major advantage of nucleophilic substitution reactions is that very high specific radioactivities are obtainable. Under the reaction conditions used, fluoride is a more powerful nucleophile than most other anions. It is not necessary to add carrier fluoride to obtain high yields; hydroxide and carbonate are commonly used bulk anions. High specific activities (several hundred Ci/mmol) are required for hormone and neurotransmitter-receptor binding compounds, and also for situations where radiotracers are toxic or have highly toxic metabolites such as fluoroacetate.

Several fluorine-18 radiopharmaceuticals have been already evaluated clinically. 2-[$^{18}$F]-Fluoro-2-deoxy-D-glucose ($^{18}$F-2FDG) is the most widely used agent in conjunction with positron emission tomography (PET). The application of $^{18}$F-FDG to the quantitative determination of regional cerebral glucose utilization has been extensive in neurology. $^{18}$F-2FDG has also been applied to measuring glucose turnover in heart muscle. The wide use of [$^{18}$F]-2FDG has initiated the development of a great variety of preparation methods. Beginning with the first synthesis by the Brookhaven group using the electrophilic addition of [$^{18}$F]-$F_2$ to the protected sugar, 3,4,6-tri-O-acethyl-D-glucal (TAG), other procedures have been developed, both electrophilic and nucleophilic ones. The latter start with *no*-carrier-added [$^{18}$F)-fluoride.

Nucleophilic methods are most suitable for reactor-produced fluorine-18. In view of the advantages of $^{18}F^-$ as a precursor for radiofluorination, several attempts have been made for the production of $^{18}$F-2FDG via nucleophilic substitution. Besides the better utilization of fluorine-18 (theoretical yield 100%) this general method can provide epimerically pure $^{18}$F-2FDG via a $S_N2$ reaction at a D-mannose precursor. Phase transfer catalysts like tetraalkyl ammonium hydroxide or aminopolyether (222)-$K_2CO_3$ are successfully used for anion activation of n.c.a. fluoride in substitution reactions. Various precursor substrates have been described in the literature.

The Jülich synthesis using the tetraacetylated 1,3,4,6-tetra-O-acetyl-2-triflyl-β-D-mannopyranose is currently the method of choice with respect to simplicity and yield. It works best in the no-carrier-added state. In the presence of fluoride carrier the competing elimination reaction uses up the substrate.

Other important fluorine-18 radiopharmaceuticals have also been prepared by nucleophilic substitution. Even the dopamine receptor antagonists, the neuroleptics spiroperidol and methylspiroperidol can now be labelled with fluorine-18 in good yields using a direct a.p.e.-promoted aromatic $^{18}F^-$ for $NO_2$ exchange. Another approach to the introduction of fluorine-18 is via fluoroalkylation, and several groups have prepared [$^{18}$F]-N-fluoroalkylspiperones via phase-transfer-catalysed nucleophilic substitution.

Recently, fluorofatty acids have also been prepared with no carrier added by a.p.e.-promoted nucleophilic $^{18}F$ - for - Br exchange in high yields. Thus, both even and odd chain-length fluorofatty acids can be applied for both heart and liver metabolic studies.

## IV. INSTRUMENTATION

Since the topic of this report is the use of $^{18}F$-labelled compounds in places where PET is not available, this section will concentrate on non-PET instrumentation. It discusses, in increasing order of complexity, several non-imaging and imaging devices that might be useful in detecting and measuring $^{18}F$ activity and its temporal and spatial distribution.

As it will be evident from chapter V, almost every type of investigation has its own counting problem. It will therefore be necessary for the user to tailor the method of investigation and the measuring device so that they are well matched.

### 4.1. Non-imaging devices

4.1.1. Single probe: Except for very simple counting applications in a given geometry, the single probe with collimator will not be very appropriate owing to the strong dependence of the count rate on the position of the source and the depth variation of the field of view.

4.1.2. Dual probe, non-coincident: By using two single collimated probes facing each other, one can reduce the disadvantages of the single probe. The geometric mean of the count rates in the two channels is approximately independent of the position of the source between the detectors. It is preferable to have a complete counting channel with amplifier, single channel analyser and counter for each detector. If the signals from both detectors are routed through one amplifier/analyser

channel in order to save electronic components, a delay has to be inserted into one channel before the mixer. Otherwise, coincident signals from the two detectors will be summed electronically and will fall outside the analyser window, which will result in a drastic loss of count rate.

4.1.3. Dual probe, coincident: Two probes in coincidence without collimators are used. Lead shielding against quanta from outside the field of view is needed. The coincidence detector is specially promoted and recommended by Dr. H.N. Wagner Jr. as a simple system for non-PET measurement of positron emitters. It is the basic detector of all PET instruments. The sensitive volume is well defined and is restricted to the volume between the detectors. For extended sources, the coincidence count rate does not depend on the position of the source between the detectors. The absolute activity in the field of view in the object can be determined by doing a second measurement using an external source of known activity. For small sources, partial volume effects have to be accounted for. True coincidences, random coincidences, and single counts in both detectors should be counted in parallel. The coincidence detector is the device of choice for quantitative counting.

A possible improvement of this instrument may be achieved by replacing the standard NaI-detectors by fast scintillators. This would reduce the random coincidences. Assuming a time resolution of about 250 ps, a time-of-flight resolution of about 4-5 cm seems to be possible. This would be sufficient to discriminate, e.g. between the two hemispheres of the brain.

A common advantage of all probe systems compared to the imaging systems is the fact that only about 1/10 to 1/100 of the activity is needed to get sufficient counts. The radiation dose absorbed by the patient as well as the activity of labelled drug that has to be prepared and injected are correspondingly small.

4.2. Imaging devices

4.2.1. Rectilinear scanner: May be useful in special cases where no time information is needed. Heavy shielding and high energy collimators are needed.

4.2.2. Positron scanner: This is a planar scanner using multiple dual-probe coincident detectors. It has been developed at the German Cancer Research Centre, Heidelberg. Quantitative whole-body studies can be done with high sensitivity. Slow metabolic studies are possible in addition to the measurement of the regional biodistribution of labelled drugs. The instrument can be used for toxicologic and environmental studies. No commercial version is available.

4.2.3. Anger camera: Modern Anger cameras are not suitable for the detection of positron emitters because of the low efficiency of their thin crystals and the lack of high-energy collimators. But there are still many Anger cameras available with 1/2" thick crystal and collimators that have been designed for energies up to and over 400 keV. These systems can be used to image $^{18}F$-labelled compounds. The suitability of the collimators has to be checked in the individual case, since "high-energy" collimators from different manufacturers may be very different. Inevitably, the collimator hole pattern will be visible in the image. To avoid this, a rotating tungsten collimator has been developed at the University of Chicago. With a tungsten collimator, a sensitivity of about 1400 cps/mCi, compared to the sensitivity of 6000 cps/mCi for $^{99m}Tc$ (Searle LFOV with LEAP collimator), can be achieved. In this case the resolution is about 1,5 cm at 10 cm distance from the collimator.

The pinhole collimator is well suited for experimental studies with small animals, provided the shielding around the pinhole is reinforced.

4.2.4. Large-area positron cameras: Positron cameras using two opposing Anger camera detectors or multi-wire proportional chambers (MWPC) have been developed. Problems common to both are the extremely high single count rate and the difficulty in handling the scattered radiation from extended objects. In the probe systems as well as in the PET systems, these problems are reduced by the lead shields. For this reason, large-area systems can only be used for small objects. They have not found broader clinical application.

4.2.5. Cheaper PET systems: Quasi-continuous ring systems (Brownell) and polygonal rings using bar detectors (Mühllehner) are under development. There is a possibility that these developments may result in PET systems that are substantially cheaper than the multicrystal devices that are used now.

## V. POTENTIAL CLINICAL STUDIES WITH $^{18}F$ IN A NON-PET MODE

### 5.1. Heart

There is at least one area of cardiac work where planar imaging may be clinically useful. It has recently been demonstrated with PET that the myocardium whose blood supply is depressed following a heart attack, but which is still metabolically viable, can exhibit enhanced uptake of $^{18}F$-2FDG. This flow/metabolism "mismatch" probably indicates that the tissue can be salvaged by medical intervention such as bypass surgery. On the other hand, if both metabolism and flow are depressed to the same extent, then surgery is probably contra-indicated.

Recent experiments with dogs using an Anger camera equipped with a tungsten high-energy collimator have demonstrated the feasibility of detecting flow/metabolism mismatches without PET. The flow tracer used in these experiments was $^{201}Tl$. The method depends on comparing the ratio of counts per pixel in normal to damaged myocardium in the flow tracer study with the corresponding ratio obtained with $^{18}F$-2FDG.

It is possible that Anger cameras with high energy collimators or other planar imaging devices might also be useful in other areas, for example, to confirm gross metabolic dysfunction in the brain, or to detect tumor metastases in parts of the body with low background levels of $^{18}$F-2FDG uptake.

## 5.2. Brain

The metabolism of the neurotransmitter dopamine and the distribution of its receptor can now be investigated with 6[$^{18}$F]fluoro-L-dopa and [$^{18}$F]N-alkyl-spiperones, respectively. Dopaminergic neurons are highly localized in the parts of the brain known as the caudate nucleus and putamen (striatum). The striatum occupies a volume of approximately 30 cm$^3$ in the centre of the brain. This natural concentration permits the use of dual scintillation probes in coincidence placed at either side of the head. The arrangement would record $^{18}$F contained in a cylinder of brain tissue between the detectors, including the dopamine structure. To minimize the contribution from non-striatal tissue, both probes can be collimated in such a way that the most sensitive volume is the striatum ("Striatoscope").

6-[$^{18}$F]Fluoro-L-dopa is converted in the striatum to 6[F]fluoro-dopamine, which has been shown to be a biological analog of native dopamine. The $^{18}$F monitored is a measure of the dopamine pool. Information about the kinetics of dopa/dopamine metabolism can also be obtained. In this case, the time course of $^{18}$F in the striatum and that in the blood is monitored and then kinetic parameters are calculated from these curves with the help of an appropriate mathematical model.

A dopamine deficiency in the striatum is associated with Parkinson's disease and with some types of dyskinesia. The 6-[$^{18}$F]fluoro-L-dopa method assesses the extent of the neurochemical lesion. This has been demonstrated with PET as well as with the dual scintillation probe arrangement.

Parkinson's disease is treated with the drug L-dopa which replenishes the striatal dopamine. The drug therapy loses its effectiveness after some years. In order to design an alternative drug treatment on the basis of the neurochemical state of the patient's striatum, information on the remaining dopamine and on its receptors ($D_2$) is needed. It is hoped that the 6-[$^{18}$F]fluoro-L-dopa method and the $^{18}$F-labelled dopamine receptor binding ligands will provide the information. The effect of any drug given to promote the biosynthesis of dopamine can thus be monitored with 6-[$^{18}$F]fluoro-L-dopa.

The measurement of a dopamine receptor concentration index with $^{18}$F-labelled butyrophenones promises to be of importance in the assessment of the drug treatment of patients with psychiatric disorders. However, clinical methods have not yet been developed.

5.3. Liver:

The liver is a large organ, the functions of which may be damaged diffusively by disease, intoxication or chemotherapy. Little attention has yet been given to the design and development of positron-emitting tracers of hepatic metabolism. However, the activity of a part of this organ could easily be counted by a double collimated probe in coincidence. The kinetic analysis of the uptake curve of labelled agents may help to assess the degree of the liver dysfunction. Such an approach could be very helpful in the follow-up of a number of pathological liver conditions.

5.4. Tumors:

Malignant tumors consume energy which is provided to them by the intake of glucose. It seems that this process can be successfully monitored with $^{18}$F-2FDG:

- Single photon planar imaging using high energy collimated rectilinear scanners or gamma cameras could thus help in

mapping the tumor extension before treatment, as well as in later detection of recurrences. The procedure may be an useful adjunct to the $^{67}Ga$ imaging which has its own well-known limitations.

- As the glucose uptake in a tumor is probably closely related to its growth rate, the degree of $^{18}F$-2FDG uptake in a tumor may provide an useful insight into early tumor response to the therapy. A treatment course likely to be of little value could thus be discontinued at an early stage and replaced by an alternative one. Unnecessary damage to healthy tissues could thus be avoided.

  The changes in $^{18}F$-2FDG uptake in a tumor of known localization could be assessed before and during treatment by serial countings using dual collimated probe in coincidence.

- Similar procedures could be envisaged which made use of fluorouridine and possibly of other fluorinated precursors which may take part in the metabolic activity of a tumor.

- Fluorodopa is a precursor-analogue of melanin. This opens up possibilities for investigating the potential use of this compound in the detection and diagnosis of primary and metastatic melanoma.

## VI. NON-CLINICAL USE OF $^{18}F$

There are potential basic applications of $^{18}F$ in several fields including chemistry, biochemistry, physiology and toxicology. Production of many compounds at the hundred micro-Curie level is now sufficiently a matter of routine to allow $^{18}F$ to be used in situations where isotopes such as $^{14}C$ and tritium are usually applied. Although an $^{18}F$ compound must be freshly synthesized each day, the positron emitters are much easier to detect and quantify than $\beta^-$-emitters. The time and effort saved in avoiding having to prepare samples for liquid scintillation counting can amply compensate for the synthetic effort.

Because of the relatively short half-life, the duration of experiments with $^{18}F$ is limited to a few hours. On the other hand, very high specific radioactivities are obtainable, which allow the investigation of enzymes or receptors present in low concentrations. In physiological experiments the ability to quantify radioactivity externally can offer considerable advantages over more traditional tracer radionuclides. Thus, to give one example, in isolated perfused organs the time-course of $^{18}F$ after intraarterial injection (the "resident curve") can be measured quantitatively with high temporal resolution. This allows the estimation of physiological parameters such as membrane permeabilities, fluxes through metabolic pathways, and intracellular concentration by compartmental modelling techniques.

Experiments of this nature have been done with $^{18}F$ labelled sugars and long-chain fatty acids, which have also been used in PET experiments, and also can be used to study, for example, $^{18}F$ aminoacids, nucleotide precursors and receptor ligands.

Such organ perfusion experiments are potentially useful in investigating PET radiotracers as well as in basic biomedical research. For example, the behaviour of new $^{18}F$ compounds can be investigated under precisely controlled conditions, and the tissue can be conveniently examined for radioactive metabolites. Again, the behaviour of a more established radiotracer can be determined over wide ranges of blood flow, substrate concentrations, etc., to look at the stability of a "lumped constant", or to set limits on the precision of PET measurements made with the tracer.

Since it is possible to design synthetic routes to a wide range of $^{18}F$ compounds, basic tracer experiments with compounds containing fluorine can also be carried out. In organic chemistry, $^{18}F$ could be used in mechanistic studies. In toxicology, the tissue distribution and metabolism of industrial compounds and environmental contaminants with C-F bonds can be examined.

Similar pharmacological research is possible with fluorinated steroids, for example, where $^{18}F$, because of the high specific radioactivity obtainable, would provide an alternative to tritium for studying distributions governed by hormone receptors without the isotope exchange problems often associated with tritium.

## VII. SUMMARY AND CONCLUSIONS

7.1. Nuclear research reactors with thermal neutron fluxes in the order of $1 \times 10^{13}$ $cm^{-2}$ $s^{-1}$ can produce sufficient quantities (30-100 mCi) of fluorine-18 for biomedical applications.

7.2. Recent improvements in labelling with fluorine-18 via nucleophilic reactions have made it possible to develop efficient synthesis techniques for preparing useful quantities (3-10mCi) of radiopharmaceuticals (e.g. $^{18}F$-2FDG), which are of great interest for studying regional metabolic functions with positron-emission tomography (PET). In principle, a limited number of PET studies can be carried out in centres having a reactor but no cyclotron.

7.3. Non-PET instrumentation such as single probe, dual coincidence probe, and Anger camera with high energy collimator might present means of applying some of the PET radiopharmaceuticals in centres which do not have a PET facility. Special dual coincidence probes are of particular interest, due to the fact that activities of only a few hundred µCis are needed. The diagnostic relevance of such semi-regional and semi-quantitative measurements for heart, brain and tumor studies have yet to be evaluated and demonstrated.

7.4. Other non-medical activities in the field of pharmacology, toxicology, no-carrier-added syntheses and reaction mechanisms in fluorine chemistry can also conveniently be studied using fluorine-18 as a tracer.

## VIII. RECOMMENDATIONS TO THE AGENCY

8.1. The utilization of non-PET instrumentation such as dual-probe coincidence devices and Anger cameras with high-energy collimators involving radiopharmaceuticals labelled with positron emitters, particularly fluorine-18, should be experimentally evaluated. It is recommended that two technical contracts be awarded to selected institutes to carry out such evaluations.

8.2. The Agency should organize a small meeting of experts to assess further the medical significance of non-PET studies utilizing organic radiopharmaceuticals labelled with positron emitters.

8.3. Through the technical co-operation programme, the Agency should facilitate the training of scientists from developing countries by awarding scientific visits and fellowships.

ANNEX

INTERNATIONAL ATOMIC ENERGY AGENCY
Consultants' Meeting
on
"Reactor Production and Utilization of Fluorine-18"

Heidelberg, Federal Republic of Germany
German Cancer Research Centre
26 to 29 August 1986

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