Techniques for Positron Scintigraphy of the Brain

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Positron scintigrams were obtained in normal subjects and in patients with intracranial tumors and cerebral vascular disease, using a multicrystal positron camera. The radiopharmaceuticals were ^{68}Ga complexed with adenosine triphosphate (^{68}Ga-ATP), ^{13}N-ammonia ($^{13}NH_3$), and $^{15}O_2$. Six clinical cases are described to illustrate the different cerebral distributions of intravenously administered ^{68}Ga-ATP, $^{13}NH_3$, and inhaled $^{15}O_2$. The possible value of these agents in the study of cerebral metabolism and in differential diagnosis of intracranial disease is discussed.

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Cerebral scintigraphy performed with positron-emitting radiopharmaceuticals has some unique advantages. Recent developments in positron scintigraphic instrumentation permit imaging in two-dimensional projections and in axial tomographic sections with high spatial resolution and sensitivity (*1*). Moreover, a number of short-lived positron-emitting radionuclides are suitable for use in imaging. Several of these are cyclotron-produced (e.g., ^{11}C, ^{13}N, ^{15}O, and ^{18}F), while others are products of radionuclide generators (e.g., ^{68}Ga and ^{82}Rb). Because of their short half-lives, several of these radionuclides may be employed simultaneously in rapid-sequential studies with a relatively low radiation dose to the patient. The use of several radiopharmaceuticals with different in vivo behaviors may provide a means to differentiate among various pathologic conditions on the basis of regional circulation, permeability of the blood–brain barrier, and metabolism.

In this report we describe techniques for cerebral positron scintigraphy employing ^{68}Ga complexed with adenosine triphosphate (^{68}Ga-ATP), ^{13}N-ammonia ($^{13}NH_3$), and $^{15}O_2$. The clinical use of these agents is examined in normal subjects and patients with a variety of intracranial abnormalities. Scintigrams, obtained with a multicrystal positron camera (*1*), are shown for six cases.

MATERIALS AND METHODS

Radiopharmaceutical preparation and administration. A medical cyclotron facility is used to produce both the $^{13}NH_3$ and the $^{15}O_2$. A system similar to that described by Tilbury et al (*2*), using the $^{12}C(d,n)^{13}N$ reaction on methane gas, provides $^{13}NH_3$ dissolved in physiologic saline. The $^{15}O_2$ is produced by the $^{14}N(d,n)^{15}O$ reaction on N_2 containing 4% O_2. The radioactive gas is conducted to a gas-handling system, which removes traces of ozone and oxides of nitrogen (*3*), and is then conducted directly to the site of patient administration. The procedure employed for the preparation of ^{68}Ga-ATP has been described previously (*4*).

The doses of $^{13}NH_3$ and ^{68}Ga-ATP for adults are, respectively, 1–4 mCi (containing approximately 1 μg of stable ammonia) and 2–6 mCi (containing approximately 5 mg of ATP), each administered intravenously in 2–5 ml of physiologic saline. The $^{15}O_2$ is diluted with air to a specific activity of approxi-

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TABLE 1. MAXIMUM RADIATION DOSE ESTIMATES IN MAN FOR THREE POSITRON-EMITTING RADIOPHARMACEUTICALS

Organ	Dose (millirads) from $^{15}O_2$ in air (0.5 mCi/liter) inhaled for 10 min	Dose (millirads) from $^{13}NH_3$ (1 mCi) intravenous injection	Dose (millirads) from ^{68}Ga-ATP (1 mCi) intravenous injection
Brain	20	20	30
Liver	10	40	20
Kidneys	30	170	110
Spleen	20	60	140
Heart	50	30	10
Lungs	130	180	170
Blood	20	30	300
Whole body	20	10	40

mately 0.5 mCi/liter and is then administered by inhalation. The patient inhales the mixture for about 6–10 min (several physical half-lives of ^{15}O), at which time the inhaled activity has reached equilibrium with its own physical decay (*5*). The inhaled $^{15}O_2$ binds to red blood cells and is transported to the brain and other organs as ^{15}O-oxyhemoglobin (*6*). Table 1 lists the estimated maximum radiation exposure for these three agents, based on values from the MIRD tables (*7,8*).

Positron scintigraphy. Scintigraphy is performed with a multicrystal positron camera, described in detail elsewhere (*1*). The patient is positioned between the camera's two opposing arrays of NaI detectors. Four focal planes are chosen upon which to project and display the coincidence data; these planes are at 0.2, 0.4, 0.6, and 0.8 of the distance between the two detector arrays.

Data from the positron camera are recorded, processed, and displayed by means of the NUMEDICS nuclear medicine imaging computer system (*9*). Images are displayed on a 128 × 128 raster with 64 gray levels. Processing involves the sequential application of several computer routines; for example, random variations in the image may be smoothed by performing a nine-point running average on the image. Images obtained with this system exhibit a spatial resolution of less than 1 cm (FWHM) and an overall sensitivity of 1,000 cpm/μCi for a distributed source.

In operation, the camera is used in one of three modes. For customary two-dimensional projection where depth information is not required, the detectors are moved to their maximum separation (75 cm). The patient's head is placed such that it is centered about one of the focal planes (e.g., the 0.4 plane), and all images are subsequently displayed on this plane. A source distribution located on the focal plane used for imaging will be in sharp focus, while activity located off the plane will be diffused. In the second mode of operation, the camera provides four sets of images, each focused on one of the focal planes. The detectors are moved to their minimum separation (35 cm) so that the focal planes are separated by 7 cm. Thus, more than one plane of focus will pass through the subject's head. A third mode of operation employs multiple views obtained around the patient to reconstruct transverse axial tomograms (*10*). The spatial resolution obtained with the reconstruction algorithm currently in use is approximately 1 cm (*11*).

In each of these modes of operation, the detector arrays may be moved under computer control back and forth with respect to the patient over a maximum displacement of 2.8 cm. This motion serves to increase the number of points sampled and to disperse patterning artifacts that would otherwise appear in the images (Figs. 1A and 1B).

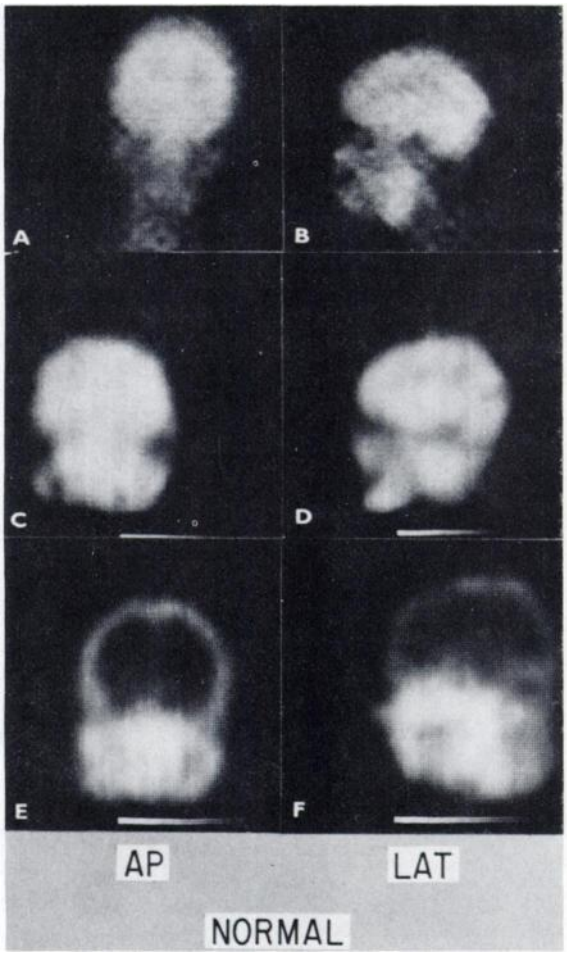

FIG. 1. Normal positron scintigrams taken with (A,B) $^{13}NH_3$ (linear scanning motion not applied), (C,D) $^{15}O_2$, and (E,F) ^{68}Ga-ATP.

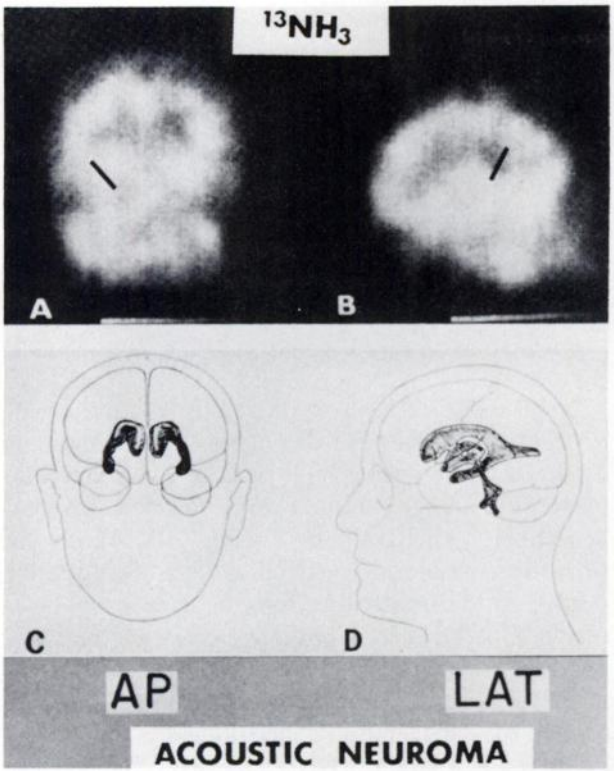

FIG. 2. Positron scintigrams taken with $^{13}NH_3$ in 52-year-old woman with right acoustic neuroma. (A,B) Images smoothed once with nine-point running average. (C,D) Sketches showing positions of cerebral ventricles in AP and LAT projections.

RESULTS

Except where noted, all the scintigrams shown here were obtained in either the anteroposterior (AP) projection or the left lateral (LAT) projection, with linear scanning motion as described above. Scans were begun 2–20 min after $^{13}NH_3$ administration and 10–140 min after ^{68}Ga-ATP. The $^{15}O_2$ scans were begun at equilibrium (*5*). Scan times varied over 100–400 sec and were typically 200 sec. Images usually contained more than 100,000 counts. Unless noted, no correction for attenuation, uniformity, or random coincidence counts was applied. Areas of abnormality are indicated on the scintigrams with arrows.

Normal studies. Significant differences occur in the cerebral distribution of the three radiopharmaceuticals $^{13}NH_3$, $^{15}O_2$, and ^{68}Ga-ATP (Fig. 1). The ^{68}Ga-ATP is prevented from entering normal brain tissue by its inability to cross the blood–brain barrier. Its cerebral distribution may be expected to resemble that of such other complexes as ^{99m}Tc-pertechnetate or ^{99m}Tc-diphosphonate (*12*). In contrast, $^{13}NH_3$ dissolved in physiologic saline and ^{15}O-oxyhemoglobin are both rapidly incorporated into the cerebral extravascular spaces. Ammonia is incorporated principally into the cerebral glutamic acid–glutamine pathway (*13*) and oxygen is metabolized to water (*14*). Differences in the cerebral distributions of $^{13}NH_3$ and $^{15}O_2$ are to be expected since $^{13}NH_3$ is distributed in the brain in proportion to blood flow and fractional extraction of ammonia into the extravascular spaces (*15*), whereas $^{15}O_2$ is distributed in proportion to blood flow and fractional extraction of oxygen by the tissue (*6,16*). The differences in behavior of these three agents at sites of cerebral abnormalities may be more pronounced due to alterations in blood–brain barrier, cerebral circulation, and metabolism.

CASE REPORTS

Case 1. *Acoustic neuroma.* A 52-year-old woman presented with signs of a right acoustic neuroma. Brain scans performed with ^{99m}Tc-diphosphonate and pertechnetate showed a dense concentration of activ-

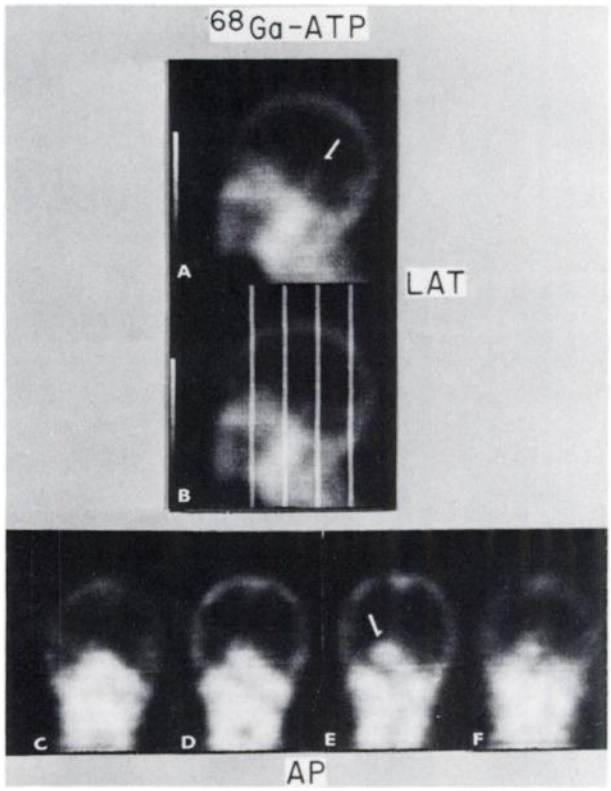

FIG. 3. Positron scintigrams taken with ^{68}Ga-ATP in 52-year-old woman with right acoustic neuroma. Lateral view (A) was obtained with maximum separation of detector planes, in which distance between focal planes is approximately equal to thickness of head and in which patient's midsagittal plane coincides with one of focal planes of camera. Four vertical lines on lateral view (B) indicate positions of four focal planes on which AP projection is displayed. Four AP views (C–F) are obtained with minimum separation of detector planes, in which distance between focal planes is 7 cm. Note that lesion is localized in depth from anterior (C) to posterior (F) by appearing in best focus when displayed on focal plane passing most closely through site of lesion (E). Lesion displayed on other focal planes appears out of focus.

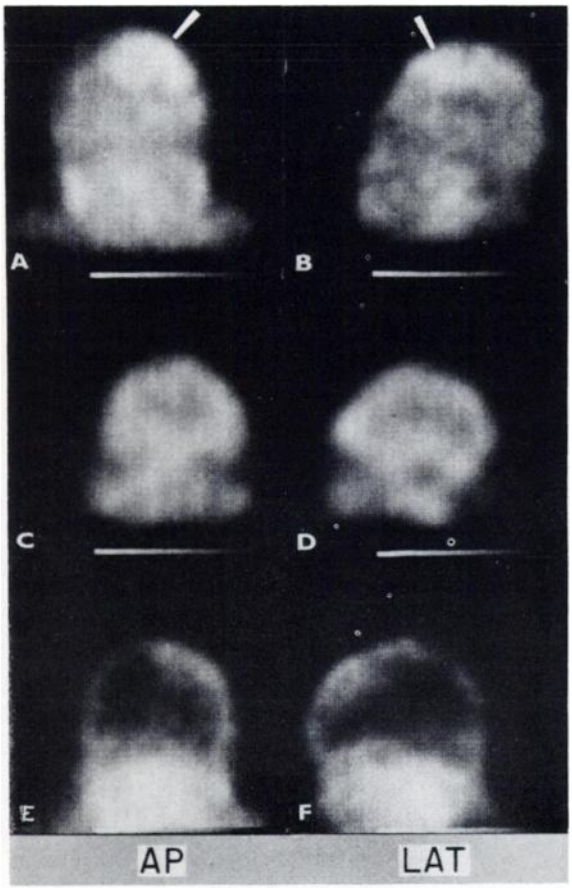

FIG. 4. Positron scintigrams in 75-year-old woman with meningioma. (A,B) $^{13}NH_3$ scintigrams after intravenous administration. (C,D) $^{15}O_2$ scintigrams obtained at equilibration in breathing air. (E,F) ^{68}Ga-ATP scintigrams obtained after intravenous administration.

ity in the right cerebellopontine angle. Right carotid and left vertebral angiography showed a large avascular mass in the right cerebellopontine angle, as well as enlargement of the right lateral ventricle.

Smoothed images obtained with $^{13}NH_3$ (Figs. 2A and 2B) show the radiopharmaceutical to be deposited predominantly in the cerebral cortex and in scalp and facial tissues, while the ventricles, skull, and mastoid sinuses take up little or no label. Figure 2 clearly shows bilateral ventricular enlargement. Differences in blood flow and $^{13}NH_3$ extraction between the acoustic neuroma and surrounding tissue were not great enough to permit identification of the tumor.

The lesion becomes visible with ^{68}Ga-ATP (Fig. 3). The 0.6 AP focal plane shows this lesion in best focus (the LAT image also shows this plane to pass most closely through the site of lesion). The lesion also appears on the other planes, but considerably out of focus. This case illustrates the value of the four focal planes in the clear detection of a tumor.

Case 2. *Meningioma.* A 75-year-old woman presented with a large posterior frontal meningioma. Bilateral carotid angiography showed a large slightly vascular mass over the left convexity in an extracerebral location, occupying the parietal and posterior frontal regions and supplied primarily by the middle meningeal artery. The lesion obstructed the superior sagittal sinus behind the coronal suture. The lateral ventricle appeared normal. An ^{74}As-arsenate positron brain scan obtained with a hybrid positron scanner showed a dense left superior frontal concentration.

Uptake of $^{13}NH_3$ in the lesion is striking (Figs. 4A and 4B). The AP view (Fig. 4A) shows the extent of the lesion on both sides of the midsagittal plane, extending inferiorly into the left cerebral hemisphere. The LAT view (Fig. 4B) shows an extensive concentration extending from the posterior portion of the frontal lobe into the superior parietal region. Uptake of $^{15}O_2$ in the region of the tumor is approximately equal to, or less than that in surrounding tissue (Figs. 4C and 4D). Gallium-68-ATP (Figs. 4E and 4F) appeared to concentrate less extensively in the lesion than did $^{13}NH_3$. The slight difference in $^{15}O_2$ uptake between tumor and surrounding tissue, compared to the increased uptake of $^{13}NH_3$ in the tumor, suggests that oxygen uptake is not increased in the tumor or the adjacent compressed edematous brain tissue. However, some mechanism has caused

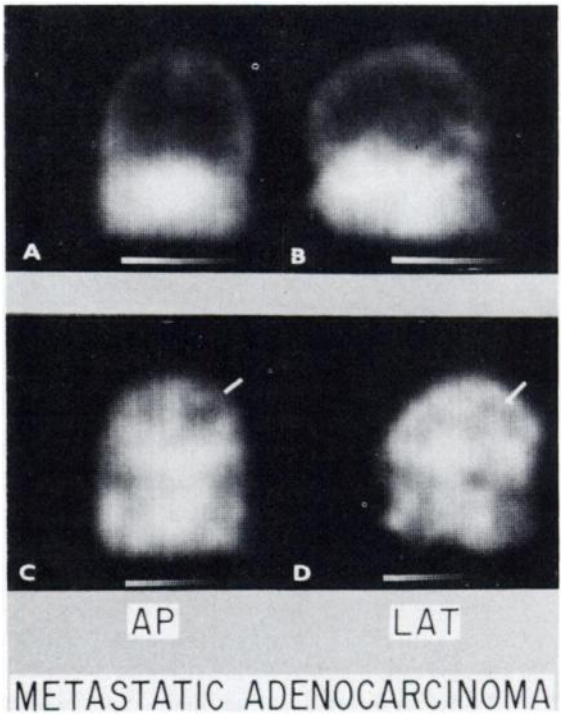

FIG. 5. Positron scintigrams obtained in 45-year-old man with metastatic pulmonary adenocarcinoma. (A,B) ^{68}Ga-ATP; (C,D) $^{13}NH_3$.

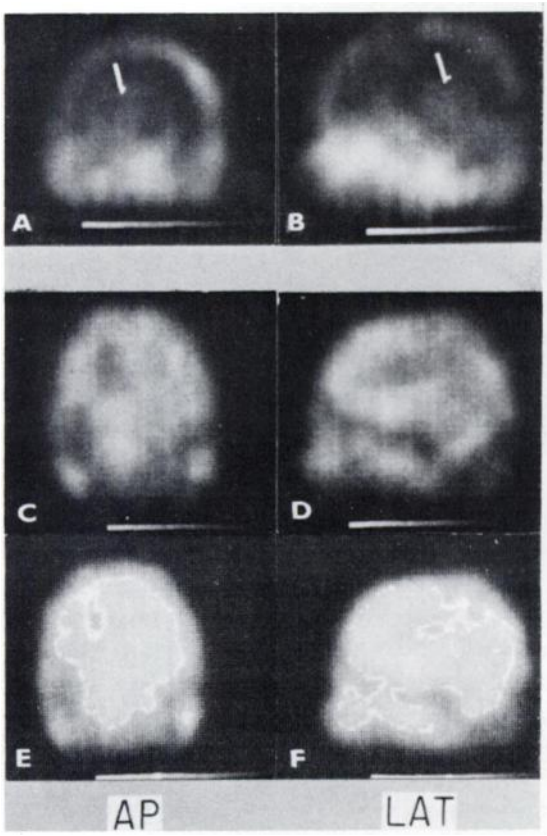

FIG. 6. Positron scintigrams in 41-year-old man with recurrent astrocytoma. (A,B) ^{68}Ga-ATP; (C,D) $^{13}NH_3$; (E,F) images C and D shown with single brightness level intensified.

a regional increase in the $^{13}NH_3$ concentration, making it even more prominent than that of the ^{68}Ga-ATP.

Case 3. *Metastatic adenocarcinoma.* A 45-year-old man with known lung carcinoma presented with left cerebral hemisphere signs. Left carotid angiography showed the peripheral branches of the middle cerebral artery to be displaced, suggesting an occipitoparietal mass approximately 5 cm in diameter with considerable surrounding edema. The left vertebral angiogram was normal.

Although the ^{68}Ga-ATP images appear normal (Figs. 5A and 5B), a reduction of $^{13}NH_3$ uptake (Figs. 5C and 5D) in the left occipitoparietal region is seen in a scan obtained immediately before the ^{68}Ga-ATP study. The reduced uptake of $^{13}NH_3$ at the site of the lesion suggests a perfusion defect or metabolic change in the region of the tumor, but without increased permeability to ^{68}Ga-ATP.

Case 4. *Recurrent astrocytoma.* A 41-year-old man was admitted with a history of a recurrent right temporoparietal astrocytoma. Radical subtotal removals were undertaken 4 years before his present admission and again 2 years later. At both times carotid angiography revealed a right posterior temporal mass. Radiographic transaxial cerebral tomography revealed enlargement of the left lateral ventricle and the frontal horn of the right ventricle, in addition to a deep right posterior temporoparietal mass of low x-ray absorption compressing the posterior right lateral ventricle. A left ventriculo–peritoneal surgical shunt was performed shortly before the scintigrams shown in Fig. 6 were obtained.

On the LAT view, ^{68}Ga-ATP uptake (Figs. 6A and 6B) in the region of the lesion is partially obscured by uptake at the site of surgery. Uptake is similarly weak in the AP view, due in part to the en face projection obtained. The $^{13}NH_3$ study (Figs. 6C and 6D, repeated in Figs. 6E and 6F with a single brightness level intensified), however, shows reduced uptake at the lesion, probably indicating a perfusion defect.

Case 5. *Glioma.* A 64-year-old man presented with left arm and hand seizures and clumsiness in the use of his left hand. A ^{99m}Tc-pertechnetate brain scan and bloodflow study exhibited a hypervascular focal lesion in the right frontal-parietal region which proved to be a glioma.

The $^{13}NH_3$ study (Figs. 7A and 7B) shows a region of decreased uptake in the superior portion of the right cerebral hemisphere. In cases of focally reduced uptake, tomographic reconstruction aids in visualization. Of the various axial tomograms which may be reconstructed, two are displayed in Figs. 7E and 7F; these are viewed superiorly. One section traverses the lateral ventricles (Fig. 7F), and the

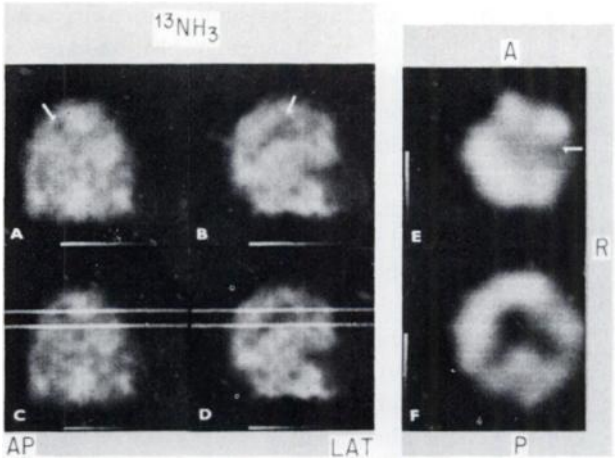

FIG. 7. Positron scintigrams taken with $^{13}NH_3$ in 64-year-old man with glioma. (A,B) AP and LAT views; (C,D) images A and B shown with lines separated by 3 cm representing positions of two reconstructed tomograms shown in E and F. (E,F) Tomograms reconstructed from 23 views taken around subject after intravenous administration of $^{13}NH_3$. Correction for attenuation was applied. Linear scanning motion was not applied.

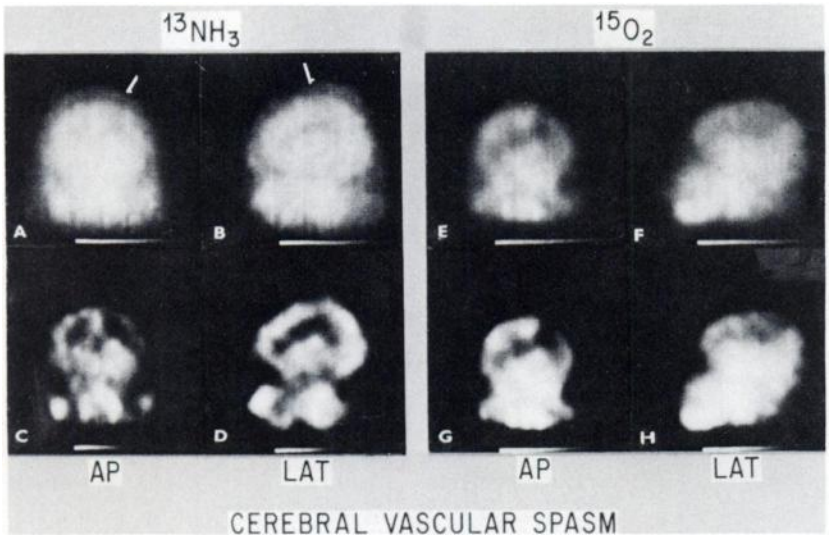

FIG. 8. Positron scintigrams in 40-year-old man with cerebral vascular spasm. (A,B) $^{13}NH_3$ scintigrams obtained after intravenous administration; (C,D) scintigrams A and B with brightness gradients enhanced; (E,F) $^{15}O_2$ scintigrams obtained at equilibration with ^{15}O physical decay during inhalation of $^{15}O_2$ in air; (G,H) scintigrams E and F with brightness gradients enhanced.

other passes tangentially immediately above them (Fig. 7E). The space occupied by the ventricles and surrounding white matter is more clearly defined in the tomograms than in the AP and LAT projections. The focal lesion is visualized in the superior tomographic plane (Fig. 7E) as a reduction of uptake in the central portion of the right cerebral hemisphere. The spatial resolution distance exhibited in these reconstructed images is somewhat greater than the 1 cm normally obtainable, because, for the sake of expedience, linear scanning motion was not employed. Therefore, except for the lesion itself and the other significant gradients of $^{13}NH_3$ uptake (e.g., the ventricular spaces and surrounding white matter against the cortical gray matter), most other major anatomic features are not discernible in this display.

Case 6. *Cerebral infarction secondary to arterial spasm.* A 40-year-old man presented with subarachnoid hemorrhage. Carotid angiography showed a large aneurysm at the bifurcation of the left internal carotid artery. The patient subsequently developed spasm of the left middle cerebral artery, with right hemiparesis and aphasia. The $^{13}NH_3$ scintigrams (Figs. 8A–D) indicate reduced uptake in the left parietal region and suggest a perfusion defect in the territory of the left middle cerebral artery. The ischemic region is more apparent in the images obtained with $^{15}O_2$ (Figs. 8E–H). The reduced uptake of both agents is probably due to reduced perfusion, whereas the greater contrast between the diseased region and surrounding tissue observed with $^{15}O_2$ may also imply that oxygen extraction in the diseased area is also reduced relative to the surrounding tissue.

DISCUSSION

These studies were performed to develop methods of measuring regional cerebral metabolism and to obtain evidence as to whether these measurements can be of benefit in differential diagnosis and treatment. Although such labeled complexes as ^{99m}Tc-pertechnetate and ^{68}Ga-ATP are useful in detecting intracranial lesions, they do not concentrate in proportion to any known metabolic function. Such agents as $^{13}NH_3$ and $^{15}O_2$, on the other hand, are actively metabolized by functioning brain tissue and may provide a means of measuring regional metabolic status. One of their advantages lies in their ability to be imaged with devices using positron annihilation detection, These devices offer the possibility of correcting for photon absorption in regional function measurements. Furthermore, as shown here and elsewhere (*11*), axial tomographic sections may be obtained in addition to the conventional two-dimensional projections.

In our five cases of tumor, $^{13}NH_3$ was markedly taken up by a meningioma, did not differentially concentrate in an acoustic neuroma, and showed reduced uptake in metastatic tumor and glioma. No differential uptake of $^{15}O_2$ was seen in the meningioma: this difference between the two agents probably indicates a difference in metabolism, particularly since the ^{68}Ga-ATP concentration was less than that of $^{13}NH_3$. The reduced $^{13}NH_3$ uptake in metastatic tumor and glioma likely relate to a decrease in perfusion in the diseased region, but a metabolic alteration cannot be excluded. The single case of cerebral ischemia also exhibited a reduction in the uptake of both $^{13}NH_3$ and $^{15}O_2$, which would be expected in an area of reduced perfusion.

These preliminary scintigraphic data do not suggest, therefore, that intracranial neoplasms can be directly and unequivocally differentiated from infarction on the basis of gross observable differences in the regional distribution of these tracers. More im-

portant is the possibility that three-dimensional positron scintigraphy can provide direct information on regional cerebral function (e.g., blood flow, oxygen metabolism, etc.). Given this advantage, criteria for routine noninvasive identification, differential diagnosis, and prognosis of intracranial disease may be developed from our knowledge of fundamental physiologic differences. This work will be continued in the hope of obtaining further data to clarify the meaning of these differences and which will suggest their use in the differential diagnosis of intracranial disease.

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