

## Chapter 20

### RADIONUCLIDE BRAIN SCANNING

Hussein Abdel-Dayem

#### Introduction

Medical imaging plays an important part in the diagnostic work-up of a patient as it can provide both anatomical and physiological visualization of different organs. Since the early part of this century, when X-rays were introduced for imaging, brain imaging has attracted lot of interest because visualization of the brain has been a challenging task and there are hardly any other investigations which can provide an insight of what is going on in the brain. During this period, brain imaging has seen continuous development and today's physician has several alternatives that he can choose for looking inside the brain. Advances in neuro-imaging moved from pneumoencephalography in the thirties to carotid angiography in the fifties. Radionuclide brain scanning was introduced in the late fifties, but it was only after  $^{99}\text{Tc}^m$  was available for clinical studies in the mid-sixties that brain scanning became the most frequent neuro-imaging study. In the early seventies it was largely replaced, specially in developed countries by X-ray computerized tomography (CT). In the eighties nuclear magnetic resonance became another advanced imaging modality competing with and complementing CT. All these developments have been increasingly complex and exorbitantly expensive and usually out of the reach of many of the developing countries.

At one stage on this road to development, radionuclide brain scanning was the only technique available for imaging of the brain. Advent of CT and MRI pushed it to the background. It regained some of the grounds lost to "allied advances" with the introduction of brain perfusion radiopharmaceuticals. Positron emission tomography is a promising functional imaging modality that at present will remain as a research tool in special centres in developed countries. However, clinically useful developments will gradually percolate from PET to SPECT. The non-nuclear imaging methods are totally instrument dependent; they are somewhat like escalators, which can go that far and no further. Nuclear imaging has an unlimited scope for advance because of the new developments in radiopharmaceuticals. As the introduction of a radiopharmaceutical is less costly than buying new instruments, the recent advances in nuclear imaging are gradually perfusing through the developing countries also. Therefore, it is essential to follow very closely PET developments because what is research today might become routine tomorrow.

#### Historical review

In the early part of this century, it was observed that fluorescein crosses the abnormal blood brain barrier (BBB) and localizes in malignant tissues. This discovery was used to detect brain tumours during surgery under ultraviolet light. Later, fluorescein was labelled with  $^{131}\text{I}$  and was used for detecting brain tumours by the help of Geiger-Muller tube.  $^{32}\text{P}$  as sodium phosphate was also utilized to detect brain tumours at surgery.  $^{131}\text{I}$  human serum albumin also behaved in the same way and because of its gamma emission, it can be used for

external counting.  $^{203}\text{Hg}$  (later replaced by  $^{197}\text{Hg}$ ) Neohydrin had better physical and chemical properties.  $^{113}\text{In}^m$  binds to plasma proteins after intravenous injection and was used also to localize brain tumours. Since the mid-sixties  $^{99}\text{Tc}^m$ -pertechnetate became the radiopharmaceutical of choice. It was replaced later by other  $^{99}\text{Tc}^m$  radiopharmaceuticals with more rapid clearance from the blood; namely  $^{99}\text{Tc}^m$ -glucoheptonate (GHP) and  $^{99}\text{Tc}^m$  diethylene triamine penta acetic acid (DTPA).

All the above radiopharmaceuticals had the property of crossing the blood brain barrier (BBB) when there was a pathological lesion in the brain and they always seeped into the focal lesions and not in the normal brain which remains as impervious to radiopharmaceuticals as to new ideas.

In the early eighties, freely diffusible compounds were introduced for the study of cerebral perfusion; first  $^{123}\text{I}$  amphetamine followed by  $^{99}\text{Tc}^m$ -labelled hexamethyl propylene amine oxime (HMPAO). Recently  $^{99}\text{Tc}^m$  ethyl-cysteine dimer (ECD) is under clinical trial.  $^{123}\text{I}$  brain receptor radiopharmaceuticals are currently under development.

These developments of radiopharmaceuticals were *pari passu* with improvements in instrumentation leading to higher sensitivity and better resolution. Of special interest and importance was the development of single photon emission tomography (SPECT). Without SPECT, brain perfusion imaging would not have been possible.

Positron emission tomography advances were also simultaneously on both the fronts: instrumentation and radiopharmaceuticals. The detectors changed from single to multiple gantries, the size of the individual crystals became smaller, electronics and computers improved and accordingly the resolution improved from 16 mm to less than 6 mm, with the hope of having 3 mm in the near future. The radiopharmaceutical developments were remarkable using either  $^{15}\text{O}$  or  $^{13}\text{N}$  Ammonia for brain perfusion measurements,  $^{18}\text{F}$  deoxyglucose for metabolic studies,  $^{18}\text{F}$  spiperone and other numerous drugs for neuro-receptors and pharmacological studies.

### Radiopharmaceuticals for brain imaging

Radiopharmaceuticals used for brain imaging can be classified as:

1. Lipophilic or hydrophilic:

- (a) Hydrophilic compounds cross the abnormal BBB, localize at the pathological site and not in the normal brain tissue.
- (b) Lipophilic compounds cross the normal BBB, localize in the normal brain cells by any of the following mechanisms:

## RADIONUCLIDE BRAIN SCANNING

- (i) active transport for metabolic functions e.g.  $^{18}\text{F}$  deoxyglucose or for neuro-receptor function e.g. dopamine, acetylcholine or opiate receptors.
- (ii) passive transport proportional to blood flow, however, the compound stays in the brain cells due to changes either in the compound structure as with  $^{99}\text{Tc}^{\text{m}}$  HMPAO or because of differences in pH between the intracellular and extracellular compartments as with  $^{123}\text{I}$  HIPDM (hydroxymethyl iodobenzyl propane diamine). Lipophilic compounds will show brain scans which will look opposite to the hydrophilic ones; i.e the normal brain tissue will show no uptake while the pathological site will concentrate the radioactivity. The blood vessels and the venous sinuses will retain activity equal to that of the background activity; i.e reflects the blood clearance.

2. Another way of classifying brain radiopharmaceuticals is according to their metabolic characteristics:

- (a) Those that become protein bound after intravenous injection as  $^{99}\text{Tc}^{\text{m}}$  HSA (human serum albumin),  $^{131}\text{I}$ -HSA,  $^{197}\text{Hg}$ - and  $^{203}\text{Hg}$ -labelled Neohydrin.
- (b) Those that distribute extracellularly as  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate,  $^{99}\text{Tc}^{\text{m}}$ -DTPA and  $^{99}\text{Tc}^{\text{m}}$ -glucoheptonate.
- (c) Those that localize intracellularly as  $^{42}\text{P}$ ,  $^{201}\text{Tl}$  and  $^{84}\text{Rb}$ .

The ideal radiopharmaceutical for brain imaging should have the following characteristics:

- (a) can be easily prepared for direct and safe administration to the patient.
- (b) reasonable cost.
- (c) physical half life of less than 24 hours, preferably 12 hours.
- (d) relatively short effective half life that permits optimum imaging.
- (e) monoenergetic gamma rays from 150 - 250 KeV.
- (f) no particulate radiation in its decay so as to minimize the radiation absorbed dose.
- (g) should have high lesion specificity.

## CHAPTER 20

The following are the characteristics of the commonly used radiopharmaceuticals for brain imaging:

### 1. $^{99}\text{Tc}^{\text{m}}$ pertechnetate:

It is bound to serum proteins, crosses the abnormal BBB, the concentration in the lesion is proportional to its protein content and is variable according to the histology of the lesion. The peak concentration in the lesion may be delayed and this delay may exceed its effective half life, making it difficult to visualize the lesion.  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate is taken up by the choroid plexus. Therefore it is essential to block the choroid plexus by giving potassium perchlorate 400 - 800 milligrams orally at least half hour before intravenous injection of technetium pertechnetate. It is also taken up by the thyroid, gastric mucosa as well as by the salivary glands. Salivary gland uptake is a problem for vertex views of the brain. Salivary and gastric uptake can be blocked by the intravenous injection of one milligram of atropine 15 minutes before intravenous injection of  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate. However, this is not routinely recommended because of the side effects of atropine specially in glaucoma or glaucoma susceptible patients. Technetium pertechnetate has a relatively slower blood clearance than other technetium radiopharmaceuticals. Therefore brain scan images has to be delayed for two hours after the intravenous injection. This delay allows for blood clearance and a lower background activity. Early images after the intravenous injection helps to differentiate vascular from nonvascular lesions when compared with the delayed images.

### 2. $^{99}\text{Tc}^{\text{m}}$ DTPA or glucoheptonate:

Both have faster blood clearance than  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate, therefore both have the advantage of higher target to non-target ratio. Both are not taken by the choroid plexus, thyroid, salivary glands or gastric mucosa. Therefore there is no need for patient preparation by giving oral potassium perchlorate or intravenous atropine. Because of faster clearance, delayed images are usually obtained 30 - 40 minutes for DTPA and 45-60 minutes for glucoheptonate after the intravenous injection.

#### Doses for $^{99}\text{Tc}^{\text{m}}$ radiopharmaceuticals:

For all three  $^{99}\text{Tc}^{\text{m}}$  radiopharmaceuticals the dose is the same:

For children : 200  $\mu\text{Ci}$  per kilogram body weight with a minimum dose of 3 mCi.

For adults: 250 - 300  $\mu\text{Ci}$  per kilogram body weight.

### 3. $^{99}\text{Tc}^{\text{m}}$ Hexamethyl propylene amine oxime (HMPAO):

It is a lipophilic compound, that crosses the normal BBB. The uptake in the normal brain

## RADIONUCLIDE BRAIN SCANNING

is proportional to the blood flow with an extraction efficiency of around 60 % at normal blood flow rates, and a lesser extraction at higher blood flow rates and the reverse at lower flow rates. However in spite of these variations in extraction at different blood flows, it correlates well with PET measurements and is useful for brain perfusion imaging in various neurological disorders. It is supplied in lyophilized kit form. It should be prepared according to manufacturers recommendations using freshly eluted  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate. It must be injected within 20 minutes after preparation. Quality control for labelling efficiency usually takes about that time. Usually it is injected first and quality control results are known after the injection. A delay in injection beyond 20 minutes is not advisable because the compound is changed gradually from a d- isomer to a l-isomer. The l-isomer crosses back to the vascular component in the brain and is not retained by the normal brain tissue. The usual recommended dose is 200 - 250  $\mu\text{Ci}$  per kilogram body weight with a minimum dose of three mCi for children. The start of imaging should be delayed for 20 minutes after the I.V. injection to allow for blood clearance. The compound is cleared by the hepatobiliary system and the kidneys. Recent recommendation is to wait for two hours after the I.V. injection for higher target to non-target ratio.

Normally cerebral perfusion images are most informative with SPECT. Ordinary cerebral images with a planar gamma camera are not much help.

Other lipophilic compounds used for radionuclide brain scanning include:

- (a)  $^{123}\text{I}$  N-Isopropyl amphetamine "IMP"
- (b)  $^{123}\text{I}$  HIPDM
- (c)  $^{201}\text{Tl}$  Diethyl-dimethyl chlorine "DDC".

All three compounds are not suitable for routine clinical use especially in developing countries either because of high cost, short half life of  $^{123}\text{I}$  or the need for in-house labelling of HIPDM or the new ligand DDC. ECD ( d- $^{99}\text{Tc}^{\text{m}}$  ethyl-cysteine dimer) is a new brain perfusion compound that is still currently in phase III clinical trials. It has faster blood clearance and therefore better target to non-target ratio than  $^{99}\text{Tc}^{\text{m}}$  HMPAO.

### Imaging techniques

Review of the patient's clinical history is important in order to optimize the imaging technique. There are general recommendations that have to be observed for the highest quality of images. These include patient preparation, selection of the proper position either anterior, posterior or vertex views for the cerebral flow study, use of high specific activity in the smallest possible volume for intravenous injection which has to be given as a bolus injection, by using Oldendorf technique.

The cerebral angiogram is a dynamic depiction of the intracranial circulation. It is

acquired every one second for digital acquisition and displayed or acquired every 2-3 seconds for analogue formatter. The anterior view is the one most commonly used. In children, the posterior view may be considered in cases of suspected congenital anomalies. The vertex view is used infrequently for lateralisation of the lesions. Computer analysis by generating time activity curves over both carotid and middle cerebral hemispheres may be helpful (Fig. 20.1).

### 1. Static acquisition

Usually four projections are obtained; anterior, posterior, right and left laterals. The anterior view is obtained with the head in flexion in order to see the frontal areas. It is important to exclude facial activity as far as possible without excluding the temporal regions or the occipital lobes so that most of the counts are acquired mainly from the brain area. The total number of counts for the anterior view under these conditions should be at least 500 000 counts, if using  $^{99}\text{Tc}^{\text{m}}$  pertechnetate, 400 000 for  $^{99}\text{Tc}^{\text{m}}$  glucoheptonate and 300 000 for  $^{99}\text{Tc}^{\text{m}}$  DTPA. The time for the total counts for the anterior view should be used as the fixed acquisition time for the other views. Occasionally a vertex view is helpful in localizing the lesions. In this case, shielding of facial and shoulder activity is necessary by using lead apron. Occasionally orbital view is obtained. It is acquired with the head in 30 degrees extension. In children a converging collimator might be helpful, however attention should be given to the geometric disfigurement that it might produce. The converging collimator is of special value in the posterior view to enlarge the posterior fossa. In all other acquisitions, the parallel hole, low energy, preferably high resolution collimator should be used (Fig. 20.2).

### 2. SPECT Acquisition

SPECT imaging has been recognized to be useful for better definition of the lesions in the brain, to separate superficial lesions of the cranial vault from deep seated lesions and for better resolution of lesions in the posterior fossa. In order to improve the resolution for SPECT images the distance between the face of the collimator and the head should be as small as possible. Sometimes the shoulders of the patient limits this positioning. In order to overcome this problem, modifications have been made either in the detector shielding or in the collimators. Developments in the collimators involve either fan beam collimators, slanting holes or long bore collimators (Fig. 20.3).

Quality control of the imaging device is essential before starting any SPECT imaging. Most important procedures are the centre of rotation, field uniformity and stability of the system.

Acquisition recommendations for SPECT are usually as follows: a full circular rotation of 360 degrees, 64 projections, 64 x 64 x 8 matrix, time of acquisition varies according to the radiopharmaceutical used. It varies from 20 - 25 seconds per projection for  $^{99}\text{Tc}^{\text{m}}$  HMPAO and 40 - 45 seconds for  $^{123}\text{I}$  IMP. Usually a high resolution collimator is recommended, if HMPAO or IMP is used. A general purpose collimator will be

## RADIONUCLIDE BRAIN SCANNING

satisfactory, if using  $^{99}\text{Tc}^m$  pertechnetate, glucoheptonate or DTPA. For data processing, images are usually prefiltered and processing parameters varies from instrument to instrument. In general, more smoothing is needed, the lower the number of counts per projection. Usually processed data are displayed in one pixel thick transaxial, sagittal and coronal slices.

### Clinical indications of radionuclide brain scanning

Before the introduction of C.T. on a wide scale in modern hospitals, radionuclide brain imaging constituted a large portion of the workload of nuclear medicine departments. At present, radionuclide brain scanning can be divided into

- (a) old-fashioned type done with  $^{99}\text{Tc}^m$  pertechnetate, DTPA or glucoheptonate and
- (b) the new-fashioned type done with cerebral perfusion compounds like  $^{123}\text{I}$  IMP,  $^{123}\text{I}$  HIPDM or  $^{99}\text{Tc}^m$  HMPAO and, in future,  $^{99}\text{Tc}^m$  ECD.  $^{123}\text{I}$  IMP and HIPDM are not likely to be easily available in the developing countries and currently even in developed countries, they are largely replaced by  $^{99}\text{Tc}^m$  HMPAO. In developing countries, due to the unavailability of CT or MRI imaging, radionuclide brain scanning still plays a substantial role in the investigations of patients, suspected of having brain pathology. For these reasons, this Chapter would mostly describe current applications with  $^{99}\text{Tc}^m$  pertechnetate, DTPA or glucoheptonate and  $^{99}\text{Tc}^m$  HMPAO SPECT studies.

#### 1. Brain tumours

- (a) Gliomas: They arise from primitive glial cells, forms 50 % of all intracranial tumours in adults and children, has a variety of cell types and a wide range of malignancy. The highly malignant astrocytomas (grade III and IV) are characterized by vascularity, edema, and necrosis; rarely spreading outside the brain and is usually fatal within few months. In radionuclide angiogram, these tumours are noted by early vascularity, intense uptake in the arterial phase lasting through the venous phase. The delayed images with  $^{99}\text{Tc}^m$  hydrophilic compounds show avid concentration of the radiopharmaceutical, the speed and intensity of which are proportional to the grade of malignancy, vascularity of the tumour as well as the degree of disruption of the BBB. Other gliomas, especially grade I and II astrocytomas, are not easily detected due to low vascularity and less intense concentration of the radiopharmaceutical. With  $^{99}\text{Tc}^m$  HMPAO, these tumours are usually seen as areas of less concentration (cold areas) of radioactivity. CT and MRI imaging are better suited for the early diagnosis of tumours with low grade malignancy. Their sensitivity varies from 90% - 95% versus 80% - 90% for radionuclide brain scanning.

## CHAPTER 20

- (b) Meningiomas. Meningiomas occur usually in adults, characterized by high vascularity, slow growth, usually located close to the cranium, sometimes accompanied by bone erosion or reactive sclerosis and large superficial draining veins. It is easily diagnosed on the brain scan. It is characterized by intense arterial uptake, progressively increasing and stabilizing in the venous phase and remaining intense in the delayed images (Fig. 20.4).  $^{99}\text{Tc}^{\text{m}}$  cerebral perfusion compounds will show hyperaemia in the angiogram phase that fades away in the delayed images, because of the blood clearance. Perfusion images are not useful in the diagnosis of these patients. Although the sensitivities of CT, MRI and radionuclide brain scanning are equal yet, CT and MRI are preferred for their three dimensional visualization which is helpful in surgical evaluation.
- (c) Metastatic Tumours. They constitute about 25 % of all intracranial tumours. Most common sites for primaries are lungs, breast, prostate, malignant melanomas, kidneys and gastrointestinal tract. They are usually multiple and there are no preferred sites for their location. They are usually fatal within a year but can remain silent for several months. Therefore it is important to look for brain metastasis in asymptomatic patients with high risk for brain metastasis (e.g. small cell type lung carcinoma, breast and kidney malignancies) before contemplating surgery for the primary. The intensity of the uptake of the hydrophilic type of radiopharmaceuticals in the brain scan is variable depending on their size, vascularity, grade of malignancy, rate of growth and the impairment of the BBB. They are usually not detected in the radionuclide angiogram. Brain metastasis in  $^{99}\text{Tc}^{\text{m}}$  HMPAO scans will appear as areas of less radioactive uptake and are not very useful. The sensitivity of  $^{99}\text{Tc}^{\text{m}}$  hydrophilic radiopharmaceuticals for detecting brain metastasis varies from 75 % to 87 % versus 85 to 95 % for X-ray CT or MRI. These figures were reported with planer imaging for the radionuclide procedures. However the sensitivity for SPECT imaging has not been carefully looked at. The resolution of the radionuclide techniques is not expected to be less than one cm, even with SPECT, versus a few millimetres with CT or MRI. The latter would be preferred whenever they are available.
- (d) Other brain tumours such as primary sarcomas, fibrosarcomas or lymphomas are rare. Pituitary tumours, cranial nerve tumours, brain stem gliomas and pinealomas are better diagnosed by CT or MRI. Primary vascular brain tumours as hemangiopericytomas or hemangioblastoma are very rare, and are usually located in the posterior fossa. In these situations also, usually CT or MRI plays a major role in the diagnosis.

Other radionuclides of special interest for radionuclide imaging of brain tumours and metastasis are  $^{67}\text{Ga}$  citrate and  $^{201}\text{Tl}$ . Gallium is non-specific because it cannot differentiate between tumour tissue and infection. Thallium on the other hand is specific because in our experience it is taken up by viable tumour tissue and not by acute inflammatory lesions. Chronic granulomatous lesions such as tuberculosis might take up  $^{201}\text{Tl}$ . However the intensity of uptake will be much less than tumour uptake. Recent approach of quantitating

## RADIONUCLIDE BRAIN SCANNING

thallium uptake in brain tumours has shown that the ratio of uptake in the tumour to the contralateral normal side is proportional to the grade of malignancy of the tumour and might reflect the prognosis and the future behaviour of the tumour.  $^{201}\text{Tl}$  imaging for brain tumours is also helpful in differentiating recurrent tumour from tumour necrosis or post-operative changes. In this regard it might be superior and, at least, supportive to CT and MRI.

### 2. Cerebrovascular disorders

- (a) Cerebrovascular occlusion. It has a complex pathogenesis; thrombosis is the cause in 70% of the cases, embolism and haemorrhage being less common. It leads to cerebral hypoxia which might be poorly recognized in the early phase of the disease. Cerebrovascular disease can manifest as episodes of transient ischemic attacks (TIA) due to microembolism from fragile atheromas mostly in the carotid or vertebral arteries in the neck or base of the skull. These ischemic episodes might vary in severity from transient unconsciousness to complete hemiparesis. The symptoms are variable according to the branches involved; which might be motor, sensory, visual or auditory in nature. In other words, signs and symptoms depend on the artery involved, location and type of occlusion and extent of brain damage.

The sequence of events in ischemic infarct is characterized by initial central necrosis with perivascular engorgement and local edema. During this period, which lasts for 10 - 14 days, the brain scan is normal, although the radionuclide cerebral angiogram might show an area of decreased perfusion in the arterial, capillary and venous phases. After the third week, there is increased focal uptake in the  $^{99}\text{Tc}^{\text{m}}$  pertechnetate, DTPA or the glucoheptonate brain scan. This increased uptake plateaus in three to four weeks and decreases gradually to normal in six to eight weeks. If the developments of collaterals is inadequate, this increased uptake might persist up to one year. In such a case, it might be difficult to differentiate cerebral infarct from brain tumour. However, an infarct can be recognized by lack of growth, its location in the territory of a vessel and its usual flame like shape with irregular margins. The earlier the resolution of this uptake, the better is the prognosis. If there is an abnormal brain scan in one to seven days, it is usually due to emboli leading to haemorrhagic infarct. It is postulated that sometimes in embolic infarct, the embolus becomes fragmented and the blood flow can pass through the site of the obstruction into the ischemic infarct. Infarcts of the brain stem, internal capsule and basal ganglia are difficult to visualize on the  $^{99}\text{Tc}^{\text{m}}$  pertechnetate brain scan.

The radionuclide angiogram is very important and should always be done whenever there is a suspicion of vascular abnormality. It is important to decide before the study which positioning will be most informative depending on where the lesion is suspected. In 75% of the cases the anterior position is most useful because the middle or the anterior cerebral branches and their territories are commonly

## CHAPTER 20

involved. If there is suspicion that posterior cerebral or the vertebral artery is involved, the posterior view should be used.

During the first week of the incident, the radionuclide angiogram will show ischemic area with normal brain image in the delayed scans. After the first week, the brain scan will show what is called as the "flip flop" appearance, i.e early ischemia at the side of the infarct followed by delayed venous washout and increased uptake in the later part of the angiogram and in the delayed images.

$^{99}\text{Tc}^{\text{m}}$  bone seeking radiopharmaceuticals are known to show positive uptake in the area of the infarct. This is helpful in differentiating infarct from other lesions. The mechanism of this uptake is not clear. It may be due to avidity of these compounds for necrotic tissues.

The radionuclide cerebral angiogram and the brain scan correlate well with CT, clinical findings and remain to be cost effective. However there is delay of days or weeks before both of them become positive. The brain scan takes at least seven days while the CT shows changes in affected tissues after 48 hours. On the other hand radionuclide brain scanning with brain perfusion radiopharmaceuticals as  $^{99}\text{Tc}^{\text{m}}$  HMPAO or  $^{123}\text{I}$  IMP have higher sensitivity for detecting changes in perfusion early after cerebrovascular accident (CVA).

During the first 24 hours brain scanning with  $^{99}\text{Tc}^{\text{m}}$  HMPAO is POSITIVE in 95% of the cases in defining the location of the occlusion versus 70 - 75% with CT (Fig. 20.5). There is a definite advantage with the radionuclide brain studies with  $^{99}\text{Tc}^{\text{m}}$  HMPAO, HIPDM or  $^{123}\text{I}$  IMP over CT or MRI in transient ischemic attacks in defining the degree of stenosis and the status of the collaterals in symptomatic patients and in deciding whether they can benefit from surgical treatment of establishing communication between the external and the internal carotid circulation. Further information in this respect can be obtained by doing semiquantitative cerebral perfusion studies before and after intravenous administration of Diamox, a drug which produces vasodilatation of the normal intracranial vessels. Atheromatous vessels show a lesser or no response to this drug.

### (b) Cerebral haemorrhage

- (i) **Intracranial haemorrhage:** It can be due to trauma, ruptured aneurysm, inflammatory vascular lesions, A-V malformations, tumours or blood dyscrasia. The signs and symptoms are variable according to the extent, location and underlying pathological state. The brain scan is usually normal in the early images but abnormal in the delayed images. Radionuclide brain scanning with cerebral perfusion compounds, on the other hand, is positive right from the early phase. The lesion is seen as an area of decreased

## RADIONUCLIDE BRAIN SCANNING

perfusion. In addition it has the advantage over X-ray and MRI of showing the extent of associated vascular spasm in the neighbouring territory which is usually predominant in the early period. This information might be of value in the management and prognosis of the patient.

- (ii) **Subarachnoid haemorrhage:** The most common cause is rupture of an arterial berry aneurysm. It is usually diagnosed by cautious lumbar puncture, contrast angiogram and CT. Blood in the subarachnoid space leads to arterial spasm which may persist up to three weeks and might lead to cerebral infarct. Therefore it is important to do a brain scan using  $^{99}\text{Tc}^{\text{m}}$  HMPAO in order to determine the time for surgical intervention, if needed. The regular radionuclide brain scan with  $^{99}\text{Tc}^{\text{m}}$  pertechnetate is of little value in these patients.
- (iii) **Arteriovenous Malformations:** A-V malformations are usually congenital or acquired, can be single or multiple, usually located in the cerebral cortex and have a tendency to bleed and/or calcify. Clinically they produce focal seizures. They are easily diagnosed by CT with contrast enhancement or by MRI. The radionuclide angiogram is characteristic with increase in the arterial phase which decreases in the venous phase. This differentiates them from meningiomas which are usually superficial in location and which show in the angiogram increased arterial phase with further increase in the venous phase. The brain scan shows increased activity in the early part within minutes after the injection of the radiopharmaceutical. It becomes faint or almost absent in the delayed scan taken two hours after the injection (Fig. 20.6).

### 3. Verification of brain death

With the current progress in organ transplant and with the possibility of maintaining unconscious patients on life sustaining equipment for long periods of time, there is need for an accurate diagnosis of acute brain death. There are several requirements laid down for this in the American and the European practice. Among these is a proof of absent intracranial circulation. This could be done by either a contrast angiogram which is an invasive procedure and has several risks. The radionuclide angiogram is a valid alternative that is non-invasive. It can be done with a mobile gamma camera at the bedside.  $^{99}\text{Tc}^{\text{m}}$ -pertechnetate is the radiopharmaceutical most commonly used for this. The success of the test depends on injection of a good bolus with total dose in as small a volume as possible injected according to Oldendorf's technique. If for any reason, the injection is not proper or there is a failure in acquisition of the angiogram due to camera or computer failure, the physician can still rely on the delayed images of the brain scan which show absence of radioactivity in the venous sinuses. However delayed images might show slight radioactivity in these sinuses due to communication between the extracranial and the intracranial venous circulation through the communicating diploic venous channels through the cranial vault.

## CHAPTER 20

Some investigators recommend the use of a tourniquet over the scalp to suppress such a communication between these two circulations.

In our experience,  $^{99}\text{Tc}^{\text{m}}$  HMPAO provides more accurate information for this purpose and should replace  $^{99}\text{Tc}^{\text{m}}$  pertechnetate. Normally  $^{99}\text{Tc}^{\text{m}}$  HMPAO is taken up by the normal brain tissue, if there is any intracranial circulation, no matter how diminished it is. If there is no intracranial circulation there will be NO activity inside the calvarium in the brain. There is no need for the angiographic phase of the study. If a mobile gamma camera is available, static images can be obtained at the bed side. There is no need for SPECT images. The study is very easy to interpret. If there is no activity inside the cranial vault in the brain tissue, the diagnosis of brain death can be safely made. If there is any activity seen in the brain, it would be advisable to avoid the diagnosis of brain death in spite of other clinical evidences. The study can be repeated whenever death is suspected later.

### 4. Intracranial infections

Intracranial infections such as brain abscess, ventriculitis or specific infections as tuberculosis or coccidiomycosis are usually diagnosed by CT or MRI. The role of the radionuclide brain scan is very limited.  $^{99}\text{Tc}^{\text{m}}$  pertechnetate brain scan will show areas of increased uptake in the delayed images in the lesion. In ventriculitis, it will take the shape of the ventricles. In other diseases, it could be solitary or multiple. There is no role for cerebral perfusion brain scan in these entities. A gallium scan will show increased uptake in the areas involved although it is rarely necessary.

In the following five conditions of encephalitis, epilepsy, dementia, psychological disorders and acute head injury there is no role for the radionuclide brain scan with  $^{99}\text{Tc}^{\text{m}}$  pertechnetate, DTPA or glucoheptonate. Brain scanning with cerebral perfusion compounds plays an important role and is more sensitive than CT or MRI in delineating the location of damage to the brain. Its role in acute head injury is supplementary to CT and is superior to it specially in the first 24 - 48 hours.

### 5. Encephalitis

Herpes encephalitis is difficult to diagnose. The only definitive test for its diagnosis is brain biopsy. The clinical picture is usually confusing. Peripheral blood picture, lumbar puncture and CT are usually normal. The cerebral perfusion brain scan with  $^{99}\text{Tc}^{\text{m}}$  HMPAO is characterized by marked hyperaemia of the involved part of the brain. The intensity of uptake is usually so high in the early part of the disease that it can be easily seen on planer images and there is no need for SPECT images. The intensity of uptake subsides with the regression of the disease or with successful treatment. Therefore it is essential to do the test as soon as possible once the diagnosis is suspected. Follow up scans will help in evaluating the regression of the disease (Fig. 20.7).

## RADIONUCLIDE BRAIN SCANNING

### 6. Dementia

The differentiation of senile dementia from multi-infarct dementia, Alzheimer disease or other psychological disorders or depression is important for early diagnosis, management planning and medicolegal advice. Certain types of dementia are characterized by special pattern on the positron emission tomography scans using either  $^{18}\text{F}$  deoxyglucose,  $^{13}\text{N}$  ammonia or labelled receptors.  $^{99}\text{Tc}^{\text{m}}$  HMPAO or  $^{123}\text{I}$  IMP cerebral perfusion scans are comparable to PET scans, easier to perform and likely to be available in many developing countries. Multi-infarct dementia is characterized by multiple small areas of decreased perfusion scattered over the cerebral cortex with no preference between the frontal or parietal lobes. Occasionally areas of luxury perfusion are detected. These are related to the possible etiology of this disease as infarcts due to micro-emboli followed within few days by luxury collateral circulation. The areas of luxury perfusion show as areas of increased perfusion sometimes detected at the periphery of small areas of decreased perfusion. They are usually transient and clears within few weeks.

Alzheimer disease has a characteristic pattern of bilateral symmetrical areas of decreased perfusion involving both temporal and parietal lobes. It rarely affects the frontal lobe.

Depression is characterized by decreased perfusion of the frontal lobes. This pattern is reversible with successful treatment.

### 7. Psychological disorders

PET studies have proved helpful for identifying certain abnormalities in glucose metabolism, neuro-receptors and cerebral perfusion in some psychological and neurological disorders. Recent developments were able to label some dopamine receptors with  $^{123}\text{I}$ . It is too early to evaluate the results with them. Cerebral perfusion studies with  $^{99}\text{Tc}^{\text{m}}$  HMPAO have been reported to be comparable to those acquired by PET radiopharmaceuticals in patients with schizophrenia, drug abuse, and other psychological disorders. We have shown that schizophrenia is accompanied by increased perfusion to the basal ganglia, usually bilateral in the majority of the cases. There is also associated ventricular dilatation in more than half of the cases. Areas of decreased perfusion due to cerebral damage have also been recognized and are thought to be secondary to electro-convulsive therapy.

In other centres cerebral perfusion studies done in association with and without psychometric testing had shown that  $^{99}\text{Tc}^{\text{m}}$  HMPAO is a reliable and reproducible test for monitoring cerebral perfusion changes and effect of treatment in many psychological disorders.

### 8. Epilepsy

Epilepsy is a complex disorder, which could be primary or secondary to brain damage due to intracranial trauma or infection. Certain types are resistant to medical treatment and requires surgical approaches. In these cases it is essential to localize accurately the focus of

epilepsy and to confirm it by more than one test in order to plan the right surgical approach. CT and MRI as well electroencephalogram have low sensitivity varying between 25-35%. Invasive electrode electroencephalographic monitoring is the most accurate technique. PET studies with  $^{18}\text{F}$  deoxyglucose proved to correlate well with invasive EEC in more than 90% of the occasions. Cerebral perfusion studies with  $^{99}\text{Tc}^{\text{m}}$  HMPAO also proved to correlate well with PET studies. Areas of increased or decreased perfusion correlated well with areas of increased or decreased glucose uptake.

The findings in epilepsy of changes in cerebral perfusion depends on the timing of the injection, whether in the interictal or in the preictal or in the ictal phase. In the interictal phase, the area of the epileptic focus is usually recognized as an area of decreased perfusion, rarely as an area of increased perfusion. If the injection is made in the preictal or in the ictal phase, the area of the focus of the epilepsy is characterized by increased perfusion (Fig. 20.8).

### 9. Head injury

Previously  $^{99}\text{Tc}^{\text{m}}$  was frequently used for the diagnosis of subdural haematoma following head injury. This indication has decreased after the use of CT. This is mainly because there is a delay of seven to ten days before a brain image shows an appearance characteristic of subdural haematoma. A membrane has to form around the haematoma which eventually shows increased uptake of the radiopharmaceutical in the delayed static images. The usual location of the haemorrhage is on the surface of the brain. The flow study shows an area of decreased flow on the surface of the brain with a concavity to the outside.

Acute head injury is currently considered as the most important clinical indication for cerebral perfusion imaging using  $^{99}\text{Tc}^{\text{m}}$  HMPAO especially in the immediate period following the trauma. It has also proved very helpful in the follow up in defining residual damage to the brain. Soon after the trauma when the patient is in coma with more than one medical and surgical problems, the most important question facing the physician is the assessment of the damage to the brain and based on that, what is the prognosis of the patient.

Changes in cerebral perfusion could be focal or non-focal. Non-focal lesions have diffuse decreased perfusion, or asymmetric perfusion between right and left cerebral hemispheres or decreased fronto-occipital slope. Normally the frontal lobes should have an equal or greater perfusion than the occipital lobes. Reversal of the fronto-occipital ratio is noticed in cases of increased intracranial pressure. Diffuse decreased cerebral perfusion is presumably due to diffuse axonal injury due to the sudden deceleration induced by the trauma. Focal lesions are usually due to cerebral contusion, cerebral haemorrhage or pressure from a haematoma on the surface due to subdural haemorrhage or fracture. Subarachnoid haemorrhage causes diffuse spasm with big focal defects. Usually the defects are those of decreased perfusion. The lesions might vary in size. The small lesions are less than half the size of one cerebral lobe, and the larger are bigger than the size of half a cerebral lobe. These lesions can involve any part of the cerebral hemisphere but rarely the cerebellum.

## RADIONUCLIDE BRAIN SCANNING

In addition to the focal and non-focal lesions trauma can induce surface or meningeal lesions. These can be detected on the brain scan, on the surface of the brain and causing pressure on the underlying cerebral cortex. Non-focal lesions usually resolve and bear good prognosis. The prognosis of focal lesions depends on their location, size and number. Brain stem, cerebellar, temporal and parietal lesions have worse prognosis than frontal or occipital lesions. Obviously the smaller the number and the size of the lesions, the better the prognosis. There is no relation between the period of coma, the nature of the lesions and the time of recovery.

### Radionuclide cisternography

The study of the pathophysiological changes in the pathways of the cerebrospinal fluid (CSF) is possible by injection of a radiotracer in the subarachnoid space. Normally the CSF is produced from the choroid plexuses in the lateral and third ventricles. It is transported probably by vascular pulsations to the fourth ventricle. Through foramina of Luschka and Magendi, it passes to the subarachnoid space in the posterior fossa. It ascends over both sides of the cerebral hemispheres along the Sylvian fissures to the vertex of the brain where it is absorbed by the arachnoid villi to the venous circulation. In the spinal cord, there is a two directional flow of CSF, downwards and upwards. There is a balance between CSF production and absorption. Any obstruction in the flow of the CSF will cause proximal dilatation and stasis.

Radiopharmaceuticals used to study CSF flow should have special characteristics. They should not be irritant to central nervous system (CNS) membranes. They should not be proteins which can cause reactions. The physical half life of this isotope should be long enough to continue the study up to three or four days. It should not be absorbed from the subarachnoid space but should be absorbed from the arachnoid villi. Once it is in the venous circulation, it is excreted by the kidneys. In the early days,  $^{131}\text{I}$  Human Serum albumin was used. It did cause occasional reactions in the meninges producing signs of meningism. At present,  $^{169}\text{Yb}$  ( $T_{1/2}$  32 days), and  $^{111}\text{In}$  ( $T_{1/2}$  28 days) DTPA are the radiopharmaceuticals of choice.

Current indications for Radionuclide Cisternography are the following:

- (a) Differentiating obstructive from communicating hydrocephalus.
- (b) Diagnosis of CSF leak from the nose, sphenoidal or middle ear regions.

For these indications, the radiopharmaceutical is injected in the subarachnoid space at the level between L2-3 vertebrae. Images are taken immediately after the injection to verify the accuracy of injection. Planar images are taken of the head - posterior, anterior and both laterals - at 2-6, 24, 48 and 72 hours. Tomographic images give better resolution and definition of sites of radionuclide accumulation.

## CHAPTER 20

In cases of CSF leak, the placement of a cotton swab for several hours in the nose or ear on the side of suspected leak and subsequent counting of the swab increases the accuracy of the detection of the CSF leak (Fig. 20.9).

Although contrast dynamic X-ray CT cisternography is competing with radionuclide cisternography, it is more difficult to do and interpret and not suitable for use in developing countries for the detection of the leak.

- (c) evaluation of patency of CSF shunts by direct injection in the tube or in the ventricle and dynamic imaging every few seconds for the shunt and the site of drainage in the peritoneal, pleural or venous sites.

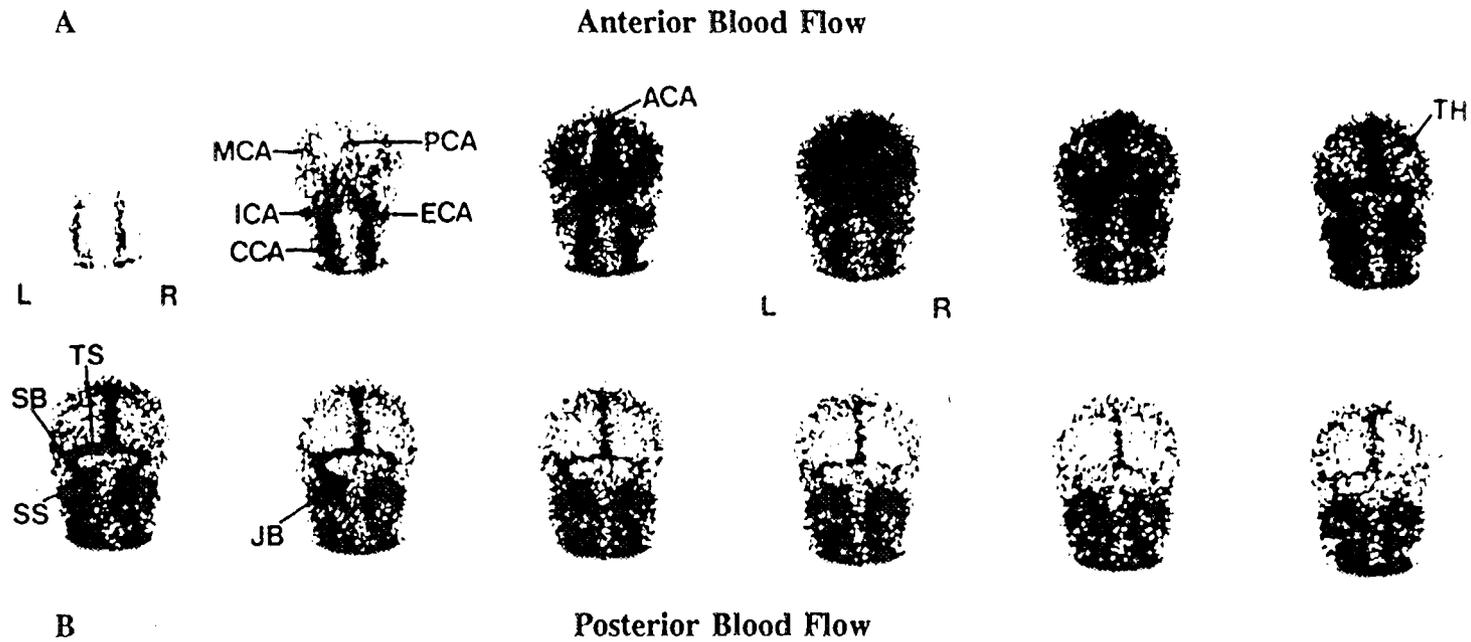
The role of radionuclide cisternography to evaluate congenital anomalies in the CSF flow is now completely taken over by X-ray CT and MRI.

We have not covered in this chapter a number of items such as quantitation of cerebral perfusion studies, the use of  $^{133}\text{Xe}$  gas etc. Further readings in these areas are recommended.

## RADIONUCLIDE BRAIN SCANNING

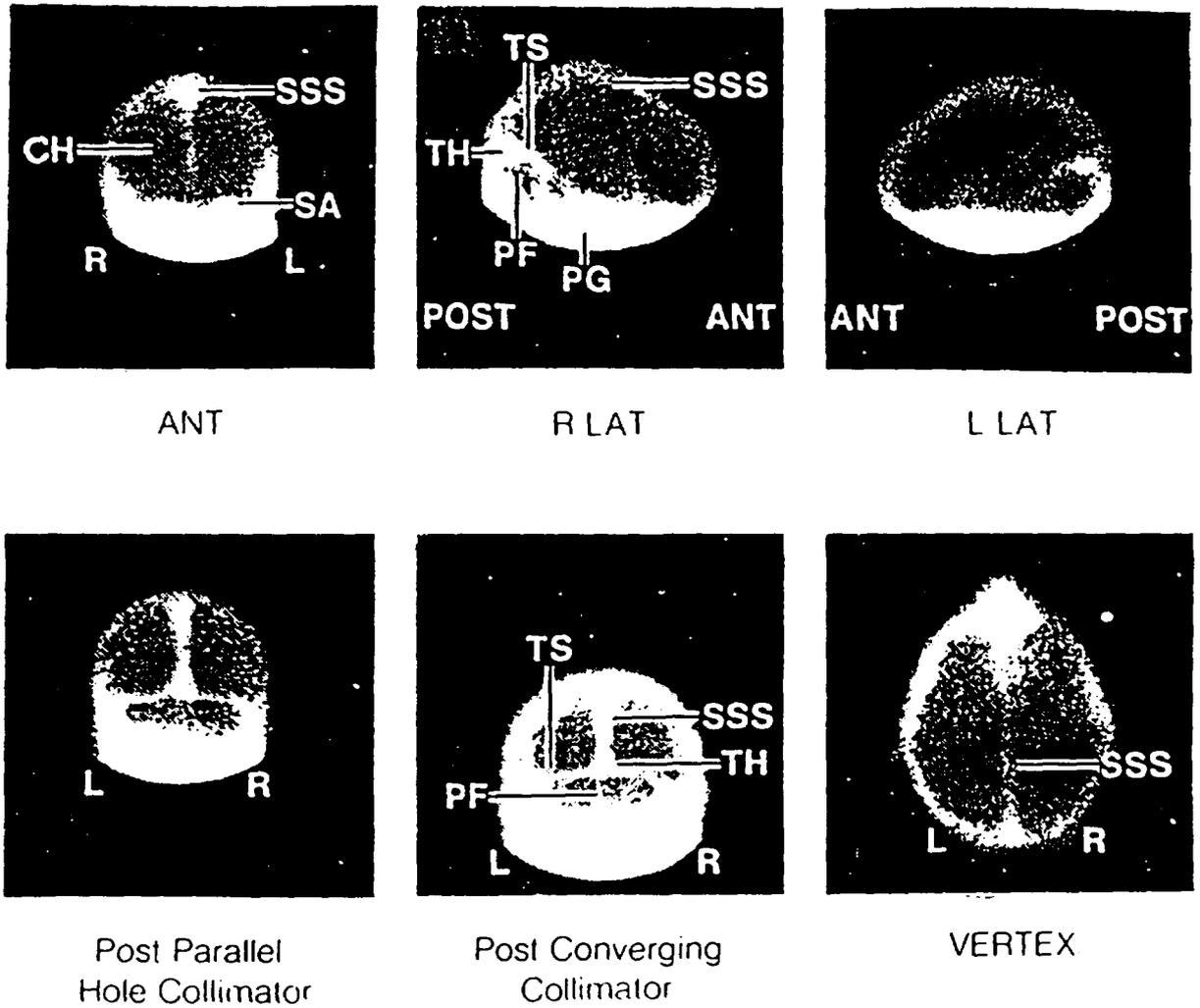
### SUGGESTED READING.

- [1] ROLLO, F.D., CAVALIERI, R.R., BORN, M., BLEI, L., CHEW, M., Comparative evaluation of brain imaging agents, *Radiology*, 123 (1977) 379.
- [2] TETALMAN, M.R., DEUTCHMAN, A.H., SCHEU, J., OLSEN, J., CHILES, J., The optimal pharmaceutical for brain imaging, *J. Nucl. Med.* 19 (1978) 673.
- [3] HOLMAN, B.L., LEE, R.G.L., HILL, T.C., LOVETT, R.D., LISTER-JAMES, J., A comparison of two cerebral perfusion tracers. N-isopropyl <sup>123</sup>I p-iodoamphetamine and <sup>123</sup>I HIPDM, in the human. *J. Nucl. Med.* 25 (1984) 25.
- [4] BONTE, F.J., STOKELY, E.M., Single-photon tomographic study of regional cerebral blood flow in stroke, *J. Nucl. Med.* 22 (1981) 1049.
- [5] BUDINGER, T.F., Revival of clinical nuclear medicine brain imaging. *J. Nucl. Med.* 22 (1981) 1094.
- [6] SCHWARTZ, J.A., BAXTER, J., BRILL, D., BURNS, J.R., Radionuclide cerebral imaging confirming brain death, *JAMA* 249 (1983) 246.
- [7] BIERSACK, H.J., GRUNWALD, F., REICHMAN K., Functional Brain Imaging with Single-Photon Emission Computed Tomography Using <sup>99m</sup>Tc-labelled HM-PAO, *Nucl. Med. Annual*, FREEMAN, L.M., ed. Raven Press, Ltd. New York (1990).



**Fig. 20.1** Radionuclide cerebral angiogram (Posterior View) arterial, capillary and venous phases are seen in sequence. CCA - common carotid artery, ICA - internal carotid artery, ECA - external carotid artery, MCA - middle cerebral artery, PCA - posterior cerebral artery, ACA - anterior cerebral artery, TS - Transverse Sinus, SS - Sigmoid Sinus, JB - jugular bulb.

RADIONUCLIDE BRAIN SCANNING



**Fig. 20.2** Static Brain Scintigram. Normal. CH - cerebral hemispheres, SSS - superior sagittal sinus, SA - supraciliary arch, TS - Transverse Sinus. TH - Tropic of Herophili, PF - posterior fossa, PG - parotid gland.

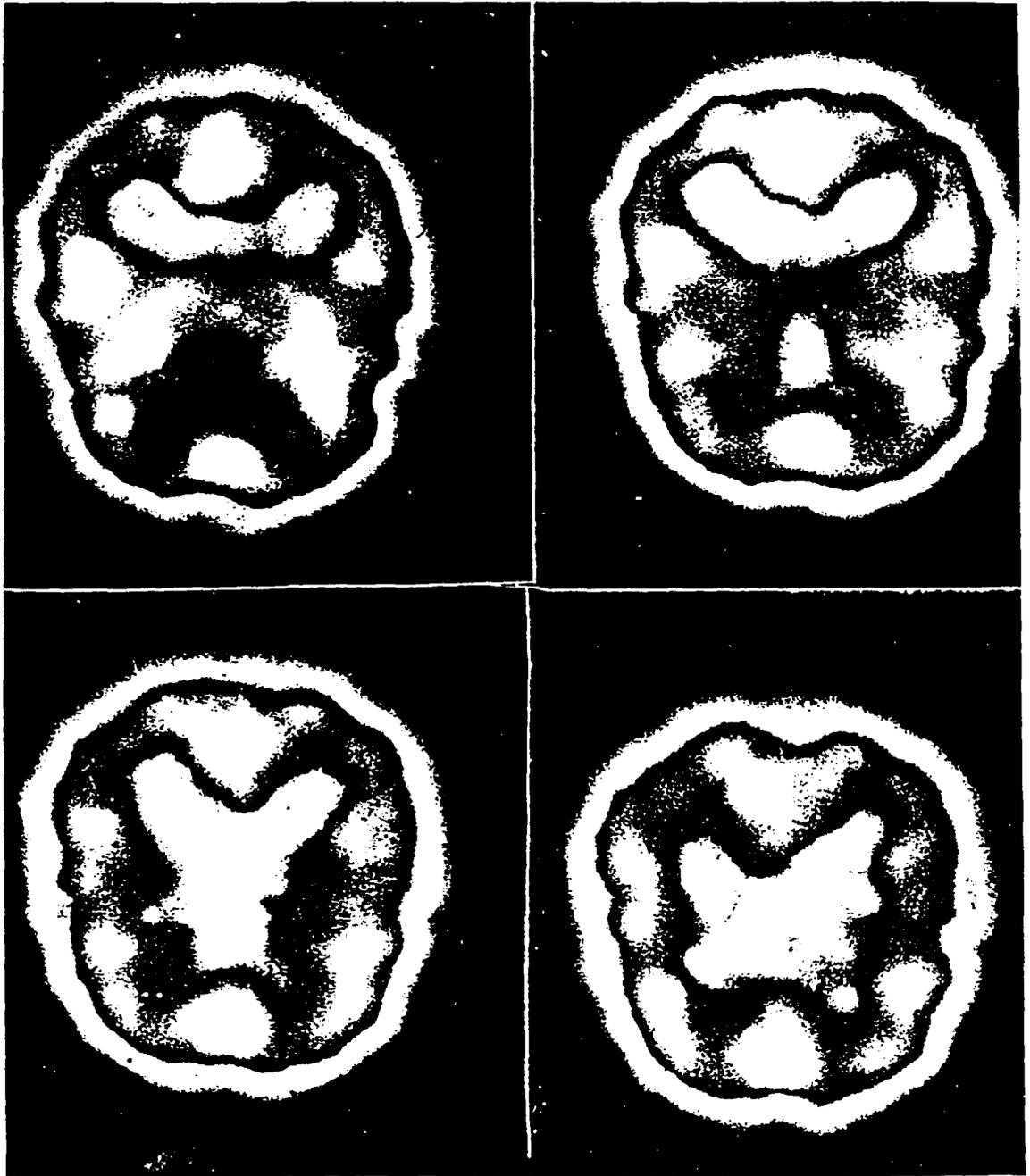


Fig. 20.3 A. shows normal HMPAO  $^{99m}\text{Tc}$  SPECT STUDY in Transaxial,  $^{99m}\text{Tc}$  HMPAO, and separation of grey matter and white matter perfusion.

RADIONUCLIDE BRAIN SCANNING

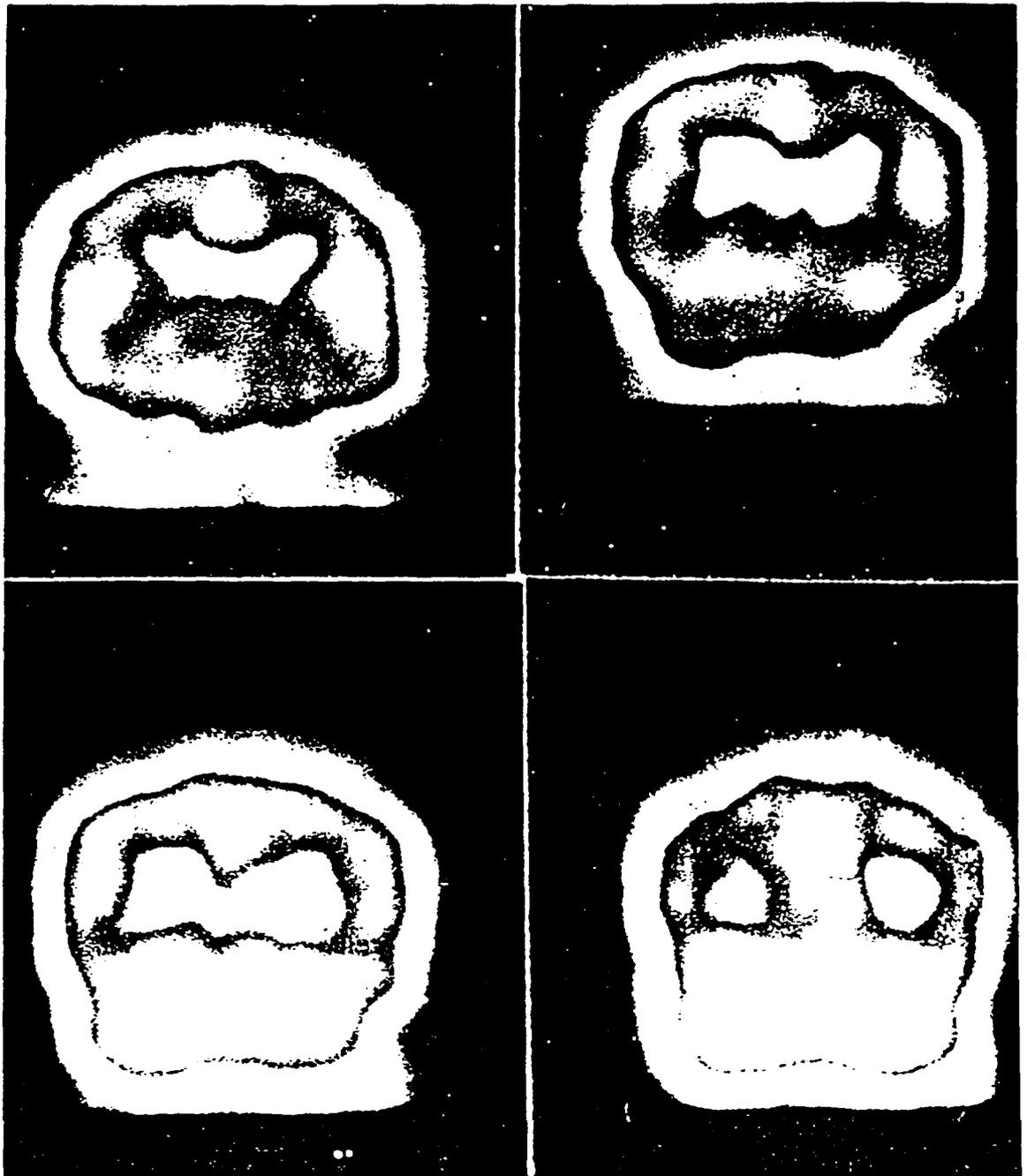


Fig. 20.3 B. shows normal HMPAO  $^{99m}\text{Tc}$  SPECT STUDY in Coronal sections. Note homogenous distribution of  $^{99m}\text{Tc}$  HMPAO, and separation of grey matter and white matter perfusion.

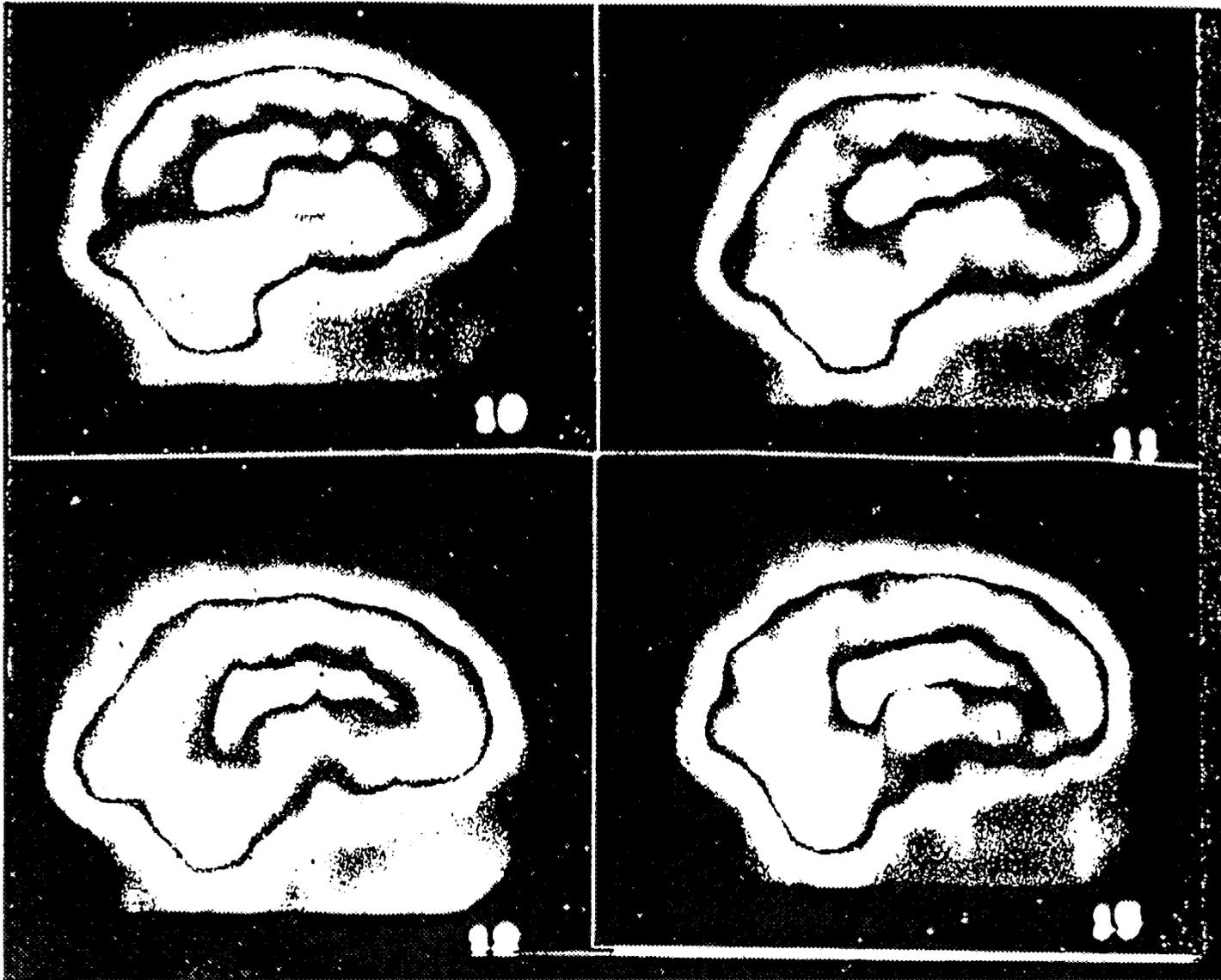


Fig. 20.3 C. shows normal HMPAO  $^{99m}\text{Tc}$  SPECT STUDY in Sagittal sections. Note homogenous distribution of  $^{99m}\text{Tc}$  HMPAO, and separation of grey matter and white matter perfusion.

RADIONUCLIDE BRAIN SCANNING

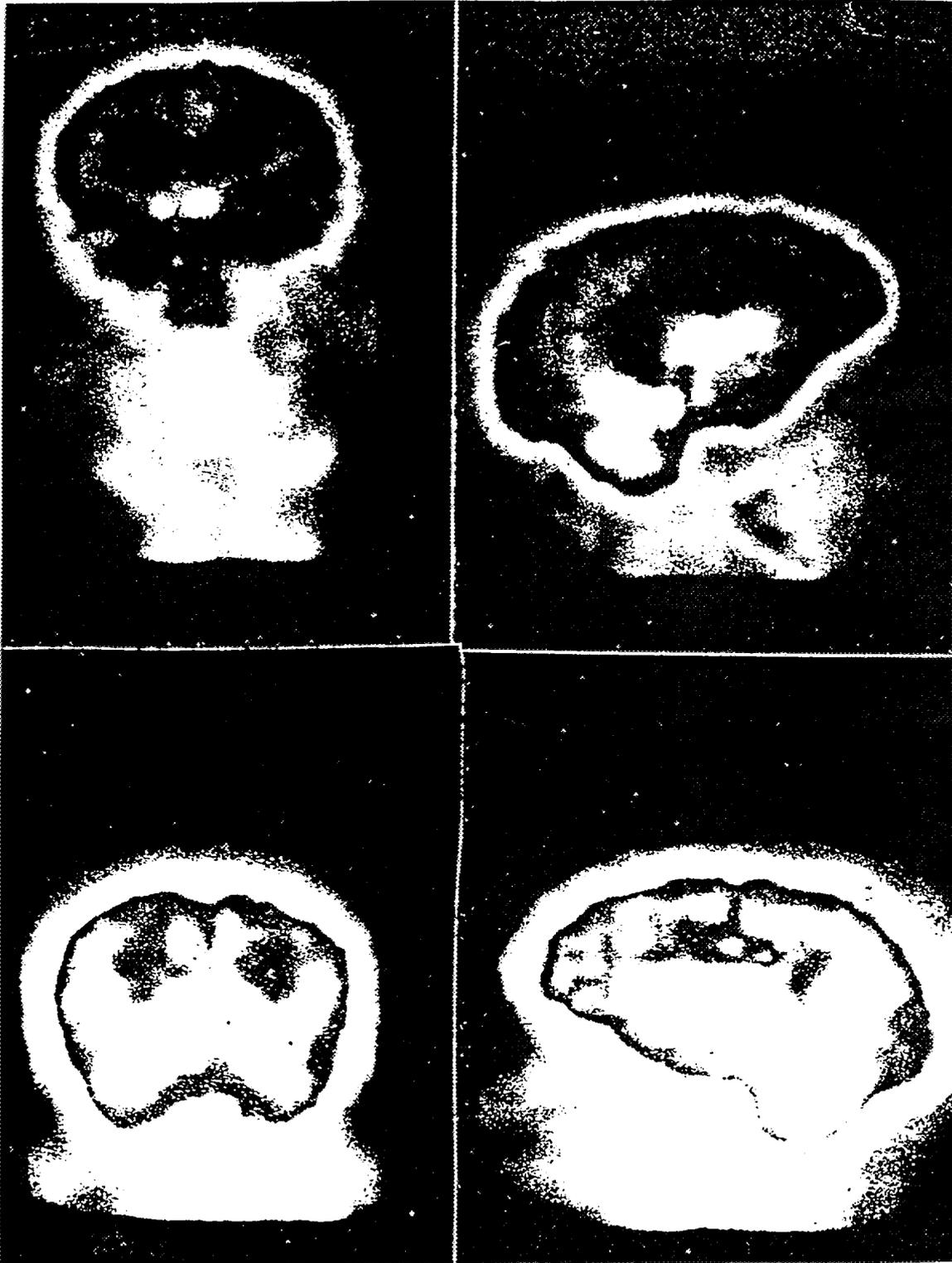


Fig. 20.3 D. shows normal  $^{99m}\text{Tc}$  HMPAO Planar study for comparison. Clockwise are Anterior, RL, LL and posterior views.

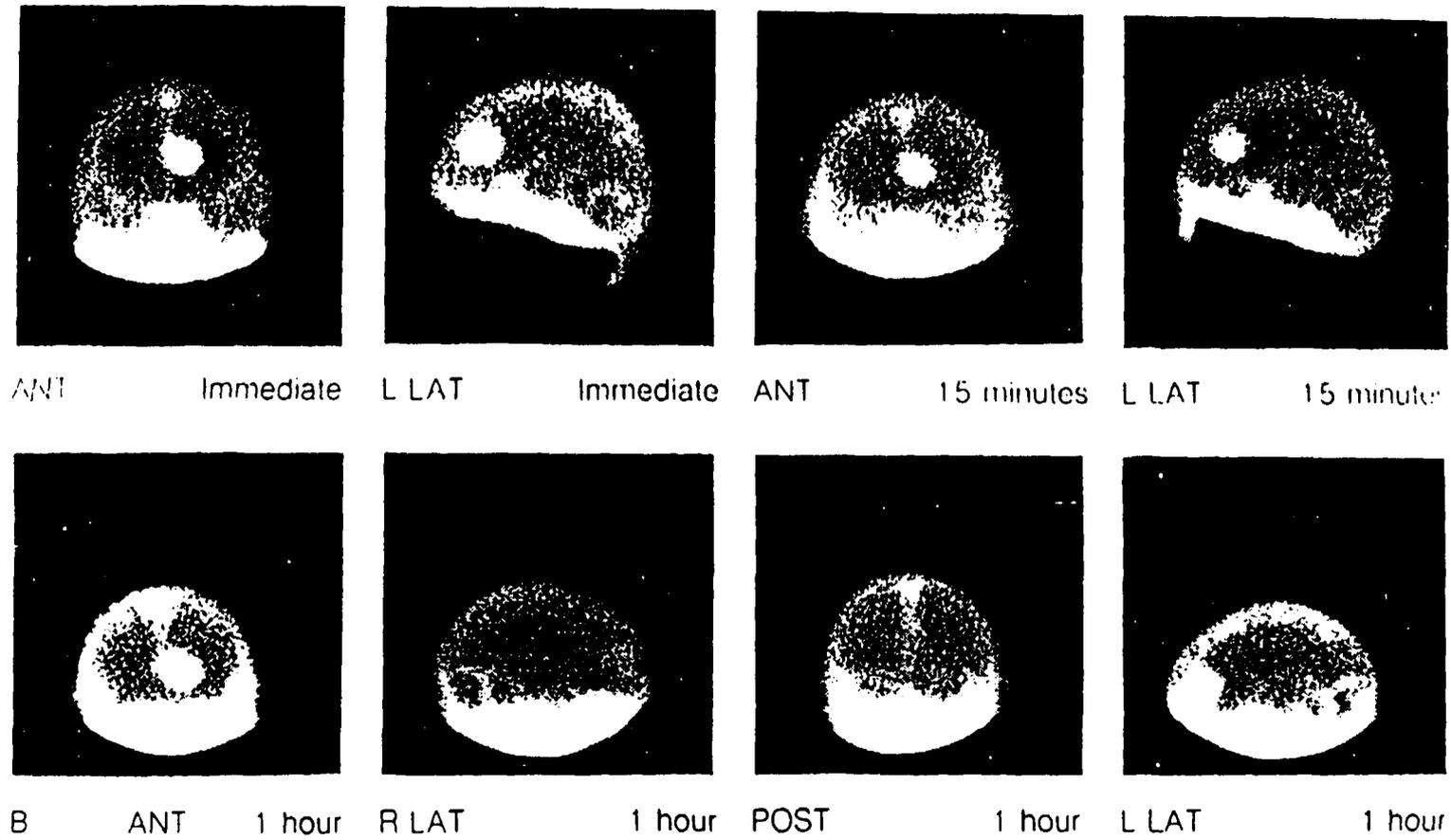


Fig. 20.4 Serial Scintigram: Para sagittal meningioma showing intense early radionuclide uptake which remains in delayed images also.

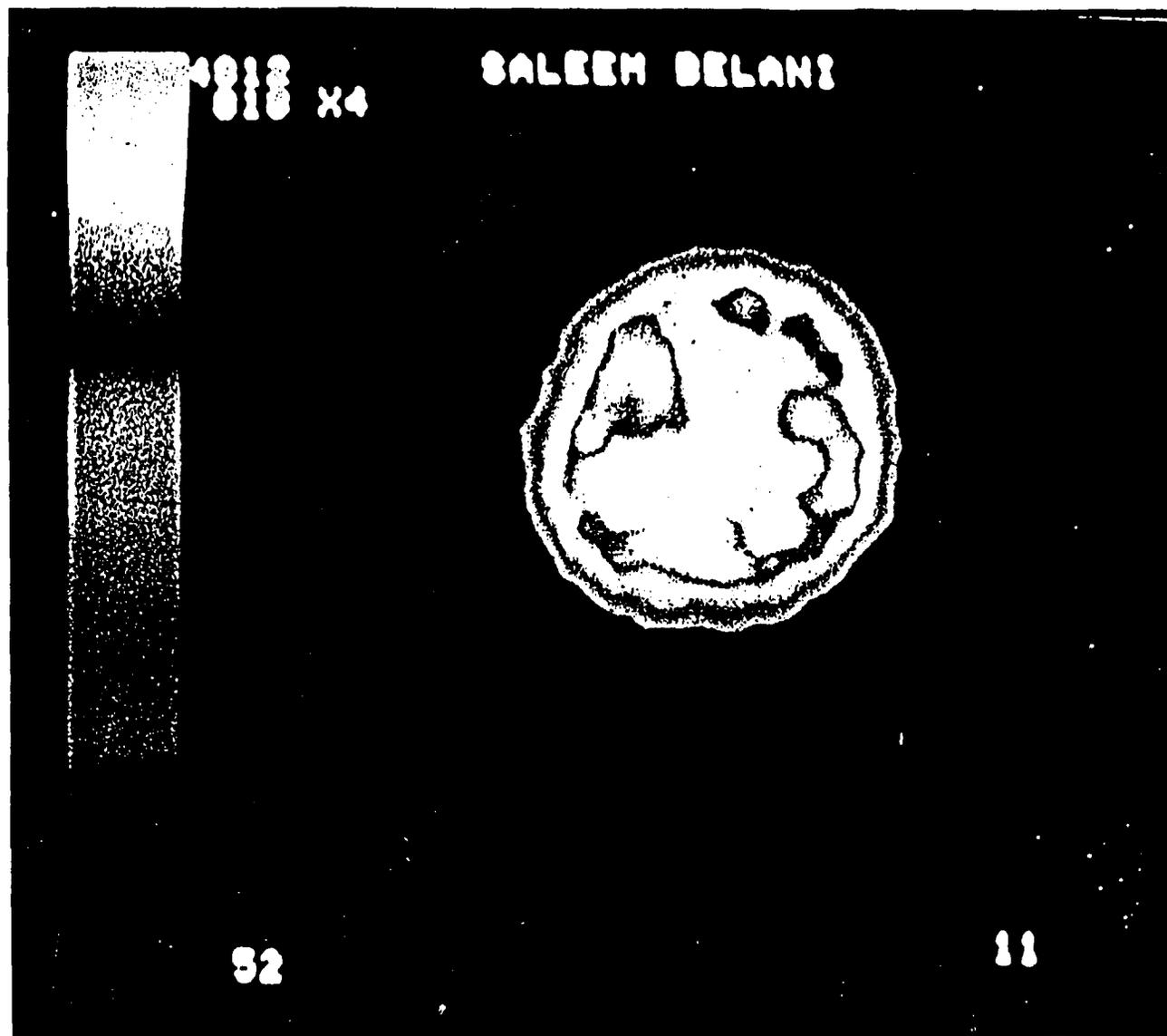


Fig. 20.5  $^{99}\text{Tc}^m$  HMPAO SPECT study showing diminished perfusion in the region of internal capsule on the left-side. CT scan was normal. Patient had sudden onset right sided hemiplegia.

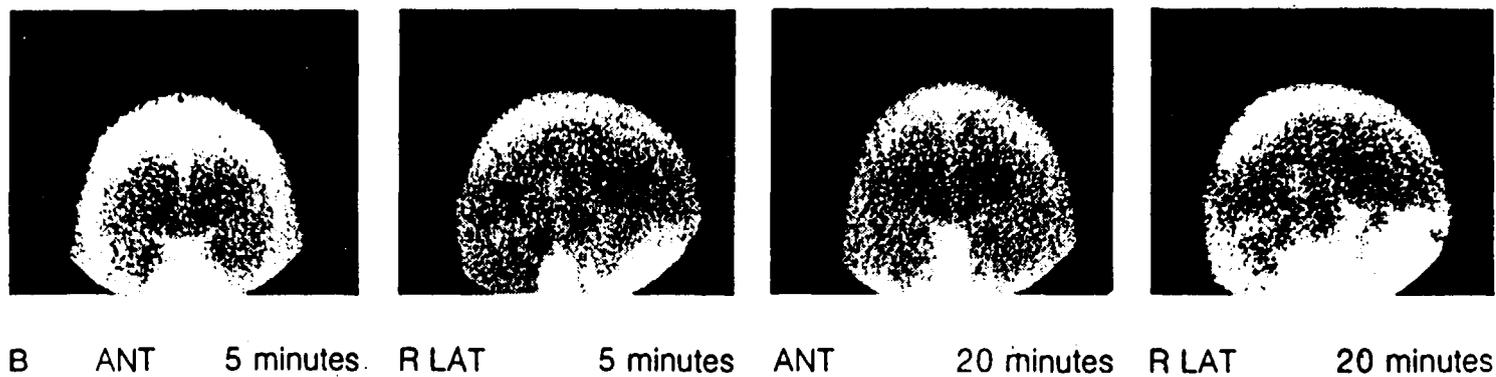


Fig. 20.6 Serial Scintigram. AV malformation Rightside, better seen in the early image (arrows) than in delayed images.

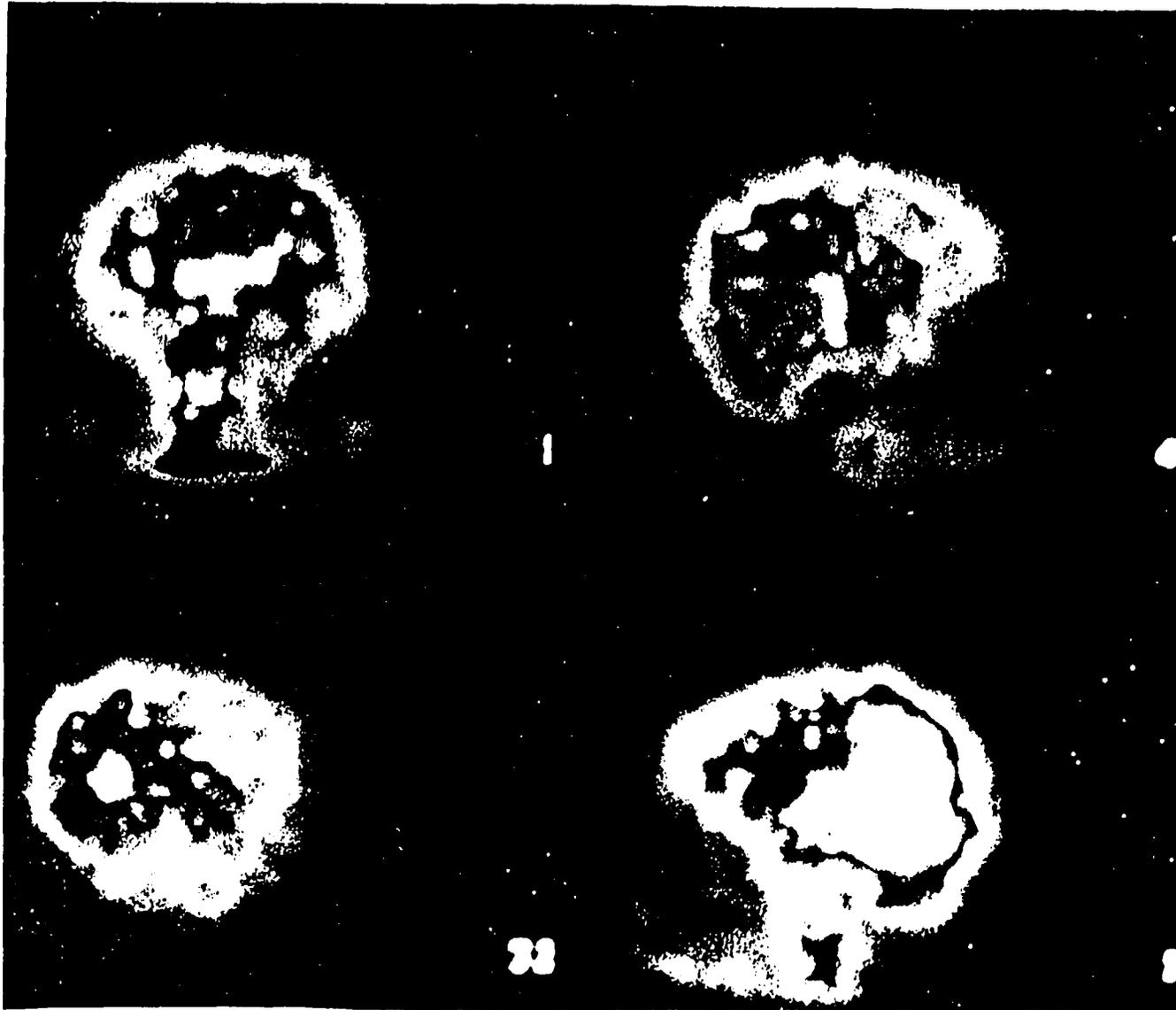
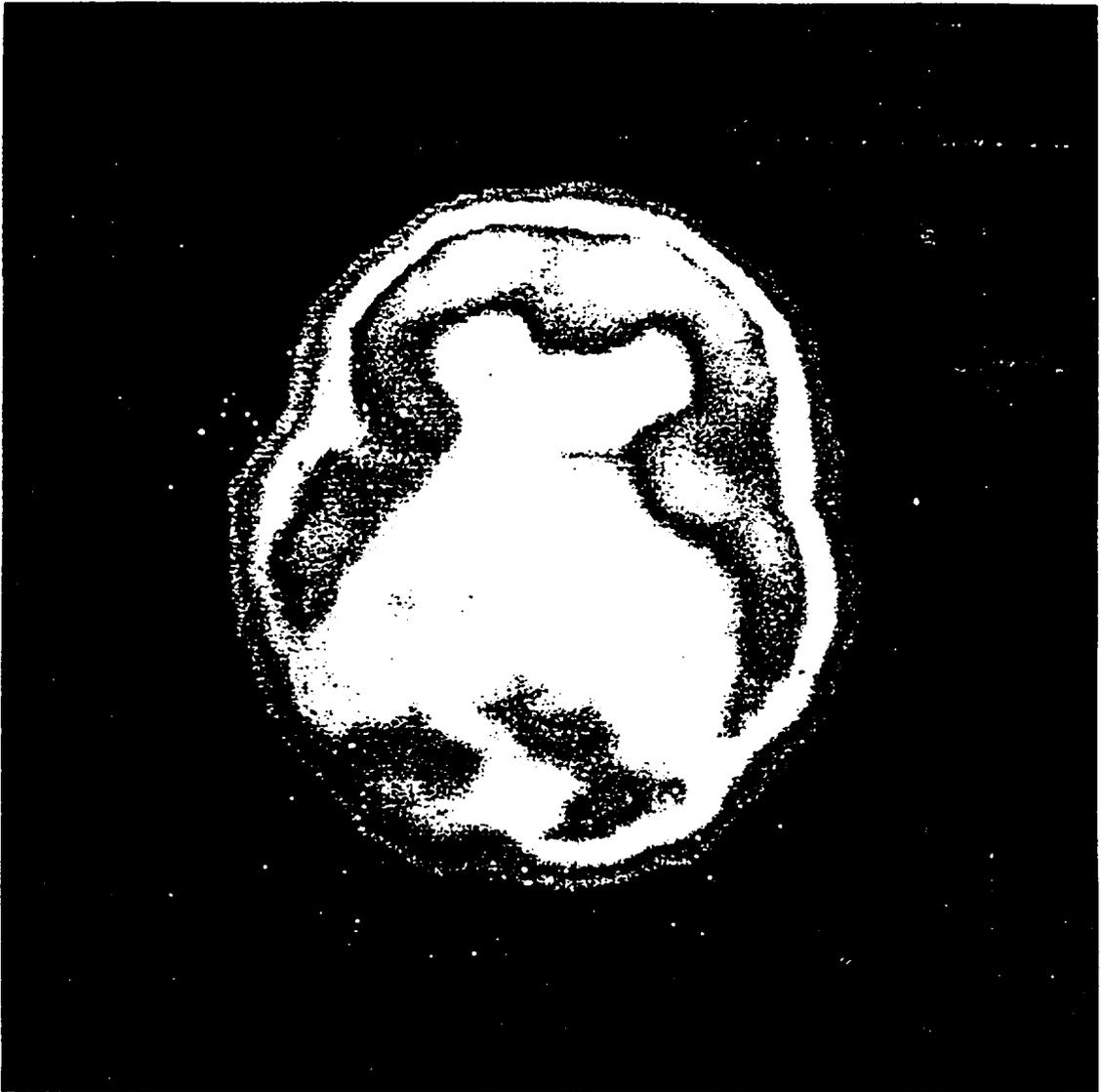


Fig. 20.7  $^{99}\text{Tc}^m$  HMPAO study in Herpes Encephalitis showing marked uptake in LT parieto-temporal region.



**Fig. 20.8**  $^{99m}\text{Tc}$  HMPAO SPECT STUDY (Transaxial slice) in interictal phase showing decreased perfusion in the right parieto-occipital region.

RADIONUCLIDE BRAIN SCANNING

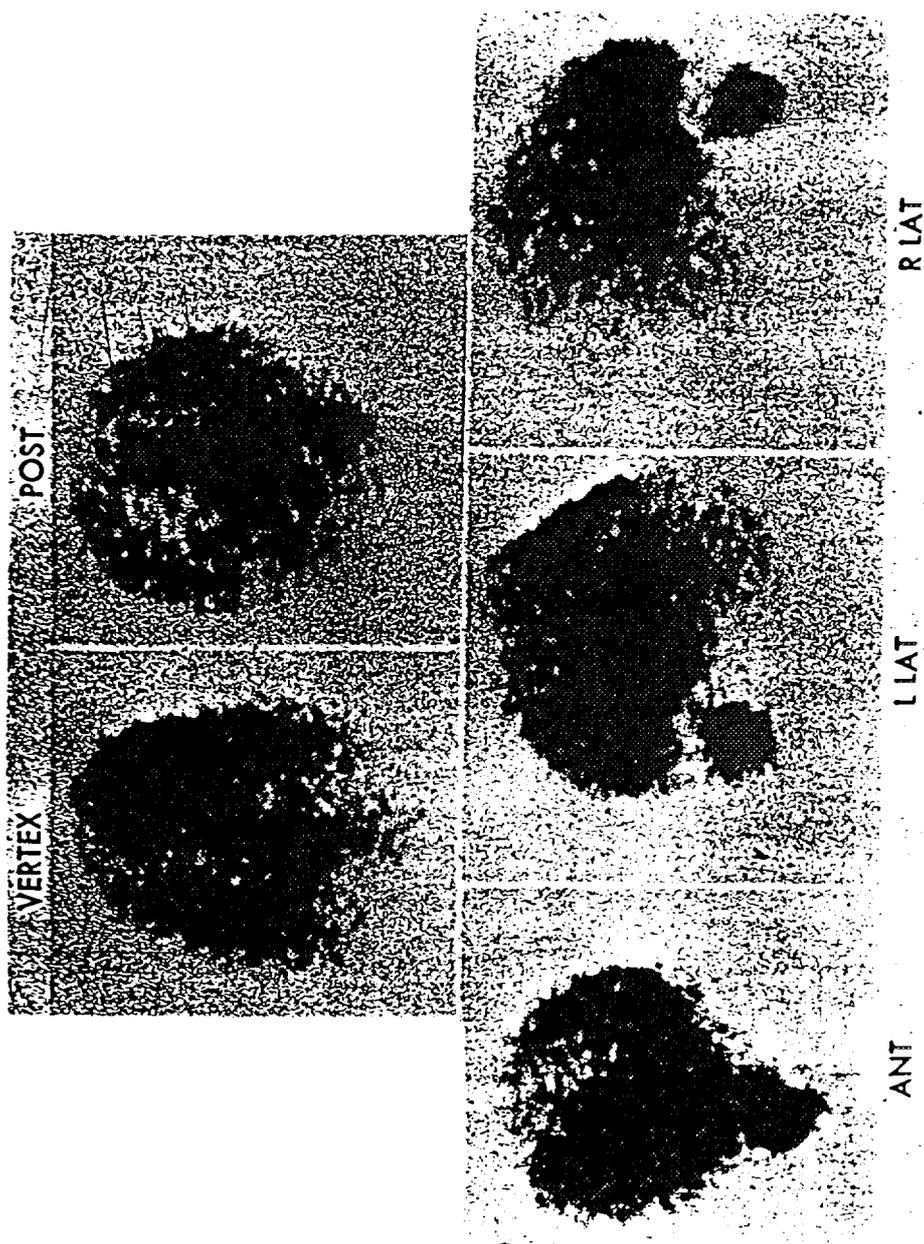


Fig. 20.9 Cisternogram showing CSF rhinorrhoea.

## CHAPTER 20