The advances in neuroimaging using x-ray computed tomography (CT) and magnetic resonance imaging (MRI) are well known. Nuclear medicine has also seen a substantial increase in the application to neurology and psychiatry, using both positron emission tomography (PET) and single photon emission tomography (SPET). The major areas of progress will be reviewed in this article (Table 1).

### Table 1. Nuclear medicine in neurology and psychiatry.

| Brain perfusion (rCBF) | Neurotransmission (neuroreceptors) | Oncology |
|------------------------|-----------------------------------|----------|
| Normal database        | Dopamine: post-synaptic           | Tumour recurrence vs Necrosis |
| Stroke                 |                                   |          |
| Epilepsy               | - schizophrenia                   |          |
| Dementias              | pre-synaptic transporter          |          |
| Alzheimer              | - Parkinson's disease             |          |
| frontal lobe           | - Alzheimer's disease             |          |
| multi-infarct          | benzodiazepine                    | Lymphoma |
| Depression             | - alcoholism                      | vs       |
| ME/CFS                 | 5-HT (serotonin):                 |          |
| Brain death            | - schizophrenia                   |          |
| Head trauma            | acetylcholine                      |          |
| Encephalitis           | - Alzheimer's disease             |          |

CFS = chronic fatigue syndrome
ME = myalgic encephalomyelitis
rCBF = regional cerebral blood flow
various neuroactivation paradigms (Fig 2) or before and after treatment.

Brain death

The diagnosis of brain death is often difficult, especially in barbiturate poisoning, hypothermia, trauma and in patients on artificial life support. Uptake of brain blood flow tracers requires cellular integrity, and thus absent tracer uptake is compatible with brain death or at least with irreversible cessation of brain function (Fig 3).

Brain trauma

CT and MRI are clearly the first imaging techniques to be used in this situation. However, brain blood flow tomograms are more accurate in demonstrating the extent and severity of trauma as they show perfusion impairment in areas of intact anatomy which also correlates with neuropsychological rating. A normal study is reliable in excluding the sequelae of mild head injury. This is of increasing clinical and medico-legal importance in the whiplash syndrome.

Viral encephalitis

Brain blood flow is markedly reduced, often on a regional basis, in HIV positive patients with neurological involvement, even when CT and MRI appear normal (Fig 4). An exception is acute herpes simplex encephalitis in which increased and focal blood flow is seen in the medial temporal cortex.

Chronic fatigue syndrome

Our studies have consistently demonstrated impaired blood flow in the brain stem of patients with chronic fatigue syndrome (Graph 2), but this finding remains controversial.

Fig 2. A motor activation task is displayed in coronal slices of the brain. The task minus control clearly shows activation of the contralateral parietal cortex.
Acute stroke

In the first 24 hours after acute stroke, changes on CT may be absent or only of a minor nature (Fig 5). Brain blood flow tomograms and nuclear medicine studies have contributed greatly to our understanding of the acute metabolic and vascular changes in stroke. They can yield useful data if performed early after onset of stroke. Poor outcome is predicted by the presence of severe and persistent hypoperfusion, large defects, cross-cerebellar diaschisis and a low flow defect/CT volume ratio. Nuclear medicine brain blood flow studies are ideally suited:

- to assess the effect of acute infarction on long-term outcome
- to document the extent of spontaneous or therapeutically induced early reperfusion and its relationship to outcome
- to study the effect of treatment on brain blood flow and metabolism.

Nuclear medicine is also used to identify the haemodynamic compromise of brain areas affected by stroke, to assess vascular reserve, identify patients at risk, and help to stratify patients referred for carotid endarterectomy. This is often achieved by assessing the adequacy of collateral circulation with scans that identify the response of brain blood flow to carbon dioxide, acetazolamide or adenosine.

Epilepsy

Blood flow tomograms are of considerable value in localising epileptogenic foci that cannot be demonstrated by traditional methods. It is now known that nuclear medicine PET and SPET techniques can detect the site of a focus whether or not an anatomical lesion (eg gliosis) can be seen with other techniques (eg with MRI). This is particularly relevant in intractable temporal lobe epilepsy where the identification of the focus can guide a surgical therapeutic intervention. Both interictal and ictal studies are possible, with the latter showing the highest sensitivity in lesion detection. The mesial temporal lobe exhibits impaired flow between fits, with major increases of flow during an ictal study. Immediate post-ictal studies are highly predictive of the site of a focus (Fig 6).
The dementias

Blood flow maps are sensitive to early pathology in the dementias, and senile dementia of the Alzheimer type has been extensively studied. Early in the disease, when clinical manifestations are incipient, typical findings include significant impairment of blood flow in the temporal and parietal lobes of the brain. The frontal lobe can also be involved, and blood flow impairment is often seen to affect both sides of the brain. The diagnosis of Alzheimer's dementia continues to rely on clinical criteria and the exclusion of other diseases; this may result in a 10–20% false-positive rate. A commonly encountered problem is the differentiation of early Alzheimer’s from depression. Brain blood flow impairment in depression is predominantly frontal, and this pattern can often help to distinguish depression from Alzheimer’s. With an increasing elderly population, these studies are gaining ground. However, Pick’s disease also shows frontal lobe abnormalities. In multi-infarct dementia, scattered multiple areas of impaired blood flow are seen which can be helpful in establishing the diagnosis.

When effective treatments emerge for the dementias, brain blood flow maps will have an increased role because of their ability to provide an objective, sensitive and reproducible measure with which a longitudinal assessment to response can be determined (Fig 7).

Neuroreceptor imaging

The most rapidly changing field in nuclear medicine is that of neuroreceptor imaging. Receptors are present at

Fig 4. An HIV-positive patient with neurological involvement. Minor changes are seen on computed tomography (left) but significant impairment of flow is evident, mainly to the right brain.

Fig 5. Acute stroke. The computed tomography study shows some impairment, but the area of abnormal flow is much wider and cross-cerebellar diaschisis is demonstrated.
the cell surface and have the ability to bind specific compounds known as ligands. They can pass on information within the cell or to the surrounding milieu, and often act as messengers, regulating the activity of the target cell. Tables 2-4 summarise the most widely investigated receptors. Many of these studies are vital in elucidating mechanisms of drug interaction in vivo and are helpful in drug discovery programmes. Alterations in receptor expression are clearly implicated in a number of disease states. Major progress has been made in the labelling of ligands with readily available radionuclides such as iodine-123 ($^{123}$I) or technetium-99m ($^{99m}$Tc), and these techniques can now be performed in any department with conventional nuclear medicine equipment. The clinically most important developments are summarised below.

**Key Points**

- Cerebral blood flow and perfusion studies depict functional abnormalities even in the absence of structural lesions seen with computed tomography and magnetic resonance imaging
- Brain SPET with T1-201 plays a definitive role in the differential diagnosis of tumour recurrence and post-therapy necrosis. It is essential in HIV +ve patients with intracranial masses that do not respond to medical therapy
- Neurotransmission studies already have a role in the differential diagnosis of movement disorders, particularly Parkinsonian syndromes, and will be progressively used to assess therapy efficacy, particularly in psychiatry

### Parkinson and parkinsonian syndromes

Parkinson's disease affects 1% of individuals over the age of 60. The diagnosis of this condition remains essentially clinical, but it is not always easy to confirm early onset of disease, provide evidence for drug-induced movement disorder or differentiate between different syndromes. Parkinson's disease results from degeneration of the dopaminergic secreting neurons of the brain, and these can now be imaged with appropriate ligands.

**Fig 6.** A $^{99m}$Tc HMPAO blood flow study and display of the long axis of the temporal lobe with significant reduction of blood flow in the mesial cortex in the interictal phase of a patient with temporal lobe epilepsy.

**Fig 7.** A typical pattern of abnormal flow in Alzheimer's dementia.
Table 2. Neuroreceptor imaging ligands.

| Radionuclide | Ligand      | Receptor                  |
|--------------|-------------|---------------------------|
| ¹²³I         | IBZM        | Dopamine D₂               |
|              | Iomazenil   | Benzodiazepine            |
|              | Idodexetimide | Muscarinic acetylcholine |
|              | QNB         | M₁⁺M₂ muscarinic          |
|              | Oestradiol  | Oestrogen                 |
|              | MIBG        | Norepinephrine            |
| ¹¹¹In        | Octreotide  | Somatostatin              |
| ¹⁸F          | Setoperone  | 5HT₂ (serotonin)          |

IBZM = iodobenzamide  
MIBG = metaiodobenzylguanidine  
QNB = quinuclidinyl benzylene

Table 3. Neuroreceptor imaging: new ligands.

| Radionuclide | Ligand                | Receptor                  |
|--------------|-----------------------|---------------------------|
| ¹²³I/¹⁸F     | IPH (epibatidine)     | Nicotine acetylcholine    |
| ¹⁸F          | Fluorocarazolol       | Beta-adrenoreceptor       |
|              | Fluorotrifluoro-piperazine | serotonin (5HT)        |
| ¹³¹C         | Carboxynaphthyl-tropane | 5HT + DA                |
|              | Carfentanil           | M₁- opioid               |

DA = dopamine

Table 4. Dopamine transporter ligands.

| Radionuclide | Ligand          |
|--------------|-----------------|
| ¹²³I         | βCIT βCIT-FP    |
| ¹⁸F          | IPT             |
| ⁹⁹mTc        | Trodat-1        |
| ¹⁸F          | DOPA            |

CIT = carboxymethoxy-iodophenyltropane  
DOPA = dopamine  
FP = fluoropropyl  
IPT = iodopropen-carboxymethoxy-chlorophenyl nortropane

Early disease can be diagnosed even prior to the manifestation of clinical symptoms (Fig 8). The effect of treatment can now be objectively monitored by imaging and by measuring the uptake of specific ligands in the striatum of individual patients.

Schizophrenia

Nuclear medicine techniques have been used to test the hypothesis that antipsychotic drug action is mediated primarily through action at dopaminergic pathways in the limbic system. Occupancy rates of different antipsychotic drugs in clinical use can be determined by imaging with appropriate labelled ligands, such as iodobenzamide and epidepride. Antipsychotic drugs (classical, atypical and other newly developed agents) can be shown to exhibit variable D₂/D₃ receptor occupancy in the striatum and temporal (limbic) cortex. Classical antipsychotic drugs have high occupancy rates in the striatal and temporal cortical D₂/D₃ receptors, whilst drugs such as clozapine exhibit much higher limbic occupancy. These tracer studies have shown that drugs such as sertindole and olanzapine target selectively the limbic cortical D₂/D₃ receptors.

Studies of this nature are of value in evaluating the mode of action of antipsychotic drugs and in determining whether further increases in dose are likely to be ineffective because of already high levels of receptor binding.
Brain tumours
Several tracers are available for the study of brain neoplasia. The selection of a lesion for brain biopsy, the grading of tumour via the uptake of metabolic tracers, and the differentiation between tumour recurrence, radiation necrosis and scar, have all benefited from this approach. Thallium-201 (201TI)-chloride, a potassium analogue, has been particularly successful in discriminating between cerebral lymphoma and toxoplasmosis in AIDS (Fig 9). Single lesions on MRI with focal accumulation of 201TI strongly suggest lymphoma, as do multiple lesions with high 201TI uptake. 123I-methyl tyrosine is an interesting tracer which allows the investigation of the transport of this amino acid in brain tumours.

Cerebrospinal fluid studies
Studies of the cerebrospinal fluid (CSF) with tracers such as 99mTc-diethylenetriamine pentacetate (DTPA) or Indium-111 (111In)-DTPA permit the investigation of normal-pressure hydrocephalus, of communicating and non-communicating hydrocephalus, shunt patency evaluation and suspected CSF leakage detection.

Conclusion
Despite the substantial advances in neuroimaging with x-ray CT scanning and MRI, the emergence of the newer techniques of functional magnetic resonance and magneto-encephalography, nuclear medicine and radioactive tracer methods continues to have an important role in the study and clinical care of patients with psychiatric or neurological disease. The exquisite biochemical sensitivity of nuclear medicine, often in

Fig 9. 201TI chloride tracer uptake in a patient with lymphoma and AIDS (Ly = CNS lymphoma).

Fig 10. The evolution of nuclear medicine and brain scanning: from its beginning with blood-brain barrier imaging and computer-assisted data processing (a) (b), to brain blood flow maps (c) neuroreceptor imaging, with impairment of the benzodiazepine receptor displayed on to a fused magnetic resonance imaging map in (d), and a display of the presynaptic dopamine transporter studied with 123I-FP-CIT and displayed in (e).
the picomolar range, offers unique advantages in the early detection of altered metabolism and function. An impressive range of specific radiopharmaceuticals allows targeted investigation of an increasing spectrum of neurochemical pathways and biological signals in the brain (Fig 10).

Further reading

1 Murray IPC, Ell PJ. Nuclear medicine in clinical diagnosis and treatment (2nd edn). Edinburgh: Churchill Livingstone, 1998.

Nuclear medicine techniques are used to monitor the effects and side effects of therapeutic interventions, for example the effect on renal or cardiac function, to determine optimal delivery of radioactive and non-radioactive drugs, and to deliver radiation therapy to specific sites using therapeutic radionuclides.

The effectiveness of radionuclide therapy depends on several factors:

- the specificity of the localisation of the radiopharmaceutical
- the type of irradiation (β- or α-particles, Auger electrons) in relation to the microscopic binding site localisation
- the time the radionuclide/radiopharmaceutical remains at the site of uptake (residence time)
- the time over which the radiation is delivered (the half-life of the radionuclide attached to the delivering radiopharmaceutical)

- the sensitivity of the target tissue to the radiation.

The range of available diagnostic and therapeutic procedures, some of which are illustrated in Tables 1–3, could therefore be considered by clinical group.

Endocrinology

The most commonly used agent in this group, which has been used for over 50 years, is iodine-131 (131I) for the treatment of both benign and malignant thyroid conditions. The iodine enters the cell by the specific iodide transport mechanism and is subsequently trapped and organified. 131I has an energetic β-emission which can penetrate several cell diameters around the cell that has taken up the iodine and cause cell death. The likelihood of response to 131I can be demonstrated by imaging before therapy with either 131I or 123I. The therapy is highly successful and safe for the treatment of thyrotoxicosis (toxic nodules and Graves disease) in all age groups from children to adults. More recently, its use in reducing the size of benign non-toxic goitres has been demonstrated in those patients who are unsuitable for surgical therapy.1,2

### Table 1. Commonly used and established therapeutic agents of proven benefit.

| Radionuclide | Radiopharmaceutical | Emission | Disease process treated |
|--------------|---------------------|----------|-------------------------|
| 131I         | Sodium Iodide       | Beta     | Graves disease          |
|              |                     |          | Toxic adenomas          |
|              |                     |          | Plummer's disease       |
|              |                     |          | Multinodular goitres    |
| 131I         | Sodium Iodide       | Beta     | Differentiated thyroid cancer |
| 131I         | MIBG                | Beta     | Neuroblastoma           |
|              |                     |          | Malignant phaeochromocytoma |
|              |                     |          | Medullary carcinoma of the thyroid |
|              |                     |          | Carcinoid                |
| 32P          | Sodium phosphate    | Beta     | Polycythaemia rubra vera |
| 90Y          | Yttrium citrate     | Beta     | Inflammatory arthropathies|
| 89Sr         | Strontium chloride  | Beta     | Haemophilic arthropathies|
|              | MIBG = metaiodobenzylguanidine |          | Bone metastases (prostate, breast) |