

- 7 Miller AD, Palmer TD, Hock RA. Transfer of genes into human somatic cells using retrovirus vectors. *Cold Spring Harbor Symp Quant Biol* 1986;51:1013-20.
- 8 Willis RC, Jolly DJ, Miller AD, *et al*. Partial phenotypic correction of human Lesch-Nyhan (hypoxanthine-guanine phosphoribosyltransferase-deficient) lymphoblasts with a transmissible retroviral vector. *J Biol Chem* 1984;259:7842-9.
- 9 Williams DA, Orkin SH, Mulligan RC. Retrovirus-mediated transfer of human adenosine deaminase gene sequences into cells in culture and into murine hematopoietic cells in vivo. *Proc Natl Acad Sci USA* 1986;83:2566-70.
- 10 Dzierzak EA, Papayannopoulou T, Mulligan RC. Lineage-specific expression of a human β -globin gene in murine bone marrow transplant recipients reconstituted with retrovirus-transduced stem cells. *Nature* 1988;331:35-41.
- 11 Anderson WF, Kantoff P, Eglitis M, *et al*. Gene transfer and expression in nonhuman primates using retroviral vectors. *Cold Spring Harbor Symp Quant Biol* 1986;51:1065-72.
- 12 Grosfeld F, van Assendelft GB, Greaves DR, Kollias G. Position-independent high-level expression of the human β -globin gene in transgenic mice. *Cell* 1987;51:975-85.
- 13 Yee J-K, Jolly DJ, Moores JC, Respass JD, Friedman T. Gene expression from a transcriptionally disabled retroviral vector. *Cold Spring Harbor Symp Quant Biol* 1986;51:1021-6.
- 14 Anson DS, Hock RA, Austen D, *et al*. Towards gene therapy for haemophilia B. *Mol Biol Med* 1987;4:11-20.
- 15 Ledley FD, Darlington GJ, Hahn T, Woo SLC. Retroviral gene transfer into primary hepatocytes: implications for genetic therapy of liver-specific functions. *Proc Natl Acad Sci USA* 1987;84:5335-9.
- 16 St Louis A, Verma IM. An alternative approach to somatic cell gene therapy. *Proc Natl Acad Sci USA* 1988;85:3150-4.
- 17 Wilson JM, Jefferson DM, Chowdhury JR, Novikoff PM, Johnston DE, Mulligan RC. Retrovirus-mediated transduction of adult hepatocytes. *Proc Natl Acad Sci USA* 1988;85:3014-8.
- 18 Gregg RG, Smithies O. Targeted modification of human chromosomal genes. *Cold Spring Harbor Symp Quant Biol* 1986;51:1093-100.
- 19 Doetschman T, Maeda N, Smithies O. Targeted mutation of the Hprt gene in mouse embryonic stem cells. *Proc Natl Acad Sci USA* 1988;85:8583-7.
- 20 Mansour SL, Thomas KR, Capecchi MR. Disruption of the proto-oncogene int-2 in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes. *Nature* 1988;336:348-52.

PET scanning

Provides information on function

The acronym PET stands for positron emission tomography. This uses the tomographic principles of radiation detection and subsequent image reconstruction, but it is more than an imaging technique. Positron emission tomography measures local tissue concentrations of radioisotopes in the body and differs from tomographic imaging with techniques such as computed tomography or magnetic resonance imaging in that it provides functional information.

The versatility of this approach is shown by the wide range of variables that have already been measured and potentially can be measured in humans.^{1,2} Local tissue perfusion, blood volume, glucose and oxygen consumption, and fractional extractions of various metabolites and substances have all been quantitated and imaged with accuracy. In this, the use of a positron emitting isotope as a tracer is crucial. Radioactive forms of oxygen, nitrogen, and carbon can be made and substituted for the same stable elements in the molecules to be studied, thus avoiding alterations of the normal metabolic rate after introduction into the body that may result from the use of "foreign" isotopes such as iodine or technetium. The activity passing through a volume of scanned tissue can then be measured.

The variety of functions that can be assessed and imaged is limited by the availability of tracers that can be rapidly labelled chemically with the isotopes, which have extremely short half lives (for example, the half life of oxygen-15 is 2.1 minutes and that of carbon-11, 20 minutes). Measuring the amount of a labelled molecule in the tissues depends on several chemical, physical, and biological factors, any of which may be the focus of primary, clinical, or biological interest. The development of new PET tracer techniques depends on isolating this focus.

Measuring the oxygen and glucose metabolism has been widely used to investigate cerebral function and disease during the 10 years that PET has been used in humans. The brain uses these substrates as the sole providers of metabolic energy, and hence the consumption of glucose or oxygen, or both, reflects total neuronal function. Techniques have been used to highlight areas of the brain that participate specifically in performing motor, verbal, visual, and other tasks.³ As the methods have become more complex so rapid measurements, which can be repeated at the same session, are now possible, permitting complex analyses of neuropsychological functions and of responses to external stimuli.⁴ Metabolic measurements are also valuable in delineating areas of the brain with disturbed function—for example, the abnormalities of parietal and posterior temporal metabolism described in patients with early Alzheimer's disease.⁵ Another example is identifying

subjects at risk of Huntington's disease by finding low energy metabolism in the caudate nucleus. This pattern is universal in the established disease and its finding in apparently healthy people has raised the possibility of presymptomatic identification of gene carriers.⁶ Conversely, raised metabolism is found during pathological excitation, such as in epilepsy. PET has been found clinically useful in assessing patients with partial complex epilepsy for treatment with temporal lobectomy by detecting hypometabolic areas in a temporal lobe during the interictal period.⁷⁻⁹

Measuring haemodynamic variables such as tissue perfusion and blood volume together with oxygen metabolism has helped our understanding of ischaemic and pre-ischaemic states¹⁰⁻¹² and is being developed further for evaluating haemodynamic compromise in patients with stenotic and occlusive disease of arteries in the neck. This ability to measure and image hypoxia and ischaemia is also proving useful in studying myocardial ischaemia¹³ and the local physiology of tumours of the brain and other organs.^{14,15} More recently, methods have been introduced to measure the function of neurotransmitter systems in Parkinson's disease,¹⁶⁻¹⁸ schizophrenia,¹⁹⁻²¹ and partial complex epilepsy.^{22,23} Other tracers are being developed for the serotonergic system.²⁴⁻²⁸ In a few cases tracers have already been used for imaging and measuring the function of both presynaptic and postsynaptic components of a neurochemically distinct pathway.

The scope for labelling a wide range of chemicals and pharmaceuticals is immense. Recent advances suggest that further tracers will be identified and new methods developed in the coming years, while the performance of the PET scanners will probably also improve. The combination of metabolic and transmitter specific tracers is particularly attractive for investigating neurological disease, particularly the degenerative disorders of the deeper cerebral structures. The prospect of being able to classify in life some degenerative diseases presenting as dementias or akinetic-rigid syndromes will allow us to study their natural course and possible treatments.²⁹ Other applications are likely in oncology,³⁰ cardiology, and local blood-brain barrier function.^{31,32}

PET is a general technique which may be applied to any part of the body. Apart from metabolic and transmitter studies it may be used to measure tissue concentrations of any labelled substance or drug and its rate of change with time.³³ Nevertheless, its clinical utility is frequently questioned. Certainly, the technique is difficult (because of the short lived isotopes), expensive on capital costs, (necessitating a cyclotron, PET scanner, hot cells, and computing facilities), and

demands multidisciplinary teams with considerable skills to carry out and, above all, interpret the tomograms. Nevertheless, experience from over 50 centres in the world has shown that this essentially non-invasive technique can provide unique quantitative functional information and that it is an important addition to our understanding of the pathogenesis and evolution of human disease.

RICHARD S J FRACKOWIAK
Assistant Director (Clinical Sciences)

TERRY JONES
Assistant Director (Scientific)

MRC Cyclotron Unit,
Hammersmith Hospital, London W12 0HS

- 1 Phelps ME, Mazziotta JC, Schelbert H. *Positron emission tomography and autoradiography: principles and applications for the brain and heart*. New York: Raven Press, 1986.
- 2 Frackowiak RSJ. Positron emission tomography in neurology. In: Kennard C, ed. *Recent advances in neurology* 5. Edinburgh: Churchill Livingstone, 239-77.
- 3 Mazziotta JC, Phelps ME. Human sensory stimulation and deprivation: positron emission tomographic results and strategies. *Ann Neurol* 1984;15 (suppl):50-60.
- 4 Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 1988;331:585-9.
- 5 Frackowiak RSJ, Pozzilli C, Legg NJ, et al. Regional cerebral oxygen supply and utilisation in dementia: a clinical and physiological study with oxygen-15 and positron tomography. *Brain* 1981;104:753-8.
- 6 Mazziotta JC, Phelps ME, Pahl JJ, et al. Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. *N Engl J Med* 1987;316:357-62.
- 7 Engel J, Kuhl DE, Phelps ME. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science* 1982;218:64-6.
- 8 Engel J, Kuhl DE, Phelps ME, Mazziotta JC. Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes. *Ann Neurol* 1982;12:510-7.
- 9 Franck G, Sadzot B, Salmon E, et al. Regional cerebral blood flow and metabolic rates in human focal epilepsy and status epilepticus. In: Delgado-Escueta AV, Ward AA, Woodbury DM, Porter RJ, eds. *Advances in neurology*. New York: Raven Press, 1986:935-48.
- 10 Frackowiak RSJ. The pathophysiology of human cerebral ischaemia: a new perspective obtained with positron tomography. *Q J Med* 1985;57:713-27.
- 11 Gibbs JM, Wise RJS, Leenders KL, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid artery occlusion. *Lancet* 1984;ii:310-4.
- 12 Wise RJS, Bernardi S, Frackowiak RSJ, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke: the transition from ischaemia to infarction as reflected in the regional oxygen extraction. *Brain* 1983;106:197-222.
- 13 Camici P, Araujo LI, Spinks T, et al. Increased uptake of 18F-fluorodeoxyglucose in post-ischaemic myocardium of patients with exercise induced angina. *Circulation* 1986;74:81-8.

- 14 Brooks DJ, Beaney RP, Thomas DGT. The role of positron emission tomography in the study of cerebral tumours. *Semin Oncol* 1986;13:83-93.
- 15 DiChiro G, DeLaPaz RL, Brooks RA, et al. Glucose utilisation of cerebral gliomas measured by (18F)-2-fluorodeoxyglucose and positron emission tomography. *Neurology* 1982;32:1323-9.
- 16 Leenders KL, Palmer AJ, Quinn N, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *J Neurol Neurosurg Psychiatry* 1986;49:853-60.
- 17 Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science* 1986;231:258-61.
- 18 Wagner HN, Burns HD, Dannals RF, et al. Imaging dopamine receptors in the human brain by positron tomography. *Science* 1983;221:1264-6.
- 19 Farde L, Wiesel F-A, Hall H, Hallidin C, Stone-Elander S, Sedvall G. No D2 receptor increase in PET study of schizophrenia. *Arch Gen Psychiatry* 1987;44:671-2.
- 20 Wong DF, Wagner HN, Tune LE, et al. Positron emission tomography reveals elevated D2 receptors in drug-naive schizophrenics. *Science* 1986;234:1558-63.
- 21 Farde L, Hallidin C, Stone-Elander S, Sedvall G. PET analysis of human dopamine receptor subtypes using 11C-SCH23390 and 11C-raclopride. *Psychopharmacology* 1987;92:278-84.
- 22 Savic I, Roland P, Sedvall G, Persson A, Pauli S, Widén L. In vivo demonstration of reduced benzodiazepine receptor binding in human epileptic foci. *Lancet* 1988;ii:863-6.
- 23 Frost JJ, Mayberg HS, Fisher RS, et al. Mu-receptors measured by positron emission tomography are increased in temporal lobe epilepsy. *Ann Neurol* 1988;23:231-7.
- 24 Wong DF, Lever JR, Hartig PR, et al. Localisation of serotonin 5HT2 receptors in living human brain by positron emission tomography using N1-(11C)-methyl-2-Br-LSD. *Synapse* 1987;1:393-8.
- 25 Blin J, Pappata S, Kiyasawa M, Crouzel M, Baron JC. (18F)setoperone: a new high affinity ligand for positron emission tomography study of the serotonin-2 receptors in baboon brain in vivo. *Eur J Pharmacol* 1988;147:73-82.
- 26 Tedroff J, Aquilonius SM, Hartvig P, et al. Monoamine reuptake sites in the human brain evaluated in vivo by means of 11C-nomifensine and positron emission tomography; the effects of age and of Parkinson's disease. *Acta Neurol Scand* 1988;77:192-201.
- 27 Syrota A, Pailotin G, Davy JM, Aumont MC. Kinetics of in vivo binding of antagonist to muscarinic cholinergic receptor in the human heart studied by positron emission tomography. *Life Sci* 1984;35:937-45.
- 28 Wieland DM, Rosenspire KC, Hutchins GD, Schwaiger M. Validation of 6-[¹⁸F]fluorometaraminol (FMR) for positron tomography. *Circulation* 1988;78:II-598.
- 29 Leenders KL, Frackowiak RSJ, Lees AJ. Steele-Richardson-Olszewski syndrome: brain energy metabolism, blood flow and fluorodopa uptake measured by positron emission tomography. *Brain* 1988;111:615-30.
- 30 Bergstrom M, Ericsson K, Hagenfeldt L, et al. PET study of methionine accumulation in glioma and normal brain tissue: competition with branched chain amino acids. *J Comput Assist Tomogr* 1987;11:208-13.
- 31 Brooks DJ, Lammertsma AA, Beaney RP, et al. Measurement of regional cerebral pH in human subjects using continuous inhalation of 11CO₂ and positron emission tomography. *J Cereb Blood Flow Metab* 1984;4:458-65.
- 32 Phillips PC, Dhawan V, Strother SC, et al. Reduced cerebral glucose metabolism and increased brain capillary permeability following high dose methotrexate chemotherapy: a positron emission tomographic study. *Ann Neurol* 1987;21:59-63.
- 33 Baron JC, Roeda D, Munari C, Crouzel C, Chodkiewicz JP, Comar D. Brain regional pharmacokinetics of 11C-labelled diphenylhydantoin: positron emission tomography in humans. *Neurology* 1983;33:580-5.

Regular Review

Treating mild hypertension

Agreement from the large trials

Report of the British Hypertension Society working party

It is now generally accepted that treating moderate or severe hypertension improves the prognosis. With malignant hypertension the improvement was sufficiently clear for historical comparisons to justify active treatment,¹⁻⁵ and benefit in more moderate but still severe hypertension was shown in small studies of simple design.^{6,7} Although the risks of milder hypertension have been shown,⁸ the value of treating those without evidence of damage to end organs such as the heart, kidney, and eye has until recently remained untested. Many large, carefully designed studies were, however, started in the 1970s to test the value of treatment (table I).

The last of these studies was reported in 1987,²⁰ and no major prospective trial remains to be reported in the immediate future. The British Hypertension Society accordingly set up a working party to establish how far it is possible to give firm advice about treating patients with mild hypertension. Although reached independently, our conclusions are broadly consistent with those reached by a recent joint conference organised by the World Health Organisation and the International Society of Hypertension.²¹

The large scale trials have used fundamentally different control groups. Some have employed placebo⁹⁻¹¹ or untreated^{12,16} controls; others have compared two forms of treatment. In two trials regimens based on β blockers have been compared with regimens that have specifically excluded β blockers.^{19,20} In addition, the Medical Research Council study allocated patients in the treatment group to regimens based upon bendrofluazide or propranolol.¹⁵ These three last studies therefore deal with the question of possible specific benefit from β blockers. Two United States trials compared multiple interventions carried out by specialist physicians with usual ("referred") care.^{17,18} The absence of an untreated control group in these studies reduces their relevance in assessing the value of treatment. The design of these trials and a summary of the main results are presented in tables I and II.

The effect of antihypertensive treatment (as opposed to multifactorial treatments) may be assessed only from trials that included an untreated or placebo treated control group. There are appreciable differences in the incidence of end points (such as deaths or cardiovascular events) among these