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REA

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ABSTRACT

Seventeen patients with partial epilepsy had EEG monitoring concurrent with cerebral emission computed tomography (ECT) after ^{18}F-fluorodeoxyglucose (^{18}FDG) and ^{13}N-ammonia were given intravenously as indicators of local cerebral glucose utilization ($LCMR_{glc}$) and relative perfusion, respectively. In 12 of 15 patients who had unilateral or focal electrical abnormalities, interictal ^{18}FDG scan patterns clearly showed localized regions of decreased (20%-50%) $LCMR_{glc}$, which correlated anatomically with the eventual EEG localization. These hypometabolic zones appeared normal on x-ray computed tomography in all but three patients and were unchanged on scans repeated on different days. In 5 of 6 patients who underwent temporal lobectomy, the interictal ^{18}FDG scan correctly detected the pathologically confirmed lesion as a hypometabolic zone, and removal of the lesion site resulted in marked clinical improvement. In contrast, the ictal ^{18}FDG scan patterns clearly showed foci of increased (82%-130%) LCMRglc which correlated temporally and anatomically with ictal EEG spike foci and were within the zones of interictal hypometabolism (3 studies in 2 patients). $^{13}NH_3$ distributions paralleled ^{18}FDG increases and decreases in abnormal zones, but $^{13}NH_3$ differences were of lesser magnitude. When the relationship of $^{13}NH_3$ uptake to local blood flow found in dog brain was applied as a correction to the patients' $^{13}NH_3$ scan data, local alterations in perfusion and glucose utilization were usually matched, both in the interictal and ictal states. We conclude that the interictal ^{18}FDG-ECT scan is useful now in

aiding localization of the dysfunctional cerebral zone most likely to be responsible for seizures in patients considered for temporal lobectomy. With further development, ECT may help in categorizing better the various forms of the disorder and in elucidating the basic mechanisms of epilepsy in man.

In epilepsy, altered cerebral function is seldom accompanied by changes in structure that are detectable by radiographic procedures. Diagnosis and classification of this altered function depends heavily on the use of electroencephalography (EEG) which records electrical activity associated with neuronal activity. EEG is extremely useful, but has limitations. It is often difficult to lateralize or to localize a seizure origin [11] and to assess the severity and extent of underlying cerebral involvement. Other measures of altered cerebral function are possible in epilepsy.

In the normal state, changes in neuronal activity are accompanied by changes in cerebral metabolic rate (CMR) and proportionate changes in cerebral blood flow (CBF) [8, 16, 62, 64], but, in diseased brain, blood flow may not be so regulated [36, 38, 59]. It has been established that both generalized and focal epileptic seizures are associated with increased CBF and increased CMR, and that both are decreased immediately after the seizure [22, 26, 54, 55]. For example, House et al [22] demonstrated a tight couple among electrical discharge, mean CBF, and mean CMR_{O_2} in experimentally induced generalized seizures in cats. For better spatial resolution, investigators have used the ^{14}C-deoxyglucose (^{14}C-DG) autoradiographic method [64] to demonstrate changes in local cerebral glucose ($LCMR_{glc}$) associated with penicillin induced epilepsy in the rat and monkey [4, 29], and in the kindled rat [9]. There is need for the same kind of localized data from man. In the spontaneous ictal state in man, regional increases in CBF have been visualized directly

[45] and measured by the ^{133}Xe-CBF method [21, 26, 27, 39, 63], but corresponding in vivo measurements of CMR have been limited to whole brain determinations by means of the Kety-Schmidt technique [30]. We report here the first measurements of cerebral metabolism and circulation by emission computed tomography (ECT), resolved in three dimensions, and performed concurrently with EEG recording of epileptic patients who were in the unperturbed interictal or spontaneous ictal state.

ECT is a noninvasive scanning method which produces a cross-section picture of brain radioactivity in man, following intravenous injection of a labeled indicator [31, 41]. The quantitative ECT method was first applied to absolute measurements of local cerebral blood volume [32] and $LCMR_{glc}$ [33, 34, 60] in man, using approaches similar to quantitative autoradiography, but with pictures of lesser spatial detail. In the project reported here, we applied ECT to patients with partial epilepsy, concurrent with EEG monitoring, using ^{18}F-fluorodeoxyglucose (^{18}FDG) [23, 33-36, 51, 52, 60, 61] and ^{13}N-ammonia ($^{13}NH_3$) [36, 46, 48, 50, 53] as indicators of $LCMR_{glc}$ and relative perfusion, respectively.

The ^{18}FDG-ECT method reported in this paper was based on the ^{14}C-DG autoradiographic method of Sokoloff et al [64], as extended to man with ^{18}FDG and ECT by Reivich et al [60, 61] and Kuhl et al [33], accomodated to dephosphorylation of $^{18}FDG\text{-}6\text{-}PO_4$ by Huang et al [23] and validated by Phelps et al [52]. ^{18}FDG enters the brain from the blood, is phosphorylated by brain hexokinase, and the metabolic product, $^{18}FDG\text{-}6\text{-}PO_4$, remains fixed

with little further metabolism. Calculations of $LCMR_{glc}$ depend on a model of the biochemical behavior of deoxyglucose and glucose in the brain [23, 52, 61, 64]. The time course of specific activity in cerebral capillary blood is estimated by measuring arterialized venous blood samples obtained while the blood is clearing of tracer [52]. Local cerebral ^{18}F concentrations are measured by ECT scans at times greater than 40 minutes after injection, and, with knowledge of predetermined rate constants and lumped constant (LC), $LCMR_{glc}$ is calculated for each zone in the tomographic image. The method measures exogenous glucose utilization occurring primarily during the first 10 minutes after injection, the utilization being equal to the glycolytic rate under the assumption that there is no net glycogen accumulation or glycogenolysis. In normal brain, Sokoloff et al [64] have found LC to be stable, regardless of alterations in pCO_2, blood glucose concentration, and state of anesthesia, and the calculation of $LCMR_{glc}$ is quite insensitive to even severalfold inaccuracies in the values of rate constants [23, 64]. The magnitude of inaccuracy caused by assuming normal values of LC and rate constants in calculating $LCMR_{glc}$ for abnormal cerebral zones of epileptic patients during moderate interictal ischemia and marked ictal hyperemia remains to be determined by experiment. Until then, absolute values of $LCMR_{glc}$ for abnormal brain tissue, as we report here, must be interpreted with some caution.

We chose $^{13}NH_3$ [24, 46, 48 53] as an indicator of relative cerebral perfusion because ammonia has a cerebral uptake that

varies with capillary perfusion, a cerebral fixation time of less than one minute, a static cerebral distribution which is desirable for ECT scanning, a short physical half-life (10 min) which permits use prior to an ^{18}FDG scan without residual interference, and simple chemical preparation. We made no attempt to quantify $^{13}NH_3$ distributions in absolute units of LCBF. Phelps et al [48, 53] have reported that after a bolus intravenous injection, $^{13}NH_3$ is rapidly extracted from the blood into brain tissue through the diffusible form of NH_3, is rapidly incorporated into a glutamate-glutamine pool of large size and slow turnover rate, and thus is effectively trapped in a cerebral distribution that depends nonlinearly on local capillary perfusion. For example, we found that after either local compression or a penicillin induced seizure focus in the dog cerebral cortex, the relative distribution of trapped $^{13}NH_3$ underestimated both increases and decreases in the relative distribution of LCBF as measured by the microsphere method [37]. Alterations in local $^{13}NH_3$ uptake matched large LCBF decreases, were less than half as great as LCBF alterations when flow changes were between -20% and +50%, and increased only 37% for 100% LCBF increases. In stroke patients, Kuhl et al [36] found the direction of change in relative local $^{13}NH_3$ uptake was appropriate for known alterations in LCBF, i.e., decreased in ischemia and increased in hyperemia. But, it is not well known how $^{13}NH_3$ uptake in diseased human brain is influenced locally by alterations such as depletion of the glutamine pool, decreases in glutamine synthetase, alterations in the blood brain barrier, or

marked changes in the blood-brain pH gradient [40, 41, 48, 50].

In this project we questioned if this ECT method could detect characteristic local alterations of cerebral metabolism and perfusion associated with the interictal and ictal state in patients with partial epilepsy, and how these data would compare with simultaneous EEG recordings and results of temporal lobectomy.

METHODS

Radionuclides

For preparation of ^{18}FDG, ^{18}F-labeled F_2 was produced in the UCLA nuclear medical cyclotron by the ^{20}Ne (d, α) ^{18}F nuclear reaction and synthesis was by the method of Ido et al [25]. Specific activity was 10-15 mCi/mg. Radiochemical purity, as assayed by high pressure chromatography, was greater than 95% ^{18}FDG; the remainder was determined by thin-layer chromatography to be deoxymannose. The usual intravenous dose for adult patients was 5-10 mCi; the dose for children was less.

^{13}N was produced in the cyclotron by the ^{16}O (p,α) ^{13}N nuclear reaction, followed by reduction of the ^{13}N compounds to ammonia with deVarda's alloy [66]. The radiochemical purity of the product was greater than 99% $^{13}NH_3$, and contained less than 10^{-4}M carrier ammonia, as determined by liquid and gas chromatography. The usual intravenous dose for adult patients was 20 mCi; children received less.

Emission Computed Tomography

Emission computed tomography was performed with the ECAT

positron tomograph [49] (ORTEC, Inc. Life Sciences, Oak Ridge, TN) operated in the medium-resolution mode. The full-width-at-half-maximum (fwhm) measure of spatial resolution was 1.3 cm (intrinsic) and 1.7 cm (final) within the image plane, and 1.8 cm in the axial direction. For $^{13}NH_3$ scans started several minutes after injection, the count rate was approximately 22,000 counts/min/mCi injected. For ^{18}FDG scans started 40 minutes after injection, the count rate was approximately 25,000 counts/min/mCi injected. Scan duration was adjusted so that each image contained 1-1.5 million counts. The $^{13}NH_3$ scan (^{13}N physical half life - 10 min) preceded the ^{18}FDG scan (^{18}F physical half life - 2 hours) by at least one hour, sufficient time to allow radioactive decay of ^{13}N and avoid interference. Most commonly, six levels were scanned sequentially, parallel to the canthal-meatal plane, from upper cerebellum to above the cerebral ventricles.

Calculation of $LCMR_{glc}$ in units of mg/100g/min required measurement of local cerebral ^{18}F concentration by ECT, measurement of the time-course of blood ^{18}F activity and glucose concentration, and knowledge of certain rate constants and a lumped constant (LC) [23, 36, 52, 61, 64]. Details of our method have been reported previously [23, 36, 52]. The first ^{18}FDG scan was begun 40 minutes after injection, when it was assumed that a near steady state condition had been established.

Regions of interest were selected on the tomograph display screen, and local values of ^{13}N concentration, ^{18}F concentration, or $LCMR_{glc}$ were then determined. ^{13}N and ^{18}F concentrations for

anatomical zones were averaged among multiple levels and normalized to the maximum concentration (visual cortex = 100) among the levels. D_{N-13}, D_{F-18}, and D_{MR} were defined as the percentage differences existing between selected zones and the corresponding contralateral zones for mean values of ^{13}N concentration, ^{18}F concentration, and $LCMR_{glc}$ respectively. In calculating mean CMR_{glc} for whole brain in each subject, averages of gray and white CMR_{glc} were determined for the zones listed in Table 2 and were weighted on the assumption that the brain is 50% gray and 50% white matter.

Electroencephalography

All epileptic patients underwent scalp EEG recording at the time of scanning. Gold disc electrodes were applied according to the international ten-twenty system using either electrode paste or collodian. Recordings from sphenoidal and intracerebral depth electrodes were also made in some patients. In patients considered for anterior temporal lobectomy, concentric bipolar and multicontact stainless steel electrodes were routinely implanted bilaterally into amygdala, hippocampal pes, hippocampal gyrus, orbital frontal cortex, and supplementary motor cortex [6]. Scalp and depth EEGs were recorded on 16 and 18 channel electroencephalographs (Model 8, Grass Instruments, Quincy, MA). In evaluation of the EEG tracings, attention was paid to asymmetries of baseline activity, the distribution and intensity of spike activity, and the correlation of these with the patient's behavioral state.

Subjects

Seven normal males underwent $^{13}NH_3$ scanning (median age 24 years, range 18 years - 30 years) and ten normal males underwent ^{18}FDG scanning (median age 23 years, range 21 years - 35 years). Four of these subjects had both $^{13}NH_3$ and ^{18}FDG scans, eight had determinations of $LCMR_{glc}$, and three had a second determination of $LCMR_{glc}$ on another day.

Seventeen patients with partial epilepsy (median age 20 years, range 4 years - 45 years) underwent cerebral ECT scanning during surface or depth EEG recording. In each patient, the partial seizure pattern was diagnosed on clinical or EEG grounds, usually with behavioral features that suggested automatisms. There were frequent seizure episodes that were resistant to adequate drug therapy, and there was no evidence of progressive CNS disease, brain tumor, psychosis, or marked mental retardation. These patients were divided into four subgroups according to lateralization and localization of EEG abnormalities (Table 1), and results of ECT scans were compared with those of EEG and XCT.

RESULTS

Control Studies

In normal subjects, the cerebral activity distributions were the same for ^{18}FDG and $^{13}NH_3$ scans (Table 2), and there was no difference between left and right hemispheres. The mean coefficient of variation among subjects for normalized zonal concentations of ^{13}N and ^{18}F was 6%; for zonal $LCMR_{glc}$, it was 15%. When ^{18}FDG scans were repeated on the same normal subjects,

the average variations from the mean in paired determinations of normalized zonal ^{18}F concentration and mean CMR_{glc} were 3% and 12%, respectively. Mean CMR_{glc} was 5.28 ± 0.76 mg/100g/min (mean ± SD; N = 8).

Interictal Studies

The interictal distributions of ^{13}N, ^{18}F, and CMR_{glc} in the contralateral hemisphere of patients with unilateral EEG localizations (groups I and III) were very similar to distributions found in normal subjects (Table 2); mean CMR_{glc} was 5.05 ± 0.82 mg/100g/min (mean ± SD; N = 6) and 5.28 ± 0.76 mg/100g/min (mean ± SD; N = 8), respectively. Excluding focal zones of decrease, mean CMR_{glc} for the remaining brain was normal in all 17 patients.

The interictal ^{18}FDG scan showed localized cortical regions of decreased $LCMR_{glc}$ (D_{MR} = -14% to -58%), which correlated anatomically with EEG spike foci in 12 of the 15 patients who had focal or unilateral EEG localization (Table, Figures 1-3). In abnormal zones, D_{MR} was approximately 1.2 D_{F-18}. There was a corresponding, but lesser, decrease in $^{13}NH_3$ concentration within these hypometabolic zones (D_{N-13} = -6% to -22%). The local depressions in metabolism and perfusion were unchanged in distribution and magnitude in interictal scans repeated on different days in four patients. No differences could be seen between interictal scans made during periods of high and periods of low spike activity in paired interictal studies of three patients. The presence of depth electrodes had no apparent effect on ECT scan results.

XCT scans were performed on all patients. Twelve had normal scans, two had atrophic lesions distant from the epileptic focus, two had atrophic lesions which coincided with the EEG focus but which were smaller in extent than the defect shown on ECT, and one had hemiatrophy corresponding to the EEG localization and the ECT findings (patient #15).

Six patients had anterior temporal lobectomies for intractable partial complex epilepsy [6, 12]; all showed pathological lesions in the resected temporal lobe specimen (Table 1), and all had marked clinical improvement after surgery. Although preoperative XCT showed none of these lesions, preoperative ^{18}FDG scans were abnormal in 5 of these patients; decreased $LCMR_{glc}$ coincided with the resection site and the extent of this metabolic deficit was larger than the extent of structural damage found at pathological evaluation. One subject, patient #3, was found to have left hippocampal sclerosis after a normal interictal ^{18}FDG scan, which was of poor technical quality. Abnormal ^{18}FDG scans are compared with the sites of surgical excision in Figure 3.

Ictal Studies

Three studies were performed in two patients during behavioral seizure activity. In contrast to interictal results, the ictal ^{18}FDG scan patterns clearly showed foci of markedly increased $LCMR_{glc}$ (D_{MR} = +82% to +130%) which correlated temporally and anatomically with ictal EEG spike foci. In both patients, the hypermetabolic ictal focus coincided anatomically with the zone of interictal hypometabolism. There were

corresponding focal increases in $^{13}NH_3$ concentration, similar in location, but of lesser magnitude (D_{N-13} = +26% to +42%). In abnormal zones D_{MR} was approximately 1.2 D_{F-18}.

The scan results of patient #15 are shown in Figure 4. This 12 year old girl had onset of right-sided tonic clonic seizures at age 6 years. These progressed to almost continuous occurrence and four months later, right hemiparesis appeared. Later, she underwent left internal capsulotomy and stereotaxic thalamotomy and the frequency of seizures decreased. At the time of our studies, XCT showed left cerebral hemiatrophy (Figure 4). The interictal EEG recorded unilateral diffuse and multifocal abnormalities lateralized to the left hemisphere. The interictal ECT scans showed marked reduction in glucose utilization and perfusion throughout the entire left hemisphere; for cerebral cortex, D_{MR} = -46% to -72% and D_{N-13} = -22% to -53%. Ictal ECT scans were made when there were repetitive episodes of bilateral jerking of the extremities and the face, which correlated with high voltage 4-5 cps spike and sharp wave complexes in the EEG, most marked in the left parietal region. The same cortical zones which had been hypometabolic and hypoperfused in the interictal scans (dotted arrow) were now hypermetabolic and hyperperfused (solid arrow) i.e., D_{MR} = +116% to +130% and D_{N-13} = +39% to +41% (Figure 4).

The scan results of patient #2 are shown in Figure 5. This 5 year old boy had a 10 month history of right focal motor seizures. X-ray CT, 4-vessel cerebral angiography, and pneumoencephalography were normal. At the time of the interictal

scans, the EEG showed marked irregular 2-4 cps slowing on the left and a left temporal central spike focus. The interictal ^{18}FDG scan demonstrated widespread reduction in $LCMR_{glc}$ in the left temporal parietal cortex (average D_{MR} = -25%). Two identical ictal episodes were studied at an interval of 3 weeks. In each there were repetitive episodes of twitching movements of the right side of the face, which correlated with epileptiform EEG spike activity in the left frontal temporal region. The ictal ECT scans showed focal left temporal increases in $LCMR_{glc}$ (D_{MR} = +118% and +82%) and perfusion (D_{N-13} = +42% and +26%). The ictal focus of maximum metabolism and perfusion appeared similar in the two ictal ECT studies, but the surrounding cortex did not. In the adjacent anterior cortex, metabolism and perfusion were increased in the first ictal study, and decreased in the second.

Local Metabolism - Perfusion Relationship

Figure 6 relates the corresponding measurements of D_{N-13} and D_{MR} as estimates of metabolism-perfusion decreases and increases in abnormal zones during interictal studies in 9 patients and ictal studies in 2 patients. The dotted curve is the predicted locus of tissue data where change in $LCMR_{glc}$ and LCBF would be equal, or matched. This assumes that in each abnormal brain zone there was the same physiological status during $^{13}NH_3$ and ^{18}FDG scans, the relationship of $^{13}NH_3$ uptake to LCBF we found in dog brain, and the biochemical behavior for glucose found in normal human brain. If these conditions were met, there was an approximately matched change in $LCMR_{glc}$ and LCBF in abnormal

zones during both interictal and ictal states.

DISCUSSION

Restrictions in detection and quantifiation

Detection of altered local cerebral function was potentially limited by the spatial resolution of the imaging system, the relatively long fixation time of ^{18}FDG, and the relatively poor response of $^{13}NH_3$ uptake to small changes in LCBF. In addition, quantification was made ambiguous by our incomplete knowledge of both tracers' biochemical behavior in abnormal human brain.

Although ECT is analogous to quantitative autoradiography [64], spatial resolution is much more limiting in the scan method, e.g., fwhm employed in this work was 1.7 cm. Since the widths of gray and white matter structures are commonly smaller than this, quantitative estimates from the scans (Table 2) represent mixtures of the two in unpredictable proportions with underestimation of gray matter values and overestimation of white matter values. In very small tissue volumes, the occurrence of even marked activity excursions may have been missed due to loss in image contrast associated with inappropriate spatial resolution [19]. In averaging over larger structures, concentrations are quantified much more accurately by ECT.

Local events must occur simultaneously with tracer fixation if they are to be detected and quantified. The ^{18}FDG method measures glucose utilization occurring primarily during the first 10 minutes after injection, the time required for substantial ^{18}F fixation. Because of this, the method underestimates transient

increases in metabolic rates which migh be associated with neuronal activities of shorter duration. Altnough none of the ictal events reported here lasted more than a minute or two, apparently this was sufficient to increase glucose utilization significantly. The prolonged trapping requirement for ^{18}FDG, however, could have obscured the recording of any short duration hypermetabolic events associated with transient EEG spikes in our interictal scans. Even the fixation time for $^{13}NH_3$, which is on the order of a minute, may have been too long to detect interictal phenomena which last only milliseconds.

The significance of D_{MR} and D_{N-13} depends on normal glucose utilization and blood flow in the contralateral zone, the basis for comparison. It is likely that this condition was met in our patients with unilateral or focal EEG abnormalities; we found normal contralateral distributions of $LCMR_{glc}$ and ^{13}N in both interictal and ictal states. The zonal difference, D_{MR}, is calculated on the assumption that normal rate constants and LC apply bilaterally. If this is so, D_{MR} is independent of the actual value chosen for LC, but if not, the magnitudes of D_{MR} reported here have the same uncertainty as discussed above for $LCMR_{glc}$ in diseased tissue. D_{F-18} represents the percentage difference of activity concentration in contralateral regions of combined phosphorylated and non-phosphorylated ^{18}FDG. Under the conditions of this study, we found a nearly constant relationship between D_{MR} and D_{F-18}, but this would not necessarily apply to other conditions.

Significance

Interictal results:

The most important finding in this project was that the interictal ^{18}FDG-ECT scan, effectively detected dysfunctional brain zones considered most likely to be responsible for seizures in patients with partial epilepsy. Usually these zones appeared normal on XCT scan. In 13 of 15 patients who had focal or unilateral EEG abnormalities, the ECT scans demonstrated broad regions of cortical hypometabolism and hypoperfusion corresponding to the EEG localizations and lateralizations. In 5 of 6 patients who underwent temporal lobectomy, the interictal ^{18}FDG scan correctly detected the pathologically confirmed lesion as a hypometabolic zone, and removal of the lesion site resulted in marked clinical improvement.

When the non-linear response of $^{13}NH_3$ to flow change is considered, our data suggest that the depressed $LCMR_{glc}$ and LCBF are coupled within the dysfunctional zones (Figure 6). There are conflicting reports concerning the regional CBF of the epileptic focus as measured during the interictal state by the Xe-133 method in patients with partial epilepsy. Our results agree with those of Ingvar et al [26, 27] and Lavy et al [39] who found regional perfusion decreases, but not with Hougaard et al [21] and Sakai et al [63] who found regional perfusion increases. At least some of the responses in the Hougaard series were associated with supra-Sylvian meningiomas which may have been hyperemic. Only one of our patients (#10) had a meningioma; this lesion, too small to be detected by XCT, was surrounded by a larger region of hypometabolic cortex. We found no instances of

increased local perfusion in the interictal state.

The unchanging distribution and magnitude of decreased D_{MR} and D_{N-13} found in repeat interictal studies in four patients suggest that the localized hypofunction found in the interictal state represented regions of permanent brain damage that was undetectable by XCT, rather than transient suppressed function alone. Studies in the chronic epileptic monkey have indicated that continuing clinical seizures are associated with continuing neuronal damage [18]. Pathological changes in the experimental epileptic focus are characterized by glial cell proliferation, loss of neurons, and impairment in local circulation [56]. Biochemical changes in the epileptic focus have also shown the impaired energy metabolism expected from destruction of neurons and their replacement by glial cells [68]. However, this issue is not completely settled. Although hypofunction correlated well with pathological changes in the patients for whom histological evaluations were available, the extent of ECT scan deficits were larger than might have been expected from the size of these lesions. Consequently, it is still not certain that the local hypofunction in these cases represented structural damage alone, or a combined effect including neuronal inhibition during the interictal period [58].

Our paucity of XCT findings contrasts with the reports of Gastaut and Gastaut [17] and Ishida et al [28] who found abnormal XCT scans, primarily atrophic changes, in 63% and 69% of patients with partial epilepsy, respectively. Possibly this discrepancy is a result of differences in our patient referral

pattern. XCT scans were abnormal in only 5 of our 17 epileptic patients. All were atrophic lesions. In three patients (#4, #5 - Fig. 2, #15 - Fig. 4), atrophy seen on XCT coincided with both EEG and ECT localization, but in two of these the metabolic defects were more extensive than the XCT demonstrated atrophy (#4, #5). In the other two patients (#1 - Fig. 3B, #8), focal frontal atrophy was seen on XCT, but EEG and ECT localization was in the temporal lobe, and both had pathological confirmation after anterior temporal lobectomy.

When focal atrophic lesions were clearly defined in the XCT scan and were at least 2 cm wide, metabolic depressions were maximum, i.e., $D_{MR} < -58\%$. This corresponds well with our previously reported finding of $D_{MR} < -62\%$ for old cerebral infarcts in stroke patients [36]. It is clear that the interictal ^{18}FDG-ECT is a more sensitive indicator than XCT for cortical dysfunction.

No increased local uptake occurred in interictal scans of either ^{18}FDG or $^{13}NH_3$, in spite of great differences found in EEG electrical activity, not only among different patients, but also in studies of individuals repeated on different days. Increased uptake occurred only with a behavioral seizure. In one patient, interictal EEG spike discharge corresponding to a hypometabolic zone were more active than the ictal EEG spiking of another patient which was associated with intense focal hypermetabolism. These results agree with those of Engel et al [9], who found electrical afterdischarge alone was insufficient to produce demonstrable increase in local ^{14}C-DG uptake within

the amygdaloid kindled rat brain and is also consistent with the hypothesis that some interictal spikes reflect inhibitory mechanisms [10]. In contrast, Collins [3] found increased ^{14}C-DG uptake during what is considered interictal spiking in the penicillin induced focus within the rat cerebral cortex and we found increased $^{13}NH_3$ uptake in the penicillin induced focus within the dog cerebral cortex [37]. Perhaps this discrepancy was related to the difference in numbers of neuronal elements participating in the generation of interictal spike activity in these very different types of epileptic foci. In the penicillin induced seizures, over 90% of cortical neurons participate in interictal spike discharges [43], whereas extremely few elements are involved in generating interictal spikes in the epileptic focus of man [1], and presumably in the experimental kindled afterdischarge which does not become a seizure. Interictal spiking may involve too few neurons for detection now by ECT scan in man.

Ictal results:

With the appearance of active seizures, we found metabolism and perfusion increased to about twice normal in the cortical epileptic focus, which had been hypometabolic and hypoperfused in the interictal state. It has already been established that the increased neuronal metabolism associated with seizure activity induces increase in regional CBF during active seizures in man [2, 44, 45, 57], but in vivo measurements of the relationships between local metabolism and perfusion during spontaneous seizures in man have not been possible before this study. In

man, the ^{133}Xe-CBF method has been used to record regional CBF increases of 2 to 10 times normal in the epileptic focus during spontaneous seizures [21, 26 27]. The corresponding metabolic response in man has been measured only for the whole brain, by means of the Kety-Schmidt method [44, 57]. During drug-induced generalized seizures in cats, Plum et al [55] found cerebral oxidative metabolism increased over twice normal, but CBF increased even more, due to cerebral vasodilatation combined with neurogenically induced systemic hypertension. None of our patients had either generalized seizures or systemic hypertension at the time of ECT scans. Our data suggest that during partial seizures, focal increases in metabolism and perfusion are coupled, but more experience is needed to define better the relations of these quantities to each other and to the sequence of events during seizure. We interpret our ictal data with caution; $^{13}NH_3$ is not a good indicator for quantifying the large LCBF increases encountered in seizure foci; a proximate $^{13}NH_3$ and ^{18}FDG scan may not represent the same intracerebral events.

In the single patient who was studied twice in the ictal state (Figure 5), localized increased tracer uptake was similar in both ECT scans, but the uptake response in adjacent cortex was not. In ictal study I, the surrounding cortex showed normal glucose utilization and moderate hyperemia; in ictal study II, the adjacent cortex showed definite decreases in both metabolism and perfusion, not only in comparison to the corresponding contralateral values, but also to ipselateral values measured in the interictal state. These depressed values may represent

"surround inhibition", which has been defined electrophysiologically for the penicillin induced focus by Prince and Wilder [58] using intracellular and extracellular electrodes, and metabolically by Collins et al [5] using ^{14}C-DG autoradiography. Within the excessively firing focus, glucose utilization is greatly increased due to the requirement for additional energy for cation pumping, for frequent membrane repolarization and for neurotransmission, but in the surrounding cells, firing and glucose utilization are decreased, due to the continuous postsynaptic hyperpolarization caused by inhibitory circuits from the focus. Surround inhibition may represent an important control mechanism in human epilepsy.

In our ictal patients, the cortex alone was the site of increased radionuclide uptake. Studies of the penicillin induced focus by ^{14}C-DG and ^{14}C-iodoantipyrene autoradiography have shown more widespread ictal activation. In these experimental animals, unilateral seizures were accompanied by increased $LCMR_{glc}$ and LCBF, not only in the cortex, but also in the ipselateral basal ganglia and thalamus, and in the contralateral cerebellum [4, 20, 65]. It is not known if the same kind of deep activation occurs during partial seizures in man. The ^{133}Xe-CBF method is not capable of showing deep activation, and more experience is needed before we learn if it can or cannot be demonstrated by ECT.

Value in epilepsy

For most patients with partial epilepsy, conventional diagnostic methods suffice, i.e., clinical evaluation with surface EEG recording for localization and XCT for detection of

tumor or scar. But for the approximately 20% of patients who are uncontrolled by medication, additional localization information is usually required if surgery is contemplated [7, 11, 12, 15, 67]. Depth electrode studies have been extremely valuable for this, but sometimes localization of the primary epileptogenic focus is still uncertain, even when ictal activity is recorded [7, 12, 13, 67]. The ECT scan can provide an assessment of local cerebral function complementary to EEG data and with better spatial resolution. Since $^{13}NH_3$ underestimates both increases and decreases in LCBF, the metabolic tracer ^{18}FDG is the preferred indicator now.

Because of the difficulty in coordinating seizures and scans, none of our patients had an ictal ^{18}FDG scan before temporal lobectomy, and correlation of the ictal-hypermetabolic zone with local pathology and surgical result is unknown. But interictal ^{18}FDG scans were more readily obtained and correctly demonstrated, as hypometabolic zones, pathologically confirmed lesions which were considered the sites most responsible for seizures. These results indicate that the interictal ^{18}FDG scan is useful in localizing the responsible focus in patients considered for surgery, and should be especially useful when EEG abnormalities are bilateral or confusing [11, 12]. For example, the scan should help distinguish a frontal site of origin (e.g., patient #4) from a temporal site in those instances when it is difficult to differentiate by EEG a primary temporal lobe onset and a secondary onset propagated from a site distant from the recording electrodes [14, 42]. In other instances, more detailed

localization could be important. For example, in patient #5 (Figure 2), the ^{18}FDG scan gave more precise localization of the zone of decreased function than did the EEG, i.e., focal involvement in Brodman's area 18 and 19 of the occipital lobe but preservation of the primary visual area 17 about the calcarine fissure. Surgical strategy can be influenced by such information. More experience is needed to learn if a combination of surface EEG and interictal ^{18}FDG scan will obviate the need for depth electrode measurements in any patient on whom surgery is planned.

With further development, the ECT method should have potential usefulness in the study of epilepsy beyond survey of the preoperative patient. A comparison of functional mapping by ^{18}FDG-ECT in man and ^{14}C-2DG autoradiography in animals may aid validation of experimental models of epilepsy and improve our understanding of human epilepsy. ECT of ^{18}FDG, and other indicators of local physiological processes, may help in categorizing better the various forms of the disorder, and in elucidating the basic mechanisms of epilepsy in man.

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DEFINITIONS

^{14}C-DG	^{14}C-deoxyglucose
CMR_{O_2}	Cerebral metabolic rate for oxygen
D_{N-13}, D_{F-18}, D_{MR}	Percentage differences existing between selected zones and corresponding contralateral zones for mean values of ^{13}N concentration, ^{18}F concentration, and $LCMR_{glc}$, respectively.
ECT	Emission computed tomography
EEG	Electroencephalography
^{18}FDG	^{18}F-fluorodeoxyglucose
fwhm	Full-width-at-half-maximum, a measure of spatial resolution
LC	Lumped constant
LCBF	Local cerebral blood flow
$LCMR_{glc}$	Local cerebral metabolic rate for glucose

SD	Standard deviation
XCT	X-ray computed tomography

Table 1: Interictal Studies and Pathological Results

EEG Classification		Patients			Location of Abnormal Findings			Pathological Result
		#	Age	Seizures	EEG	XCT (atrophy)	$LCMR_{glc}$ (decrease)	
Group I	Unilateral	1	45	complex	*L.temp.	L.front.	L.temp.(L.front.)	L.temp.; hipp.scler
	Focal	2	5	elementary	L.temp.	normal	L.temp.	
		3	24	complex	*L.temp.	normal	normal	L.temp.; hipp.scler
		4	22	complex	L.front.	L.front.	L.front.	
		5	19	complex	*R.temp. occip.	R.occip.	R.temp.occip.	
		6	20	complex	L.temp.	normal	R.temp.	
Group II	Bilateral	7	16	complex	R>L temp.	normal	R=L temp.	
	Focal	8	31	complex	*R>L temp.	R.front.	R.temp.(R.front.)	R.temp.; tub.scler.
		9	43	complex	L>R temp.	normal	normal	
		10	23	complex	*R>L temp.	normal	R.temp.	R.temp.; mening.
		11	20	complex	*R>L temp.	normal	R.temp.	R.temp.; hipp.scler.
		12	23	complex	L>R temp.	normal	R.temp.	
		13	19	complex	*R>L temp.	normal	R>L temp.	R.temp.; hipp.scler.
Group III	Unilateral	14	4	elementary	L.hemis.	normal	L.hemis.	
	Diffuse or Multifocal	15	12	complex	L.hemis.	L.hemis.	L.hemis.	
Group IV	Bilateral	16	15	complex	bilateral	normal	R.front.par.	
	Diffuse or Multifocal	17	5	complex	bilateral	normal	normal	

These EEG localizations were derived from more extensive evaluations, including depth electrode recordings of interictal and ictal events. In some cases, the localization indicated here differed considerable from the localization of interictal EEG spike activity recorded at the time of the ECT scan [12].

Abbreviations: front. - frontal lobe; temp. - temporal lobe; par. - parietal lobe; occip. - occipital lobe; hemis. - hemisphere; hipp. scler. - hippocampal sclerosis; tub. scler. - tuberous sclerosis; mening. - meningioma.

Table 2 Cerebral distributions from $^{13}NH_3$ and ^{18}FDG scans

Brain Zones	Normal Subjects (both hemispheres)			Epilepsy Patients (Groups I, II) (contralateral hemisphere)		
	^{13}N (relative activity)	^{18}F (relative activity)	CMR_{glc} (mg/100g/min)	^{13}N (relative activity)	^{18}F (relative activity)	CMR_{glc} (mg/100g/min)
Subjects	(7)	(10)	(8)	(7)	(8)	(6)
Frontal gray	73.9±5.3	80.0±3.8	6.80±0.92	78.8±7.5	85.1±10	6.17±1.4
Temporal gray	80.4±3.9	81.8±3.2	6.84±0.45	87.4±12	94.3±10	6.56±1.3
Parietal gray	76.6±2.7	77.6±2.3	6.43±0.83	85.2±7.2	86.6±7.0	6.66±1.3
Occipital gray	72.3±3.1	76.8±3.1	6.41±0.92	78.6±9.4	78.8±12	5.93±0.92
Caudate nucleus, thalamus	81.8±4.9	80.7±5.9	6.71±0.56	84.9±13	85.8±7.7	5.82±1.0
Visual cortex	91.8±5.0	91.4±5.3	7.87±0.92	95.5±4.1	94.4±8.5	7.01±1.2
Frontal white	47.6±3.9	51.9±6.6	4.16±1.0	53.9±4.3	57.3±6.1	3.86±0.56
Parietal white	42.5±4.0	43.8±2.9	3.27±0.59	49.5±8.1	54.0±8.4	3.70±0.53
Occipital white	49.2±5.0	46.2±3.3	3.51±0.56	58.4±2.9	54.8±6.2	3.64±0.56
Mean gray	79.5±3.0	81.6±2.9	6.86±0.83	84.5±7.2	87.5±7.6	6.36±1.1
Mean white	47.3±4.1	47.8±3.7	3.70±0.71	54.0±3.3	55.4±5.9	3.73±0.55
Mean gray/ mean white	1.69±0.15	1.72±0.10	1.88±0.17	1.57±0.17	1.59±0.09	1.70±0.11

The epileptic patients listed here had unilateral EEG abnormalities (Groups I and III in Table 1). ^{13}N and ^{18}F values are relative cerebral concentrations, normalized to the maximum concentration in each subject (peak visual cortex value = 100). $LCMR_{glc}$ calculations were based on the operational equation and constants contained in references 23, 36, 52. Cerebellum values were not obtained from all subjects and are not included here. The values are the means ± standard deviations.

LEGENDS

Figure 1 Interictal scans. This four year old girl (patient #14) had persistent right-sided tonic clonic seizures and right hemiparesis of three years duration. The ^{18}FDG scans showed a marked reduction in cortical glucose utilization (D_{MR} = -49%) over broad zones of the left cerebral hemisphere (arrows); there were corresponding, but lesser decreases in $^{13}NH_3$ concentration. Diffuse and multifocal EEG abnormalities were recorded in the left hemisphere, but the XCT, cerebral arteriogram, and pneumoencephalogram were normal.

Figure 2 Interictal scan. This 19 year old woman (patient #5) had the onset of partial complex seizures at age 9. For the last 7 years she had experienced visual seizures, increasing to several times a day, half of which were followed by partial complex seizures. Focal EEG spike activity originated in the right occipital and posterior temporal region. On XCT, there was a small non-enhancing cyst in the subcortical region of the right occipital lobe which had not changed in appearance for the past four years. The ^{18}FDG scan showed a more prominent and extensive decrease in glucose utiliation (D_{MR} = -29%) within the right occipital cortex, probably in associative visual cortex. Scans at other levels showed the cortex of the posterior temporal lobe was also hypometabolic.

Figure 3 Surgically proven hippocampal sclerosis. Horizontal arrows indicate hypometabolic sites found in interictal ^{18}FDG scans (below) and corresponding temporal lobectomy sites in post-operative XCT scans (above). The temporal lobe appeared normal in all pre-operative XCT scans. (A) Patient #11. An extension of decreased $LCMR_{glc}$ to higher levels of the right temporal lobe (not shown) distinguished the appearance of this ^{18}FDG scan from an angled scan of a normal brain. (B) Patient #1. Vertical arrow indicates left frontal atrophy from trauma sustained in an auto accident which resulted from a seizure. This was noted on both pre-operative XCT and ^{18}FDG scans. (C) Patient #13. $LCMR_{glc}$ was reduced in both temporal lobes, but the decrease was greater on the right side.

Figure 4 Interictal and ictal scans of patient #15, a 12 year old girl who had a 6 year history of right-sided tonic clonic seizures and hemiparesis. XCT indicated atrophy of the left cerebral hemisphere. The interictal ^{18}FDG and $^{13}NH_3$ scans showed marked hypometabolism and hypoperfusion in the cerebral cortex of the left hemisphere (dotted arrow). In contrast, ictal scans showed marked left cortical hypermetabolism and hyperperfusion (solid arrow) coincidental with bilateral jerking of the extremities and face and epileptiform EEG spike activity, most

marked in the left parietal region. Although images are at different absolute gray scales, interictal and ictal values of $LCMR_{glc}$ for the right hemisphere were normal and similar (interictal and ictal mean CMR_{glc} = 6.46 and 5.34 mg/100g/min, respectively).

Figure 5 Interictal and ictal scans of patient #2, a five year old boy who had a ten month history of right focal motor seizures. XCT arteriography, and pneumoencephalography were normal. The interictal ^{18}FDG scan showed hypometabolism in the left temporal parietal cortex (dotted arrow). At this same site, two separate ictal studies showed marked focal hypermetabolism and hyperperfusion (F), coincidental with right facial twitching and epileptiform EEG spike activity in the left frontal temporal region. In one study, hypometabolic cortex (solid arrow) was seen adajacent to the hypermetabolic fo s, suggesting a "surround inhibition" process. Ic mean CMR_{glc} of the right hemisphere was normal. XCT was normal at the time of these scans.

Figure 6 Relationship of D_{N-13} and D_{MR} in abnormal brain zones during interictal and ictal states. The dotted curve is the predicted locus of tissue data where change in LCBF and $LCMR_{glc}$ would be matched. Solid symbols are data from single interictal studies in eight patients and two ictal studies of patient #2. Open symbols are

data from multiple sites within the abnormal zone of patient #15, during an interictal and an ictal study. In this patient, D_{MR} decreases exceeding -70% were the same in interictal and ictal studies and represented a porencephalic cyst (see XCT in Fig. 4).