ORTICOSTEROIDS are commonly administered, often for prolonged periods, to patients with brain tumors for the symptomatic relief of cerebral edema. Common consequences of long-term corticosteroid therapy include centripetal obesity with cushingoid facies, abdominal striae, disordered sleep patterns, and neuropsychiatric disturbances ranging from mild behavioral changes to major psychoses. Adrenal glucocorticoids are known to affect cell glucose utilization throughout the body and studies have shown there is an effect on brain–glucose utilization, although the mechanism of neuropsychiatric abnormalities in patients with long-term corticosteroid therapy is unclear. In preliminary work we noted by using positron emission tomography (PET) with the glucose analog ([18F]fluoro-2-deoxyglucose (FDG) that there was a marked reduction in cerebral glucose utilization in patients with Cushing’s disease who had high circulating levels of endogenous corticosteroids.

In the present study our hypothesis was that exogenous corticosteroids reduce cerebral glucose metabolism (CMRglu). Thus we measured glucose metabolism, using FDG-PET, in patients with brain tumors to evaluate the effect of exogenous corticosteroids (in this instance, dexamethasone) on glucose metabolism. Fifty-six FDG-PET studies obtained in 45 patients with unilateral supratentorial brain tumors were analyzed. Patients with brain tumors were divided into three groups: 1) patients with cushingoid symptoms, who had been treated with combinations of radiotherapy and chemotherapy taking oral dexamethasone; 2) patients not taking dexamethasone but treated with radiotherapy; and 3) patients not taking dexamethasone who had not been treated with radiotherapy. Serial FDG-PET scans were obtained in eight of the cushingoid patients. Glucose metabolism was measured in the contralateral cerebral and ipsilateral cerebellar hemispheres in patients and compared to measurements taken from 19 normal volunteers. The authors found that in the cushingoid brain tumor patients there was a marked reduction in CMRglu compared to normal volunteers and other brain tumor patients (Kruskal–Wallis test; p < 0.001). In the majority of patients who had serial FDG-PET scans, there was a decline in glucose metabolism over time and in one patient, in whom dexamethasone was reduced in dosage, there was a subsequent increase in CMRglu. The authors conclude that there is a generalized reduction in CMRglu in brain tumor patients taking dexamethasone compared to other brain tumor patients and normal volunteers, and that this effect is independent of radiotherapy, concurrent anticonvulsant medication, and transhemispheric functional disconnection (transhemispheric diaschisis).
Clinical Material and Methods

Patient Population

All patients were studied under protocols approved by committees of the National Institute of Neurological Disorders and Stroke and the Clinical Center of the National Institutes of Health. Informed consent was obtained from all subjects prior to their participation in the studies.

All patients had a unilateral brain tumor that was confirmed by magnetic resonance (MR) imaging. Patients were excluded if: 1) the cerebral hemisphere contralateral to the tumor was edematous or atrophic, had abnormal signal intensity on T₁- or T₂-weighted sequences, or was compressed by mass effect; and 2) the corpus callosum was involved by tumor or edema. Pathological diagnoses of the cerebral astrocytomas were based on the World Health Organization (WHO) classification and, for this paper, patients were separated into categories of low-grade astrocytoma (LGA), anaplastic astrocytoma (AA), glioblastoma multiforme (GBM), and oligodendroglioma.

Clinical protocols and data for the patients were as follows. Patients were divided into three groups: A, B, and C. Group A consisted of patients with cushingoid facies (confirmed by the patient and a close relative) who had been taking oral corticosteroids (dexamethasone) for at least 2 months. There were seven men and nine women in this group, with a mean age of 42 years (range 24–61 years). All patients complained of significant weight gain after the institution of dexamethasone; the majority developed striae of the abdomen and upper thighs and two patients had multiple vertebral body-crush fractures. Methods of diagnosis were surgical resection in two cases, partial surgical resection in seven, open biopsy in five and stereotactic biopsy in two cases. Pathological diagnoses were GBM in six patients, AA in eight, anaplastic oligodendroglioma in one, and LGA in one patient. Tumors involved a single cerebral lobe in seven patients (parietal in four patients, temporal in one, frontal in one, and occipital in one). The frontal lobe was involved in two, the temporal lobe in two, the parietal lobe in one, and the occipital lobe in three. Pathological diagnoses were GBM in six patients, AA in nine, anaplastic oligodendroglioma in three patients.

In Group B, patients with brain tumors had been treated with radiation therapy but had never taken dexamethasone or had not used it for at least 4 months prior to the PET scan. The patients in this group consisted of 13 men and 3 women with a mean age of 43 years (range 26–63 years). Methods of diagnosis were partial surgical resection in 10 cases, open biopsy in three, and stereotactic biopsy in three cases. Pathological diagnoses were GBM in two patients, AA in nine, and LGA in five. Gliomas were limited to a single cerebral lobe in 13 patients (frontal in seven patients, temporal in three, occipital in two, and parietal in one) or the thalamus in one patient. Frontoparietal and temporoparietal lobes were involved in two others. All patients had been treated with external-beam radiotherapy in doses varying from 54 to 70 Gy with four patients receiving less than 60 Gy. In addition, one patient had external-beam radiotherapy (60 Gy) plus IB (60 Gy) and one patient had external-beam radiotherapy (60 Gy) and a radiosurgery boost.

Group C was composed of patients who had not been treated with radiation or chemotherapy at the time of the PET study. There were eight men and five women in this group with a mean age of 43 years (range 26–66 years). Methods of diagnosis were partial surgical resection in five cases, open biopsy in two, and stereotactic biopsy in six. Pathological diagnoses were GBM in one patient, AA in two, LGA in seven, and oligodendroglioma in three patients. In five cases the tumor was restricted to the frontal lobe, in three cases to the parietal lobe, and in two cases to the temporal lobe. The frontoparietal lobes were involved in three cases. One patient had begun dexamethasone therapy (16 mg/day) the day prior to the PET scan but treatment was stopped 12 hours before commencing the PET study.

The patients were matched as closely as possible for tumor size and location across the three groups. In two patients with LGA (one each from Groups A and B) the clinical course was that of a high-grade glioma and both patients had foci of markedly increased glucose metabolism in the tumor on FDG-PET scans, suggesting that although pathology indicated low-grade tumors, the pathological assessment was inaccurate because of sampling error. No patient had corticosteroid-induced hyperglycemia. Forty-one of 45 patients were taking regular anticonvulsant medication. In the majority of cases this was used as monotherapy with phenytoin, carbamazepine, sodium valproate, or phenobarbital. Ten patients were taking two anticonvulsants for seizure control. Two patients in Group A and one patient each in Groups B and C were not taking anticonvulsant medication.

Neuroimaging Studies

Two tomographs were used for the study. All but two of the FDG-PET studies were performed using a 15-section tomograph (PC 2048-15B; Scanditronix, Uppsala, Sweden) with 6-mm inplane resolution and 6-mm section thickness. Two patients had a second PET study performed using a seven-slice scanner (PC 1024-7B, Scanditronix) with 6- to 7-mm inplane resolution and 10.5-mm slice thickness. Our FDG-PET technique has been described in detail elsewhere. Patients fasted for at least 6 hours before the study. The FDG (185 MBq) was injected...
via a peripheral intravenous line. Blood was sampled at
timed intervals throughout the study from a cannula
placed in the radial artery at the wrist to determine the
input function. For five studies the input function was
derived from “arterialized-venous” blood samples drawn
from a venous cannula placed in the dorsum of a heated
hand.9 Emission scans were performed after a 30-minute
uptake period and interleaved to cover the entire brain.
The study duration was 70 minutes. Measured attenuation
correction was performed for each study. Imaging planes
were oriented parallel to the canthomeatal line. Subjects’
eyes and ears were patched and their heads immobilized
by a thermoplastic mask molded to the contours of the
face for the duration of the study. The FDG-PET exami-
nation was conducted in a quiet, dimly lighted room. All
data were corrected for scatter and random coincidences.
Glucose metabolic rates were calculated using a modifi-
cation9 of the Sokoloff three-compartment model43 with
the following gray matter rate constants: $k_1 = 0.1020; k_2 =
0.1300; k_3 = 0.0620; k_4 = 0.0068.40$ The lumped con-
stant value was 0.4180.39 Serum blood glucose level was
measured prior to and during the PET scan.

With respect to the brain tumor, glucose metabolism
was measured in the contralateral cerebral hemisphere,
supratentorial cortex (frontal, temporal, parietal, and cerebel-
lar hemisphere).5,17 Readings were taken from circular
ROIs measuring 8 mm in diameter (12 pixels). The ROIs were positioned to sample clearly
identifiable functional anatomical landmarks on the PET
scans. There were 100 circular and one irregular ROIs.
Readings were taken with the circular ROIs in the frontal,
parietal, temporal, and occipital lobes; the precuneus;
deep nuclei (caudate, putamen, thalamus); cerebellar
hemispheres; cerebellar vermis; and brainstem. Cortical
ROIs did not overlap and were equally spaced to cover the
cortical mantle. Thus the main cerebral lobes, rather than
discrete gyri, were analyzed with the aid of an atlas.3 The
irregular ROI was drawn in the white matter of the cen-
trum semiovale above the bodies of the caudate nuclei.
Tissue sections used in the analysis were selected in
advance by the senior investigator (M.J.F.). Nineteen
normal volunteers, eight men and 11 women with a mean age
of 42 years (range 21–67 years) were also included in the
study as a control group. In the case of normal volunteers,
there is very little difference between Groups
A and C.

Mean regional $CMR_{glu}$ for normal volunteers and the
three patient groups are shown in Table 1. Regional
$CMR_{glu}$ was significantly lower in Group A compared to
normal volunteers ($p < 0.001$) in all regions analyzed.
Group A patients also had reduced $CMR_{glu}$ throughout
the supratentorial cortex (frontal, temporal, parietal, and
occipital lobes and precuneus; $p < 0.001$), ipsilateral
cerebellar cortex ($p < 0.01$), thalamus ($p < 0.001$ for Group
B and $p < 0.05$ for Group C) and basal ganglia ($p <
0.001$) compared to Groups B and C.

Figure 1 shows scatter plots of single values from each
patient for the cerebrum, parietal lobe, and cerebellar
hemispheres. Scatter plots for the individual anatomical
regions showed a similar pattern. For all regions there
were no statistical differences in $CMR_{glu}$ between those
patients who were treated with modalities other than sur-
gery (Group B) and those who were untreated (Group C).
Groups B and C had lower glucose metabolism ($p < 0.05$)
than normal volunteers in all regions except the frontal
lobe and precuneus. However, as can be seen from the
scatter plots in Fig. 1, there is overlap between Groups
B and C and the normal volunteers. In the case of the cere-
bellum, if one excludes the single outlier in the normal
volunteers, there is very little difference between Groups
B, C, and the normal volunteers. Glucose metabolism
in deep nuclei (caudate, putamen, and thalamus) was sig-
nificantly lower for Group C ($p < 0.05$) compared to nor-
mal volunteers, whereas for Group B only the putamen
showed lower glucose metabolism when compared to nor-
mal ($p < 0.05$).

Mean $CMR_{glu}$ for patients in Group A who had serial
PET studies are shown in Table 2. Six patients (Cases 4,
7, 9, 12, 13, and 16) were not taking corticosteroids at the
time of their first PET scan. Four of these six patients had
recently been diagnosed. In all but two patients (Cases 8
and 10) there was a progressive reduction in $CMR_{glu}$. In
Case 8 there was minimal change in $CMR_{glu}$ over a 4-
month period. However, the patient in Case 10 showed a
40% increase in CMR<sub>glu</sub> over a 7-month period, which coincided with a reduction in dexamethasone dosage from 26 mg per day to 4 mg per day because of the development of multiple vertebral body-crush fractures. In Fig. 2 representative FDG-PET scans are shown for Case 7; the scans were obtained before the patient began to take dexamethasone and again two months later when the patient was taking 32 mg dexamethasone per day. Enhanced MR images (Fig. 3) obtained in Case 7 within 1 week of each of these FDG-PET scans show the development of an area of gadolinium enhancement not evident on the first MR study, which involves the white matter of the right frontal lobe and adjacent gray matter. There is no evidence of cerebral atrophy between MR imaging studies. In two of the three patients who had three studies, dexamethasone dosage increased between Study 2 and Study 3. In Case 4, the dexamethasone dosage remained at 12 mg per day between Study 2 and Study 3.

Cerebral atrophy was not reported in the hemisphere contralateral to the tumor in any patient on MR imaging. However, in the patients in Group A who had serial studies minimal cerebral atrophy consisting of widening of the cerebral sulci was noted in three patients (Cases 10, 12, and 16).

**Discussion**

The main findings of this study are: 1) CMR<sub>glu</sub> is markedly reduced in patients with brain tumor who are treated with chronic oral corticosteroid therapy. Although only observed in a single case, a reduction in corticosteroid dosage was associated with an increase in CMR<sub>glu</sub>. 2) A mild reduction in contralateral CMR<sub>glu</sub> is also seen in patients with brain tumor who are not taking corticosteroid therapy. These in vivo human data indirectly support earlier in vivo animal work by Kadekaro, et al.,<sup>26</sup> who

**TABLE 1**

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal Volunteers</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Hemisphere</td>
<td>Right Hemisphere</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>8.44 ± 1.08</td>
<td>8.55 ± 1.06</td>
</tr>
<tr>
<td>frontal lobe</td>
<td>9.46 ± 1.26</td>
<td>9.55 ± 1.26</td>
</tr>
<tr>
<td>occipital lobe</td>
<td>10.31 ± 1.48</td>
<td>10.34 ± 1.40</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>10.03 ± 1.17</td>
<td>10.05 ± 1.22</td>
</tr>
<tr>
<td>precuneus</td>
<td>10.79 ± 1.35</td>
<td>10.61 ± 1.61</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>10.29 ± 1.30</td>
<td>10.31 ± 1.51</td>
</tr>
<tr>
<td>putamen</td>
<td>11.24 ± 1.62</td>
<td>11.20 ± 1.59</td>
</tr>
<tr>
<td>thalamus</td>
<td>10.64 ± 1.29</td>
<td>10.45 ± 1.32</td>
</tr>
<tr>
<td>white matter</td>
<td>2.44 ± 0.32</td>
<td>2.45 ± 0.35</td>
</tr>
<tr>
<td>total cortex</td>
<td>9.42 ± 1.19</td>
<td>9.50 ± 1.23</td>
</tr>
<tr>
<td>cerebellar hemispheres</td>
<td>7.95 ± 0.86</td>
<td>7.90 ± 0.86</td>
</tr>
<tr>
<td>cerebellar vermis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>brainstem</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Values are expressed as means ± standard deviations. Glucose metabolism in patients was measured in the cerebral hemisphere contralateral to the brain tumor, in the ipsilateral cerebellar hemispheres, and in the midline posterior fossa structures (cerebellar vermis and brainstem). Glucose metabolism in normal volunteers was measured in both cerebral and cerebellar hemispheres. CMR<sub>glu</sub> = cerebral glucose metabolism; NA = not applicable. See text for definitions of Groups A, B, and C.
reported an acute increase in cerebral glucose utilization after adrenalectomy in rats, using \[^{14}\text{C}2\text{-deoxyglucose}\] autoradiography, and an \textit{in vitro} study in which corticosterone and dexamethasone were shown to inhibit glucose uptake in cultured hippocampal neurons and glial cells with an apparently dose-dependent receptor-mediated action.\(^{23}\)

However, a number of other factors may potentially affect glucose metabolism in the contralateral hemisphere in patients with brain tumors: direct tumor infiltration, functional disconnection (diaschisis), cerebral atrophy, radiation therapy, and anticonvulsant medication. Direct tumor infiltration of the opposite cerebral hemisphere would reduce cortical glucose metabolism by compression of cortical gray matter or by deafferentation through involvement of white matter tracts. Although microscopic involvement of the opposite cerebral hemisphere could not be excluded, there was no clinical or MR imaging evidence (gadolinium enhancement or increased T\(_2\) signal intensity) indicating involvement. Thus we believe that tumoral extension is not a likely mechanism for our findings.

Von Monakow\(^{47}\) first introduced the concept of “diaschisis.” Although there has been controversy regarding its definition,\(^{48}\) the currently accepted definition of diaschisis encompasses “. . . all remote effects of acute and chronic cerebral injury.”\(^{2,30}\) Diaschitic involvement of the contralateral cerebellar hemisphere, with respect to a supratentorial lesion, and the ipsilateral and contralateral cerebral hemispheres are now generally recognized.\(^{5,16,17,37}\) Most studies of transhemispheric diaschisis have used the model of cerebral ischemia as the mechanism of cerebral injury in patients with stroke or a variety of methods to induce ischemia\(^2\) in animals, and it is apparent that

**Fig. 2.** Case 7. \[^{18}\text{F}\] fluoro-2-deoxyglucose (FDG) positron-emission tomography (PET) scans obtained in a 35-year-old man with an anaplastic astrocytoma of the right superior parietal lobe. These FDG-PET images are from studies undertaken prior to (upper) and following (lower) 2 months treatment of dexamethasone at 32 mg per day. Both studies are scaled to the same maximum value. The tumor is seen as a small focus of markedly increased glucose metabolism in the right cingulate cortex abutting onto the midline (upper). The tumor is much more evident on the second FDG-PET scan (lower); in addition, marked reduction in cerebral glucose metabolism is seen in both cerebral hemispheres. (Note: color scale indicates glucose metabolism in milligram of glucose/100 g tissue/min; the right side of brain is on reader’s left.)
TABLE 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Study 1</th>
<th>Study 2 (mos from 1st study)</th>
<th>Study 3 (mos from 1st study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>9.36 ± 0.90</td>
<td>7.05 ± 0.73 (3)</td>
<td>6.49 ± 0.72 (7)</td>
</tr>
<tr>
<td>7</td>
<td>9.37 ± 0.85</td>
<td>7.56 ± 0.84 (2)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6.67 ± 0.52</td>
<td>6.78 ± 0.63 (4)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>7.74 ± 0.84</td>
<td>6.54 ± 0.59 (7)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4.98 ± 0.47</td>
<td>8.70 ± 1.18 (7)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7.69 ± 0.69</td>
<td>4.50 ± 0.49 (2)</td>
<td>3.48 ± 0.48 (6)</td>
</tr>
<tr>
<td>13</td>
<td>5.89 ± 0.69</td>
<td>4.75 ± 0.60 (12)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>7.70 ± 0.71</td>
<td>6.35 ± 0.75 (11)</td>
<td>4.68 ± 0.57 (20)</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviations. CMRglu = cerebral glucose metabolism; FDG-PET = [18F]fluoro-2-deoxyglucose–positron emission tomography.
Steroids and brain metabolism

changes in glucose utilization rates in patients on steroid therapy should reflect a true decrease in the metabolic rate.43

We can only speculate as to the mechanism of the dexamethasone-induced reduced glucose metabolism. Dexamethasone may have a direct effect on glucose utilization within neurons and neuroglia or there may be a direct effect on glucose transport via glucose transporters. Recently, five functional facilitative glucose transporters have been cloned and identified8,32,38 and Olgemöller, et al.,35 have postulated that cortisol has a direct effect on the endothelial transport of glucose. However, glucocorticoid receptors are widely distributed in glia and neurons, which may also explain the generalized metabolic effect.1,29

Sapolsky and colleagues36,41 demonstrated in vitro and autoradiographically that glucocorticoids have a selective action on the hippocampus and the authors suggest that this action may relate to several neuropsychiatric problems. We did not specifically measure glucose metabolism in the hippocampus because the small size of the relevant structures (dentate gyrus and subiculum) are beyond the resolution of the PET tomographs we used in this study. Despite this our results indicate that the effect of dexamethasone is global rather than localized.

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663
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