EFFECTS OF INTRACAROTID ADMINISTRATION OF
NITROGEN MUSTARD
ON NORMAL BRAIN AND BRAIN TUMORS

J. D. FRENCH, M.D., P. M. WEST, M.D., F. K. VON AMERONGEN, M.D.
AND H. W. MAGOUN, PH.D.
Veterans Administration Hospital, Long Beach, California, and the Departments of Surgery, of
Anatomy, and of Biophysics, University of California, Los Angeles, School of Medicine
(Received for publication March 3, 1952)

The relative effectiveness of intravenous nitrogen mustard in the
palliative treatment of neoplastic diseases has been extensively re-
ported since the first clinical trials by Gilman and associates in 1942.5
Such therapy was found to be of limited value, however, since experience
showed that temporary regression occurred primarily in the malignant
lymphomas and only occasionally in bronchogenic carcinoma.6,10,11 The
great majority of neoplasms appeared to be resistant to the drug. Recently
this concept has been altered by Bierman et al.1,2,3,4 and Klopp et al.9 who
devised techniques for the administration of nitrogen mustard in high
dosage directly to the tumor by way of its arterial blood supply and found
even radio-resistant neoplasms to be responsive under these conditions.
This approach is particularly applicable for chemotherapy of primary and
secondary tumors of the liver, where the normal parenchyma has a double
blood supply and the neoplasm only one,1 thus permitting selective concen-
tration of the drug in the lesion.

While similar vascular anatomy is not found in the brain, the possibility
of treating intracranial malignancies was suggested by reports of such
regional therapy, since it was felt that the high resistance of nervous tissue
to irradiation might permit administration of a radiomimetic drug in suffi-
cient dosage to damage the neoplasm without destroying normal brain.
For this reason, experiments were performed in cats and monkeys to study
the effect produced by the injection of HN₂ (methyl bis β—chloroethyl
amine) into the carotid artery on function and structure of the brain.
These effects were correlated with those observed after similar injections in
3 patients suffering from primary or metastatic cerebral disease.

METHOD AND PROCEDURE

Chronic experiments were performed on 9 cats and 2 monkeys. These animals
were anesthetized with barbiturates and 0.25 to 1.2 mg./kg. body weight of HN₂
was injected into the carotid artery after its exposure in the neck. Postoperatively,
frequent observations were made and periodic EEG tracings were recorded by scalp
electrodes during the survival period of the animal. At the conclusion of each experi-
ment autopsy was carried out and pathological sections were made of the brain.

Acute experiments were made on 5 cats and 1 monkey in which from 1 to 4
mg./kg. body weight of HN₂ were injected into the internal or common carotid
artery after exposure of the vessel in the neck. In 2 cats, the procedure was carried out under barbiturate anaesthesia. The remaining animals were prepared under ether and immobilized either with Syncurine or by section of the cervical spinal cord, the animal being sustained on artificial respiration. Electro cortical activity was recorded on a Grass Amplifier and Inkwriter before, during, and after injection from screw electrodes in the calvarium. In one animal, HN₂ was applied to the cortex directly on a piece of filter paper, and later a small amount was injected directly into the brain.

Clinical observations were made following the injection of 0.20 to 0.27 mg./kg. of body weight of HN₂ into the exposed internal carotid artery in 3 patients suffering from neoplastic disease involving the brain. The drug was dissolved in saline, 0.5 mg./cc., and given at the rate of 1.0 mg./min. One patient received an equivalent additional injection 6 weeks after the first because of recurrence of symptoms. The brains were studied at autopsy in all instances.

### TABLE 1

**INTRACAROTID HN₂ - CHRONIC ANIMAL EXPERIMENTS**

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>ANIMAL</th>
<th>BRAIN DISTURBANCE</th>
<th>FACE DISTURBANCE</th>
<th>SURVIVAL PERIOD (DAYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MG/K OR OVER</td>
<td>CAT 4</td>
<td>+</td>
<td>-</td>
<td>2 DAYS</td>
</tr>
<tr>
<td></td>
<td>CAT 16</td>
<td>+</td>
<td>+</td>
<td>4 DAYS</td>
</tr>
<tr>
<td></td>
<td>CAT 17</td>
<td>+</td>
<td>-</td>
<td>7 DAYS</td>
</tr>
<tr>
<td>.75 - .90 MG/K</td>
<td>CAT 1</td>
<td>+</td>
<td>+</td>
<td>16 DAYS</td>
</tr>
<tr>
<td></td>
<td>CAT 6</td>
<td>+</td>
<td>-</td>
<td>4 DAYS</td>
</tr>
<tr>
<td></td>
<td>CAT 14</td>
<td>+</td>
<td>-</td>
<td>23 DAYS</td>
</tr>
<tr>
<td>.50 MG/K</td>
<td>CAT 8</td>
<td>+</td>
<td>+</td>
<td>10 DAYS</td>
</tr>
<tr>
<td></td>
<td>CAT 12</td>
<td>+</td>
<td>+</td>
<td>7 DAYS</td>
</tr>
<tr>
<td></td>
<td>MONKEY 2</td>
<td>+</td>
<td>+</td>
<td>42 DAYS (SACRIFICED)</td>
</tr>
<tr>
<td>.25 MG/K</td>
<td>MONKEY 1</td>
<td>+</td>
<td>+</td>
<td>42 DAYS (SACRIFICED)</td>
</tr>
</tbody>
</table>

**TWO INJECTIONS 7 DAYS APART**

<table>
<thead>
<tr>
<th>DOSAGE EACH INJECTION</th>
<th>ANIMAL</th>
<th>BRAIN DISTURBANCE</th>
<th>FACE DISTURBANCE</th>
<th>SURVIVAL PERIOD (DAYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>.75 MG/K</td>
<td>CAT 13</td>
<td>+</td>
<td>+</td>
<td>10 DAYS</td>
</tr>
<tr>
<td>.50 MG/K</td>
<td>CAT 9</td>
<td>+</td>
<td>+</td>
<td>30 DAYS (SACRIFICED)</td>
</tr>
<tr>
<td>.25 MG/K</td>
<td>CAT 11</td>
<td>+</td>
<td>+</td>
<td>30 DAYS (SACRIFICED)</td>
</tr>
</tbody>
</table>

**RESULTS**

**ANIMAL OBSERVATIONS**

The results of the chronic experiments are summarized in Table 1. All but 1 animal (Cat 11) manifested some degree of brain disturbance following the injection, varying from transient EEG changes (Monkeys 1 and 2, Cat 9) to marked hemiparesis, cerebral edema, and death. When