THE USE OF RADIOACTIVE IODINATED SERUM ALBUMIN IN THE LOCALIZATION OF INTRACRANIAL LESIONS

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In recent years radioactive isotopes have been used increasingly in attempts to localize intracranial lesions. These studies are performed during the preoperative work-up of a patient and afford ready correlation with other diagnostic procedures, such as angiography, electroencephalography, pneumoencephalography, and ventriculography, which are carried out during the same period.

It is thought that the radioactive materials reach a higher concentration at the site of pathology because of a "disruption" in the blood-brain barrier. The blood-brain barrier represents a selective permeability of blood vessels within the central nervous system. This is probably resident either in the intima of the cerebral capillaries or in the sucker feet of astrocytes and excludes selectively many molecules and electrolytes from the nervous system while allowing the usual transcapillary exchange of metabolites to occur.

In efforts made to localize intracranial pathology with radioactive materials, two more or less independent lines of endeavor have evolved. The first of these, and the one with which we are concerned here, utilizes the differential "pooling" of such radioactive substances as diiodofluorescein (DIF) and iodinated human serum albumin (RISA) by tissues within the cranial cavity that possess a capillary intima with different properties of permeability than the surrounding "normal" capillaries which maintain the blood-brain barrier. External radiation detectors are used to localize these tissues. RISA was used exclusively in this series.

The other method of radioactive survey is one with which we have had no experience. It involves the injection of such substances as P-32 preoperatively, and the use of a Geiger-Müller counter at the operating table after a bone flap has been turned. This presupposes that the general area of the brain in which the tumor resides is known. Thus, if one cannot identify neoplastic tissue grossly, the probe-counter is inserted into the cerebral substance and mapping is performed. An increased uptake in an area suggests the presence of neoplasia. In attempting total extirpation it enhances the possibility of identifying residual nests of tumor which might otherwise be missed.

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Our procedure entailed the intravenous administration of 500 micro-
curies of RISA in adults and proportionately smaller amounts in children.
This amount of radioactivity gave relatively high counting rates with scintil-
ation counters. No deleterious effects were observed in any of our patients.
All patients were premedicated with Lugol’s solution to protect the thyroid
from the radioactive iodine liberated in the metabolism of RISA. It was
found that a period of between 20 and 30 hours after injection represented
the optimal time for localization studies.

Scintillation counters consisting of NaI (Tl) crystals attached to the
requisite photomultiplier tubes, voltage supplies and recorders have been
used as detectors throughout these studies. Scalars were used to record the
total number of counts in a unit of time. Several methods of scanning with
these detectors have been tried. The preliminary work used a skull filled
with rice and sawdust to simulate a brain. This phantom brain was made
uniformly radioactive by soaking in an I-131 solution. “Tumors” of various
sizes and specific activities were placed in different positions within the
cranium and localization was attempted. A few of the methods of scanning
that have been used will be discussed briefly, with an evaluation of their
worth.

One of the first attempts at localization in this laboratory used a single
counter which moved about the head in a circular manner. The scans were
made in both spherical and cylindrical coordinates with the detector kept
at a fixed distance from the center of the head or an axis passing through this
center. This method relies on a comparison of the observed isocount con-
tours with the contours obtained from a “normal” scan. This procedure
was discarded because of the time consumed in a scan and because it was nec-
essary for the patient’s head to be held erect, a requirement that often can-
not be met.

The next course of study utilized a pair of detectors which were fixed so
that the crystals faced each other. With the median plane of the head placed
symmetrically between the counters, the scan was made in a rectangular grid
fashion. The tumor depth was determined from the difference in reading of
the two counters. This method gave good results with a “brain to tumor”
activity ratio as low as 5:1, unless it were in the center of the cavity. Al-
though this procedure showed considerable promise it was discarded as
many patients could not remain in a fixed position for the length of time
that was necessary to complete a survey.

Because of the varied conditions under which patients have been sur-
veyed, it has been found that the most flexible arrangement is the most
satisfactory. In all of the cases reported here the counter was mounted on a
flexible arm so that it could be held perpendicular to the head. In a few
instances the detector was kept at a fixed distance, but usually it was in
contact with the head.

The patient was made to don a tight-fitting cap upon which numbers were
placed symmetrically. This is shown in Fig. 1. Usually 50 to 60 positions were counted: i.e., 25 to 30 on each side of the head. The comparison of paired positions coupled with a "normal" pattern from a control made localization of radioactive concentrations possible. A 1\frac{1}{2} \times 1 \text{ inch} \ NaI (TI) crystal was shielded from the side by \frac{3}{4} \text{ inch} of lead, and from the front by \frac{3}{4} \text{ inch} of lead. The front shield contained a \frac{1}{4} \text{ inch} aperture, which allowed the crystal to "see" a half-angle of 26 degrees. The net counting rates were usually much greater than 3000 counts per minute. Because of these high counting rates a counting time as short as 20 seconds was sometimes used with a probable counting error of less than 3 per cent. To test the reliability of our procedure, at least two surveys were always made; any reading that did not reproduce to within 10 per cent was discounted. No significance was attached to readings that did not show a lateral differentiation of 10 per cent unless the over-all pattern deviated markedly from a "normal" pattern. If the differentiation was less than 10 per cent, it was almost invariably much lower, that is, in the neighborhood of 3 to 6 per cent. This is true of not only the negative cases (those in which space-taking lesions were not found), but also in the instances in which a neoplasm was missed by RISA studies.

**MATERIAL AND RESULTS**

Approximately 70 patients were studied in the course of a 1-year period, using the procedure as outlined above. Only 50 of these have been included in the following statistical analysis, the reason for this being that insufficient
follow-up data are available on all of the patients to allow for meaningful interpretation. No attempt has been made at preferential selection, our only criteria for inclusion in this analysis being histological verification of tumor type either at operation or postmortem examination, or, in the case of other disease entities, indisputable evidence of their presence by adequate follow-up studies. The exceptional circumstances to this are two: first, a deep-seated hemispherical angioma which was demonstrated by angiography but not operated upon because of the patient’s intact neurological status; and second, a tumor in the posterior portion of the 3rd ventricle having a clinical course consistent with pinealoma as well as the usual salutary response to roentgen-ray therapy.

Table 1 is a breakdown of the cases studied. The criterion as to whether the scintillation counter studies were “right” or “wrong” was based upon their ability to predict the presence or absence of a presumed space-taking intracranial lesion. From the pathophysiologic standpoint, this is possibly an erroneous presumption; in fact, one may even say that it probably is. To divide arbitrarily all intracranial lesions into those that displace cerebral tissue and those that do not is certainly not reasonable if one is to think dynamically in terms of the blood-brain barrier. For instance, where would one “pigeon-hole” the edema that is at times consequent upon cerebral thrombosis? We do not ordinarily think of an infarcted area as being a “space-consuming” lesion, and yet it is sometimes precisely that, even producing a massive shift of the ventricular system from one side to the other.

Our only justification for this artificial separation is that with the crude techniques available for differentiation of intracranial lesions, it is useful in that it helps pragmatically to decide whether a case is “surgical” or “non-surgical.” Even this is fraught with pitfalls, however, in that aneurysms, which usually are not large enough to fall into the category of “mass lesion,” are being more and more recognized as surgical lesions. The fact remains, however, that the great bulk of a neurologist’s and neurosurgeon’s referrals confront him with the questions: (1) Is this a mass lesion? (2) If so, where is it? Our results in using RISA are analysed in terms of pathological diagnoses in Table 1. The following are comments which would appear to be appropriate at this point.

Among the supratentorial gliomas, the 2 that were missed were both deep within the hemisphere and close to the mid line. Both were classed as grade IV astrocytomas. This might indicate that the cellular type among the gliomas is not especially related to their pooling of radioactive materials; or again, it might mean simply that the neoplasm was too far removed from the scalp to be detected.

The pontine gliomas, likewise, gave no hint of their presence. In dealing with the cystic cerebellar astrocytomas it was interesting to see that in both cases the uptake was somewhat greater (5 per cent) in the uninvolved cerebellar hemisphere as compared with the hemisphere that was the site of the tumor. After the diagnosis had been established in these cases, our impression
was that the cyst in a cerebellar astrocytoma may diminish the uptake of RISA on that side.

The same may be said of 2 supratentorial cysts which ultimately came to operation. One of these was a leptomeningeal cyst in the Sylvian fissure, the other a degenerated caseous lesion also in the posterior portion of the Sylvian fissure, the etiology of which was never determined, in spite of numerous cultures, immunologic studies, and varied stains obtained on the

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Cases</th>
<th>Lesion Localized by RISA Study</th>
<th>Lesion not Localized by RISA Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glioma (Supratentorial)</td>
<td>11</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>a. Astrocytoma</td>
<td></td>
<td>9</td>
<td>7</td>
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<tr>
<td>b. Oligodendroglioma</td>
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<td>1</td>
<td></td>
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<tr>
<td>c. Ependymoblastoma</td>
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<td>1</td>
<td></td>
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<tr>
<td>2. Glioma (brain stem)</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3. Glioma (cystic cerebellar)</td>
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<td>2</td>
</tr>
<tr>
<td>4. Meningioma (supratentorial)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5. Meningioma (infratentorial)</td>
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<td>1</td>
<td></td>
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<tr>
<td>6. Acoustic neurinoma</td>
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<td>7. Arteriovenous malformation</td>
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<td>1</td>
</tr>
<tr>
<td>8. Metastatic neoplasm (supratentorial)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>9. Metastatic neoplasm (cerebellar)</td>
<td>2</td>
<td>2</td>
<td></td>
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<td>10. Pinealoma</td>
<td>1</td>
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<tr>
<td>11. Subdural hematoma (bilateral)</td>
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<td>12. Cysts</td>
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<td>13. Diffuse cerebrovascular disease</td>
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<td>14. Cerebral thrombosis</td>
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<td>15. Congential aneurysm with intracerebral clot</td>
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<td>16. Cortical thrombophlebitis</td>
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<td>17. Basal arachnoiditis</td>
<td>1</td>
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<td></td>
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<tr>
<td>18. Arnold-Chiari malformation</td>
<td>1</td>
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</tr>
<tr>
<td>19. Controls</td>
<td>5</td>
<td>5</td>
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</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>36</td>
<td>14</td>
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</table>

tissue removed at surgery. Both of these were avascular and had displaced cerebral tissue mesially.

There are 2 meningiomas in our series. One of these was a pterional lesion which had grown extracranially and presented as a tumor mass just above the zygoama. The most striking uptake was obtained in this case, there being a 30 per cent difference between readings taken over the area where only skin and subcutaneous tissue separated the tumor from the counter, and those taken over the same area on the opposite side of the head. The other meningioma was located in the left cerebellopontine angle. This was not a highly vascularized lesion, yet the RISA studies pointed unequivocally to this site preoperatively.
Two acoustic neurinomas were surveyed and accurately localized preoperatively. Both were large vascular neoplasms.

The metastatic tumors presented a confused picture. The 3 supratentorial lesions (1 epidermoid carcinoma of the cervix, 2 adenocarcinomas of the breast) were located precisely at the area where the scintillation counter showed the highest uptake. However, neither of the cerebellar metastatic deposits (1 epidermoid carcinoma of the lung, and 1 adenocarcinoma of the breast) were detected by this means.

One patient in the series had bilateral subdural hematomas. Our studies gave no hint of their presence. They were of approximately equal size, each one containing about 100 cc. of fluid. This case pointed up the need for a scale of reference so that one could, if necessary, compare the relative strength of readings over the various parts of the cranium with one or more points over the extremities, or another part of the body. This might then allow one to appreciate that the counts taken over the convexities were greater or lesser than anticipated, and thus to suspect a bilateral lesion. An attempt was made to compare the uptake of the frontal, temporal and parietal areas with the occipital and suboccipital regions in this case, utilizing the percentage difference arrived at with that found in controls. Here again, nothing of significance was uncovered.

No differential uptake was noted in patients with diffuse cerebral vascular disease nor in those who had cerebral thromboses with definite localizing neurological signs. Likewise, increased uptake was not found in cortical thrombophlebitis. One case of Arnold-Chiari malformation with internal hydrocephalus in a 5-year-old girl was studied, but again a differential uptake was not found. Five controls (normals) failed to show a difference in readings taken over the two sides of the head.

In the entire series only 1 “false-positive” was encountered. This was in a 55-year-old woman who had had a radical mastectomy some years previously for adenocarcinoma of the breast. She had subsequently become psychotic. When first seen there was unmistakable evidence of a lesion in the left cerebellar hemisphere. A RISA scan pointed to pathology in the right anterior frontal region, but ventriculography confirmed the presence of a space-taking lesion in the posterior fossa. At operation a metastatic nodule was enucleated from the left cerebellar hemisphere. The patient’s papilledema subsided, her gait and co-ordination improved, but the psychosis persisted. She died some months later in another hospital, and unfortunately postmortem examination was not permitted. The possibility exists that this patient did indeed have another metastatic deposit in the frontal region which was not large enough to be demonstrated by ventriculography. Hence, this single “false-positive” may have been spurious.

In each of the cases in which accurate localization was accomplished by means of RISA, the highest uptake was invariably over the epicenter of the neoplasm. One of the authors (G.R.N.) was the surgeon in most of the cases reported herein, and entered into the experimental situation with some prejudice, having seen and examined the patient previously. The other
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Author (R.B.R.) was at all times the member of the team who positioned the scintillation counter and who made the extrapolations as to where the lesion would be on the basis of the radioactive uptake; in all instances the latter was kept ignorant of clinical findings that might localize the site of pathology. We were impressed particularly with the unequivocal nature of the results in those cases in which the lesions were correctly localized. This serves to fortify the opinion expressed by Farris et al. that they were willing to attribute considerable significance to a “positive” (localizing) scan, but that in no way did a “negative” (nonlocalizing) scan exclude a space-taking lesion.

Because of the relatively small number of cases studied, it is impossible to compare the efficacy of the RISA technique with other procedures used in localizing intracranial pathology. Statistics based on 50 cases might well be misleading rather than enlightening. After some experience with the method, however, it is difficult to refrain from adopting certain attitudes, tentative though they may be.

We have felt that the temporal factor is a distinct disadvantage of this method. The institution in which this study was done serves a large referring area, and many of the patients who are sent for definitive diagnostic and therapeutic measures represent emergency situations which must be dealt with immediately. This applies not only to trauma but to intracranial neoplasms that have decompensated and require definitive therapeutic measures within a few hours following admission. It is certainly not justifiable to subject an already comatose patient or one whose level of responsiveness is deteriorating to a delay of 24 hours for the purpose of completing radioactive iodine studies, when angiography or ventriculography may make the diagnosis in one hour.

Perhaps the greatest advantage of the RISA scan is that it is entirely atraumatic to the patient. One need not insert cannulae through cerebral tissue nor upset the equilibrium of the cerebrospinal fluid with its frequently elevated pressure and precarious balance. Nor does one run the risk of disturbing the tone of the intracranial vascular tree as may happen with angiography. These facts, coupled with avoidance of an additional anesthetic induction, are cogent considerations to be taken into account in an evaluation of the method. In general, it has been our feeling that radioactive scans with RISA, taken by themselves, are less helpful than cerebral angiography, and/or gas contrast studies, but that they are distinctly more accurate in localizing a mass than is the electroencephalogram.

In dealing with the material at hand, one cannot help but idealize the qualities desirable in any technique that attempts to locate space-taking intracranial pathology. Among others, these merit particular notice: (1) rapidity of concentration in the pathological area; (2) minimum toxicity or other hazard to the patient; (3) lack of expensive equipment; and (4) simplicity of the test itself.

In searching for such a method it would seem that an agent permeable to the blood-brain barrier in normal cerebral substance, but not to the area
in which pathology exists, would be one useful approach. It is perhaps expecting too much of a method that it should concentrate enough of the tell-tale substance—radioactive or otherwise—in such varying morbid lesions as leptomeningeal cyst, astrocytoma, and intracerebral hematoma. To search for such a material is to disregard other basic concepts in anatomy, physiology and pathology. Indeed, because of the diverse nature of material with which a neurosurgeon must work, it may be that in the future we shall learn the proper combination of diagnostic tests to perform in any given case. This would constitute an acknowledgment of the fact that no one test gives us dependable answers in all cases.

We are unable to enter into any discussion of the reasons for the apparent preferential take-up of RISA in certain of these cases because our studies have not delved into the basic physicochemical mechanisms presumed to be at work. Relative vascularity is in some ways an attractive possibility, but clearly cannot be the whole answer. For instance, the 3 supratentorial metastatic tumors enucleated at operation were all poorly vascularized, yet were accurately localized preoperatively. This subject must be left for elucidation in the future.

SUMMARY

Fifty patients have been scanned with the scintillation counter following the intravenous injection of radioactive iodinated human serum albumin. Forty-five of these were subsequently proved to have intracranial pathology. Three volunteers without symptoms or signs of central nervous system disease were included, as were 2 patients with signs and symptoms that superficially suggested neurological disease, but who were later diagnosed as suffering from neuroses. These latter have been termed “normals” or “controls.” The criterion of successful localization depended entirely upon the ability to predict the presence of a space-taking intracranial lesion. Statistics and histological diagnoses have been tabulated. This method appears worthy of further investigation. In the authors’ hands, at least, it is not yet reliable enough to use to the exclusion of other standard diagnostic tests. The limits of its clinical applicability must be more clearly defined.

REFERENCES