A COMPARATIVE STUDY OF THE USE OF DIIODOFLUORESCEIN AND IODINATED HUMAN SERUM ALBUMIN FOR THE DIAGNOSIS AND LOCALIZATION OF INTRACRANIAL NEOPLASMS*

ERIC T. YUHL, M.D., LLOYD A. STIRRETT, M.D., AND RAYMOND L. LIBBY, PH.D.

LOS ANGELES, CALIFORNIA

FROM THE NEUROSURGICAL SERVICE AND RADIOISOTOPE UNIT OF THE WADSWORTH HOSPITAL, VETERANS ADMINISTRATION CENTER LOS ANGELES AND THE DEPARTMENTS OF SURGERY AND RADIOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA AT LOS ANGELES

THE SUCCESSFUL EXTERNAL localization of brain tumors by radiotracer technics was introduced by Moore[8] in 1948. In subsequent reports, Moore and his associates,[7] and Ashkenhazy and his associates,[1, 2] have reported a high degree of accuracy in the diagnosis and localization of intracranial lesions by this method. These reports indicate that the method is a valuable diagnostic aid in neurosurgical problems and yields relatively precise localization of the lesions.

In the initial studies, radioactive diiodofluorescein was used as the tracer agent and a suitable Geiger-Müller counter as the detector of the gamma radiation. In 1951, Chou, Aust, Moore and Peyton[5] reported the successful use of iodinated* human serum albumin as the tracer material. The technic has been further amplified by the introduction of the scintillation counter.[10]

Recent reports by de Winter[6] and Belcher and Evans[3] in 1951 have emphasized some of the physical and clinical limitations of the istotope technic. These workers cast some doubt upon the reliability of the test.

It is the purpose of this report to present the results obtained at the Veterans Administration Center, Wadsworth Hospital, in the investigation of the external localization of brain tumors with both diiodofluorescein (DIF) and iodinated human serum albumin (I*HSA) and to compare the results obtained with these two agents.

METHOD

The operational setup used in this study is shown in Figures 1 and 2. A scintillation counter[4] is used as the detector of the gamma radiation which emanates from the DIF or I*HSA. The incident radiation reaching the crystal is limited to about 30 degrees by surrounding the tube with 3 cm. of lead and restricting the diameter of the port to ¾ inch.

The patients receiving DIF were given a single, sterile intravenous injection of 1.0 millicurie. Those receiving I*HSA were given 300 microcuries intravenously. Since a small amount (less than 5 per cent)[9] of the I*HSA may be broken down with liberation of radioactive iodine which may be assimilated by the thyroid gland, 0.5 cc. of potassium iodide as Lugol's solution was given orally to these patients three times a day for seven days following injection.

A total of 32 positions were surveyed on each patient in the manner described by Ashkenhazy and his associates.[2] In the present study, however, the scintillation counter was substituted for the Geiger-Müller counter as the detector of the gamma radiation. A sufficient number of counts were taken at each position to insure a counting error of less than ± 3 per cent.

* Submitted for publication September, 1952.

Initially the normal variation in radioactivity between adjacent and symmetrical contralateral positions was determined in a group of patients who were used as controls. Intracranial neoplasm had been ruled out in these patients by conventional diagnostic methods including air study. In the group of patients in which DIF was used as the tracer agent, the control counts varied from 4.6 per cent to 12.5 per cent between symmetrical positions, with a mean value of 8.4 per cent. The control counts

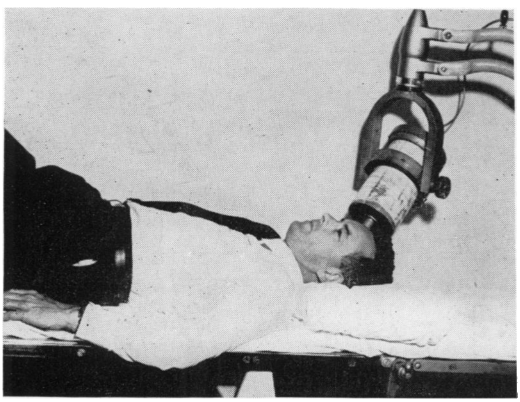

FIG. 1.—The scintillation counter with the lead shield is shown mounted on a portable roentgen ray arm.

with the iodinated albumin ranged from 3.5 per cent to 9.1 per cent, with a mean value of 6.1 per cent. From this data the upper limit of variation with DIF was chosen to be 13 per cent, and that with I*HSA to be 10 per cent. In subsequent surveys on patients suspected of having brain tumors, those positions at which the observed radioactivity values in terms of counts per second exceeded the values observed at symmetrical contralateral or adjacent positions by more than these upper limits of the normal range were considered to represent areas that might be suspected of being abnormal. Where such areas were found, checks were repeated at intervals during the survey. The only positions which were termed abnormal were those which on repeated checks showed a constant variation which exceeded the maximum values observed in the control series.

Since DIF is rapidly excreted, the survey must be carried out between 30 minutes and 2 hours after injection. I*HSA, on the other hand, is excreted at a much slower rate, and the optimal time for the survey has been determined to be 24 hours after injection. However, satisfactory surveys may be carried out as late as 48 or 72 hours after injection. These later surveys are useful for confirming the persistence of an area of abnormal radioactivity.

RESULTS

Group 1: DIF was used in surveying 24 patients suspected of having intracranial neoplasms. Seventeen of these patients were subsequently found, by conventional diagnostic methods, not to have neoplastic disease. Air study was done in each patient. Seven of the 24 patients had brain tumors proven at operation and by microscopic examination of biopsy material. A comparison of the radioactivity survey impressions and the anatomic diagnoses is shown in Table I. In all, two false positive and two false negative diagnoses were made by the isotope method. The two false negative diagnoses were made in patients later proven at craniotomy to have a large, deep-seated frontoparietal astrocytoma. An over-all diagnostic accuracy of 83 per cent was obtained in this group.

Although a fairly high degree of diagnostic accuracy was obtained with DIF, the radioactivity survey did not precisely localize the extent of the tumor in the seven patients with verified intracranial neoplasm. In only two cases was the extent of the tumor ascertained by survey. In the others, the tumor found at operation extended beyond the limits of abnormal radioactivity observed at the time of survey.

Group 2: I*HSA was used as the tracer agent in 20 patients suspected of having intracranial neoplasm. In nine of these patients, brain tumor was verified at the time of craniotomy and by examination of biopsy material. In the remaining 11 patients, brain tumor was ruled out by the conventional diagnostic methods, including air study. Two false positive diagnoses were obtained in this group of patients with the radioisotope method, yielding an overall diagnostic accuracy of 90 per cent. The diagnostic impressions and anatomic findings are listed in Table II.

TABLE I.—*Summary of the Results in 24 Patients Surveyed with Diiodofluorescein.*

Case No.	Isotope Focus	Final Diagnosis
1	None	No tumor
2	None	No tumor
3	None	No tumor
4	None	No tumor
5	None	No tumor
6	None	No tumor
7	None	No tumor
8	Right occipital	Meningioma, right occipital
9	None	No tumor
10	None	No tumor
11	Left frontal	No tumor
12	Left frontoparietal	Astrocytoma, left frontoparietal
13	Bifrontal	Astrocytoma, bifrontal
14	None	No tumor
15	None	No tumor
16	None	No tumor
17	Left frontal	No tumor
18	None	No tumor
19	Left temporal	Oligodendroglioma, left temporal
20	None	No tumor
21	None	Astrocytoma, right frontoparietal
22	None	No tumor
23	Bifrontal	Astrocytoma, bifrontal
24	None	Astrocytoma, right frontal

TABLE II.—*Summary of the Results in 20 Patients Surveyed with I*HSA.*

Case No.	Isotopic Focus	Final Diagnosis
1	Anterior midline	Lymphoma, chiasmatic
2	Right occipital	No tumor
3	None	No tumor
4	None	No tumor
5	Right frontoparietal	Astrocytoma, right frontoparietal
6	Right frontoparietal	Astrocytoma, right frontoparietal
7	None	No tumor
8	Right frontoparietal	Astrocytoma, right frontoparietal
9	None	No tumor
10	None	No tumor
11	None	No tumor
12	Left frontal	No tumor
13	Right frontal	Astrocytoma, right frontal
14	None	No tumor
15	Right occipital	Meningioma, right occipital
16	Left parietal	Glioblastoma, left parietal
17	Left temperoparietal	Astrocytoma, left temperoparietal
18	None	No tumor
19	None	No tumor
20	Right frontal	Glioblastoma, right frontoparietal

In six of the nine cases, precise localization of the lesion was obtained. In one of these six cases, the radioisotope survey was the only diagnostic test which reflected any degree of abnormality. Air study, prompted by the isotope findings, was subsequently performed on this patient and led to the discovery of a large occipital meningioma at operation.

DISCUSSION

Both DIF and I*HSA have been used successfully to aid in the diagnosis and localization of brain tumors. Ashkenhazy and his associates[2] who used DIF as the tracer agent, reported a total accuracy of 95 per cent both for the diagnosis and for exclusion of intracranial neoplasms in a series of 340 patients. In addition to the high degree of diagnostic accuracy, they were able in most instances to obtain precise focal localization of the lesions. Moore and his fellow workers[7] used DIF to study a series of 33 patients and obtained an accurate diagnosis in 28 cases. They concluded from that study that this technic is a valuable diagnostic aid and research tool, but is not accurate enough to employ as the sole diagnostic test. In a series of 34 cases reported by de Winter,[6] only one out of 20 verified tumors was successfully localized by the radioisotope method. He concluded that radioisotope survey was of little value in tumor localization.

Our experience with DIF would confirm the observations of Moore. Although we obtained a fairly high degree of diagnostic accuracy (83 per cent), the test is not as yet reliable enough in our hands to warrant using it to the exclusion of conventional diagnostic methods. Also, we were unable to obtain precise focal localization of the lesions in most cases.

The use of I*HSA as the tracer agent was introduced in 1950[5] by Chou and his associates. In their preliminary report, a series of ten patients was studied, and no erroneous diagnoses were obtained. To our knowledge, no further work has been reported on the use of I*HSA. In the series of 20 patients with which we used I*HSA, two false positive diagnoses occurred, presenting an over-all diagnostic accuracy of 90 per cent.

In our experience, the use of I*HSA presented several advantages over the use of DIF. Moore stated that when employing the Geiger-Müller tube, 400–500 microcuries of I*HSA gave the same counting rate as 1.0 millicurie of DIF. Our data show that when using the scintillation counter, 300 microcuries of I*HSA yields a two to three times higher counting rate than 1.0 millicurie of DIF.

When using DIF as the tracer agent, the survey must be completed within two or three hours after injection because of the rapid excretion of this material. As a consequence of this rapid rate of excretion, the counting rates of symmetrical areas vary considerably unless they are surveyed simultaneously. Often it is not possible to do so, and the time which elapses between surveys of symmetrical areas may be a source of error in the interpretation of abnormal areas. This variation in the count of symmetrical areas due to rapid excretion is further borne out by the aforementioned data which indicate that in the control series, the values of the counts varied as much as 12.5 per cent between symmetrical contralateral areas. The use of I*HSA minimizes these errors because of its slower rate of excretion which allows the examiner to compare various positions at any time during the performance of the test.

Another disadvantage of DIF is that it concentrates rapidly in the liver. De Winter[6] has pointed out that a right-sided asymmetry, due to increased radioactivity in the liver, results; and in his experience, interfered markedly with the reliability of the test. We have also encountered this difficulty, which necessitated adding one-half inch of lead shielding around the tube to protect the crystal from radiation emanating from the liver. Despite this lead shielding, great care must be taken by the examiner during the performance of the test to

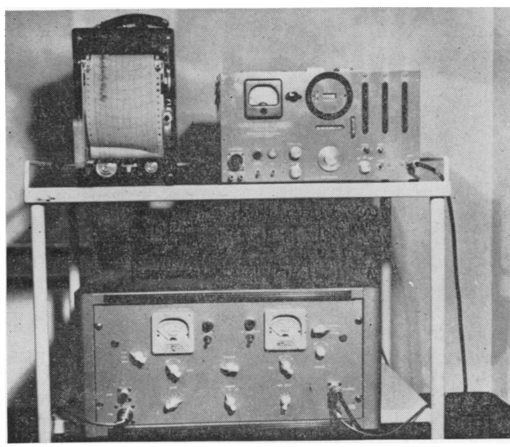

FIG. 2.—Scaler, Ratemeter and Esterline-Angus Recorder used in conjunction with the scintillation counter are shown.

make sure that the aperture of the tube does not point directly toward the liver at any time during the survey of the skull. If it does so, a spuriously increased radioactivity will be observed, due to increased radioactivity from the background of the body. I*HSA is more advantageous than DIF in this respect, because the former substance is diffusely distributed in the bloodstream thus minimizing another source of possible error.

The last consideration in choosing I*HSA as the tracer agent is the observation that in this study, the differential uptake at the site of the lesion compared to normal areas was 24.5 per cent when using this substance, whereas this value was only 16.5 per cent when using DIF. I*HSA, therefore, yields a greater differential concentration in the abnormal areas than does DIF. This increased differential uptake at the site of the lesion is the most likely explanation for the more precise focal localization we have been able to obtain with I*HSA.

SUMMARY

1. The use of diiodofluorescein and iodinated* human serum albumin for the diagnosis and localization of intracranial neoplasms has been described.

2. Twenty-four patients were surveyed with DIF, and an over-all diagnostic accuracy of 83 per cent was obtained.

3. Twenty patients were surveyed with I*HSA, and an over-all diagnostic accuracy of 90 per cent was obtained.

4. Some of the possible sources of error with the use of DIF have been enumerated, and the advantages of I*HSA have been discussed.

5. In this series, more precise focal localization of the lesions was obtained when using I*HSA than when using DIF.

BIBLIOGRAPHY

1 Ashkenhazy, M., G. V. LeRoy, T. Fields and L. Davis: The Detection of Intracranial Tumors by the Use of Diiodofluorescein. J. Lab. & Clin. Med., **34:** 1580, 1949.

2 Ashkenhazy, M., L. Davis and J. Martin: An Evaluation of the Technique and Results of the Radioactive Diiodofluorescein Test for the Localization of Intracranial Lesions. J. Neurosurg., **8:** 300, 1951.

3 Belcher, E. H., and H. D. Evans: The Localization of Cerebral Tumors with Radioactive Derivatives of Fluorescein. Brit. J. Radiol., **24:** 272, 1951.

4 Cassen, B., L. Curtis, C. Reed and R. Libby: Instrumentation for I–131 Use in Medical Studies. Nucleonics, Vol. 9, #2, p. 46, 1951.

5 Chou, S. N., J. B. Aust, G. E. Moore and W. T. Beyton: Radioactive Iodinated Human Serum Albumin for Diagnosing and Localizing Intracranial Lesions. Proc. Soc. Exper. Biol. & Med., **77:** 193, 1951.

6 de Winter, J. G.: Some Preliminary Observations on the Use of Radioactive Isotopes for the Localization of Brain Tumors. Brit. J. Radiol., **24:** 280, 1951.

7 Moore, G. E., W. T. Peyton, L. A. French and W. W. Walker: The Clinical Use of Fluorescein in Neurosurgery; the Localization of Brain Tumors. J. Neurosurg., **5:** 392, 1948.

8 Moore, G. E.: Use of Radioactive Diiodofluorescein in the Diagnosis and Localization of Brain Tumors. Science, **107:** 569, 1948.

9 Storaasli, J. T., H. Krieger, H. L. Friedell and W. D. Holden: Use of Radioactive Iodinated Plasma Protein in Study of Blood Volume. Surg., Gynec. & Obst., **91:** 458, 1950.

10 Ter-Pogossian, M., W. B. Ittner, W. B. Seaman and H. G. Schwartz: A Scintillation Counter for the Diagnosis and Localization of Intracranial Neoplasms. Am. J. Roentgenol., **67:** 351, 1952.