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The Isotope Encephalogram In Brain Tumor Diagnosis

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Scanning of the radioactive tracers in the calvarium represents a major advance of diagnostic techniques in the evaluation of intracranial disease. The pioneering work by Moore (18) at Mayo Clinic in 1948 utilized ^{131}I labeled Di-Iodo-fluorescein as the tracer detected by a Geiger-Muller tube. This now primitive system demonstrated a higher concentration of the isotope tracer in the brain tumors than in normal brain, a phenomenon to which the currently more sophisticated scanning devices still owe their success. A classical work by Giovanni Di Chiro (6) in 1961 recorded a large series of isotope encephalograms using ^{131}I labeled human serum albumin. Later Blau and Bender (2) reported a new agent for brain tumor localization, ^{203}Hg labeled Neohydrin. In their work, a comparison of physical properties of ^{131}I human serum albumin and ^{203}Hg Neohydrin showed a higher total body radiation dose from the ^{131}I tracer and a significant target organ (kidney) dose from ^{203}Hg. The experienced scanning investigators using ^{131}I human serum albumin were reporting accuracy up to 85 percent, a figure difficult to better, yet the scan images with the ^{203}Hg tracer looked more convincing, probably due to a higher concentration or migration of the tracer through the disease altered blood brain barrier. Brain scanning became more and more popular at this time and one is hard pressed to say whether ^{203}Hg chlormerodrin rode the wave of increasing clinical acceptance of scanning or perhaps created the wave. For all its ideal features of long shelf life, monoenergetic gamma emission and high affinity for brain tumors, ^{203}Hg carried an irradiation dose to the kidney which was disturbing to the point that it was listed by one observer as a contraindicated procedure in children (8). Premedication with stable Mercuhydrin reduced the dose 12-13 rads but the remaining calculated 23-27 rads (2) to kidney could not be overlooked in children or in cases requiring

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repeat or serial studies. Because of this renal irradiation dose, Sodee (23) investigated another isotope of mercury, mercuric chloride 197, which had a 99 percent gamma emission of 0.077 MeV and a 2.7 day half-life. The significantly lower energy of emission and short half-life contributed to a marked reduction of the renal irradiation dose. Mercury 197 Chlormerodrin apparently found a place in general scanning, but some controversy in regard to dosimetry compounded by ^{203}Hg contamination of commercially available ^{197}Hg chlormerodrin, limitations inherent to low-energy isotope scanning with standard equipments, attenuation of emissions by overlying tissues, etc. must bear reference (3,11,24,25). Perhaps the most recently published tracer agent is ^{99m}Tc Pertechnetate (10,14). This agent has an ultra short half-life, six hours, gamma emission of 140 keV, and is obtained by daily elution from a molybdenum^{99} "cow". The total body radiation dose from ^{99m}Tc has been calculated as 0.13 rad while the colon receives the highest single organ dose of 2.1 rads (13) from the radioactive tracer contained in the fecal contents. Wide clinical application of this tracer may develop when simplified elution and standardization techniques are developed.

To this date the search continues for diagnostic agents and methods to satisfy the requirements listed by Di Chiro (5) as follows:

1. Indicate the presence of a lesion.
2. Locate the site of the lesion.
3. Define the extension of the lesion.
4. Point to the nature of the lesion.
5. Entail minimal hazard, and cause minimal discomfort to the patient.

The success of rectilinear scanning for brain tumors has been widespread as indicated by a multitude of series reports. The high percentage of accuracy found in each report justifies the acceptance of this procedure by clinicians, especially neurologists and neurosurgeons. This high degree of accuracy may lead one to a false sense of security until consideration is given to the areas of the intracranial vault which may harbor a lesion, even a sizeable one in the shadow of the physiologic pools of tracer activity, *i.e.*, the triangle behind the eye, over the paranasal sinuses, and the confluence of vascular sinuses. Other factors often mentioned are well differentiated tumors which offer little or no alterations in the blood brain barrier and hence do not provide detectable tracer concentrations. Still additional cautions have been voiced toward misleading or at least confusing results on scanning immediately after and within three days of arteriographic examinations. The difficulty here being alterations of the blood brain barrier by the radiographic contrast medium (12).

In any given series of positive brain tumor scans a wide variation in degree of tracer concentration will be found. As yet no one series has gained sufficient stature in numbers to allow a valid retrospective evaluation to correlate the tumor types and concentrations of tracers.[1] On the other hand, there appear to be some

[1]A project of this sort is currently being pursued at this center. Beierwaltes reported preliminary findings of a similar investigation at a recent symposium (1).

instances where the appearance of the scan image will allow an educated guess that an abnormal focus by its position, shape and concentration represents a tumor rather than a cerebrovascular accident (20). It is doubtful, however, that the accuracy of such differentiations will reach that attained by making a gross pronouncement of abnormal scan pattern. One should not construe this as a criticism of brain scanning technique or interpretation, for, with the exception of the occasional arteriographic "tumor stain", no other diagnostic method at present provides a visual image of the brain lesion. Rather, the pneumoencephalogram, ventriculogram, electroencephalogram and a majority of arteriograms make the presence of a space-occupying lesion known merely by displacement or variation in size and number of vessels, ventricular chambers or electrical impulses.

A wide variation of opinions may be obtained from interpreters of scans regarding optimal techniques of recording and interpreting scans. These range from high contrast to low contrast techniques. Some require that all the scintillations from the sensitive volume of the collimated detector be recorded on film or paper while others find a record of the lesion with near exclusion of background more desirable. The ideal situation of tape recording data and obtaining multiple play-back recordings at all levels of discrimination is available to only a few investigators. Time alone obviates wide use of such elaborate systems, for at the present time the majority of clinical rectilinear scanners require from 1½ to 2 hours to complete a two-view scan of the cranial vault. In the Division of Nuclear Medicine at the University of Mississippi Medical Center the brain scan is, for the most part, a tailored study. A careful review of the patient history and findings on neurological examination is made. An aural survey is then obtained by manually scanning the head in various positions searching for the physiologic or abnormal areas of tracer concentrations. On the basis of this survey the alignment of the photorecording parameters is made for the anterior or posterior and appropriate lateral scans. When a suspicious focus is found,

TABLE I

COMPARISON OF DIAGNOSTIC BATTERY IN 118 BRAIN TUMORS FROM 558 CONSECUTIVE 203 Hg, 197 Hg CHLORMERODRIN SCANS

	Cases	*Positive*
1. Isotope Encephalogram	118	99
2. Neurological Physical	118	110
3. Skull Films	114	45
4. Carotid Arteriogram	85	70
5. Pneumoencephalogram	14	11
6. Ventriculogram	11	10
7. Electroencephalogram	12	11

additional scans are made in an effort to confirm or refute the finding. The scan images are interpreted as showing no abnormal foci of tracer activity or as positive, localizing the position and apparent extent of the abnormal tracer concentration. The ancillary studies of the neurological work-up to the time of scanning are made available to the interpreter and an effort is made to correlate the scan results and other studies in the report. At the time of scanning, anatomical and topographical landmarks; nasion, right and left pupil, outer canthus of eyes, external occipital protuberance, vertex, right and left mastoid tips are located and marked on the record. This provides for more accurate localization of abnormal foci and on many occasions the scans have accompanied the patient to surgery and guided the neurosurgeon in placement of incision and depth of exploration. In addition, these located landmarks allow for reasonably accurate super imposition of the scan records on routine and arteriographic radiographs.

In a review of 558 consecutive isotope encephalograms, 160 positive scan results were obtained. Sixty-one had subsequent nontumor diagnoses made and 118 brain tumor diagnoses were recorded, of these, 99 had positive scan results. The results of the entire neurologic battery were then reviewed. This battery consisted of the isotope encephalogram, carotid arteriogram, pneumoencephalogram, skull film, neurologic physical, ventriculogram and electroencephalogram. All seven diagnostic procedures were not required for each case but sufficient studies were obtained to clearly substantiate the nature of disease. The comparison of these studies results is shown in Table I. The position and depth of lesions were classified as supratentorial, infratentorial, deep or superficial. A lesion was considered superficial if its margin reached the periphery of the cranial vault of one or more of the scan projections or when positive evidence of position was obtained by other members of the diagnostic battery or at time of surgery. Table II records the results of this evaluation and compares the results of carotid arteriography on these cases. By the same token, the posterior fossa lesions, virtually inaccessible to diagnosis by carotid arteriography, are diagnosed by scanning

TABLE II

COMPARISON OF SCAN AND ARTERIOGRAM RESULTS

		Scan		*Carotid Arteriogram*	
		Cases	+	*Cases*	+
Supra Tentorial	Deep	40	27	30	25
	Superficial	60	56	45	39
		100	83	75	64
Infra Tentorial	Deep	13	11	7	3
	Superficial	5	5	3	3
		18	16	10	6

TABLE III

COMPARISON OF RESULTS OF BRAIN TUMOR SCANNING WITH A COMPILATION OF RESULTS REPORTED FROM 9 MEDICAL CENTERS

	Univ Mississippi		*9 Other Centers*[1]	
	Cases	*Missed*	*Cases*	*Missed*
Meningioma	16	0	95	6
Metastatic	30	4	166	33
Astrocytoma	21	2	79	31
Glioblastoma	18	2	119	7
Ependymoma	7	1	2	0
Glioma (Type Unspecified)			35	12
Pituitary and Supra Sellar Tumor	6	5	30	14
Acoustic Neuroma	5	1	9	5
Others	15	4	67	26
	118	19 (16%)	602	134 (22%)

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TABLE IV

TOTAL BRAIN TUMOR SERIES RESULTS

		Cases	*Missed*
1.	Meningioma	16	0
2.	Metastatic lesion	30	4
3.	Astrocytoma	21	2
4.	Glioblastoma	18	2
5.	Ependymoma	7	1
6.	Acoustic neuroma	5	1
7.	Brain stem glioma	4	
8.	Oligodendroglioma	3	
9.	Cholesteatoma	1	1
10.	3rd ventricle tumor	1	1
11.	Craniopharyngioma	1	
12.	Medulloblastoma	1	
13.	Basal ganglion glioma	1	
14.	Ependymoblastoma	1	
15.	Hemangioblastoma	1	
16.	Pituitary adenoma	5	5
17.	Pinealoma	1	1
18.	Neurofibroma	1	1
		118	19

in a relatively high per cent of instances. This is despite their close proximity to the confluence of sinuses and heavy neck muscle mass which are physiologic areas of higher tracer concentration. In our series, 18 infratentorial lesions were diagnosed, 16 had positive scans. This result compares favorably with a similar series reported by Rhoton *et al* (21). The relatively high per cent efficiency of the scan in detection of infratentorial lesions is attributed largely to careful exaggerated Towne's positioning of the head for the posterior scan. This is accomplished by placing sufficient support beneath the patient's chest and abdomen to allow acute flexion of the neck placing the forehead on the examining table. This position of the head is maintained by a strip of tape crossing the occiput and affixed to each side of the table. It is obvious that vertebral anteriograms would obtain a higher degree of diagnostic accuracy than carotid arteriograms in infratentorial lesions. Deterrents to wide application of the vertebral arteriogram are the technical difficulties which far exceed those of the carotid arteriogram and the associated higher patient morbidity. The brain scan has therefore, provided earlier clear evidence of infratentorial disease than previously was obtainable in this institution.

Table IV relates the type and distribution of 118 brain tumors together with the scanning results found in the series. It is apparent from this that the more common brain tumors may be expected to produce a high percentage of positive scan results. This is borne out in Table V, a compilation of reported series from nine medical centers (4,5,7,9,13,16,17,19,22). The results of the tumor scanning of the University of Mississippi Medical Center are also shown in parallel for comparison.

In this series, both ^{203}Hg chlormerodrin and ^{197}Hg chlormerodrin[2] tracers were used in 10μC/kg doses not exceeding 700 μC or 15 mgm of mercury. Each patient was premedicated with 1 cc of Mercuhydrin to attempt a blockade of the renal tubules from later absorption of the radioactive tracer. Overton (19) has recently alluded to the economics of ^{197}Hg chlormerodrin in the active scanning center. To this we wish to add a caution directed to the small, less active scanning unit. The level of carrier stable mercury increases in direct proportion with the physical decay of the ^{197}Hg. In a small patient load setting, a brain scan tracer dose after one week decay may carry a high milligram concentration of stable mercury which when administered intravenously may conceivably prove detrimental for the patient. Chlormerodrin, trade name Neohydrin® is an oral diuretic containing 18.3 mgm of chlormerodrin, equivalent to 10 mgm of nonionic mercury in each tablet. The recommended dosage of 1 or 2 Neohydrin tablets daily may obtain an effect comparable to a weekly injection of Mercuhydrin®. A 1 cc injection of Mercuhydrin delivers 39 mgm of mercury as the organic molecule meralluride sodium. The recommended dosage for Mercuhydrin is 1 or 2 cc daily or on alternate days until "dry weight" is obtained. This dose may be given intravenously but is more commonly given intramuscularly.

[2]Supplied by Medotopes Division, E. R. Squibb and Sons.

Therefore, an intravenous administration of sufficient volume of ^{197}Hg Chlormerodrin to deliver 700 μC from a shipment with three half-lives decay may exceed a therapeutic level of mercury which would ordinarily be administered orally or intramuscularly for slower absorption. In our experience as in Overton's, sufficient brain and renal scans are performed to justify twice weekly shipments of ^{197}Hg chlormerodrin and not more than 1 and a fraction half-life expires before a new shipment arrives. We have observed no untoward patient side effects from either ^{203}Hg or ^{197}Hg chlormerodrin nor has a variation in effectiveness of these tracers for scanning been perceived in this series.

Clearly, scanning has established itself as more than a simple screening procedure though it serves this purpose well. It now occupies a respected position in the neurological diagnostic armamentaria. The technique, in many ways standardized, should be modified to suit each case. This also applies to the interpretation of the scanning record. The limitations of collimator resolution, film density, contrast enhancement, scanning speeds, etc., all play a part in knowledgeable interpretation of photo scan records. With this in mind, a scan can be viewed as negative only in the clear light of other supportive negative neurologic findings. With the advent of ^{197}Hg and ^{99m}Tc, repeat scans are feasible and desirable as confirmation and follow-up procedures. This factor alone may further improve the scanning efficacy in diagnosis of intracranial disease. To this point in the development of the art and science of scanning, all but one of Dr. Di Chiro's requirements have been met with high degrees of efficiency. The one remaining, an agent to point to the nature of the lesion, may be met in part when continued series reviews establish consistent patterns in the appearance of tumor versus nontumor scans and perhaps in variable tracer concentrating abilities of various tumors. Brain scanning maintains a bright future awaiting further enhancement by improvements in tracer agents and instrumentation.

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