

CONCERNING INTRACRANIAL MALIGNANT METASTASES*

THEIR FREQUENCY AND THE VALUE OF SURGERY IN THEIR TREATMENT

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AFTER many years of effort our appreciation of the clinical symptoms indicating the existence of an intracranial tumor has so far improved that it is now possible to state with some assurance whether or not such a lesion is present. Hand in hand with our increased knowledge of the evidence pointing to this diagnosis has come a great advance in the surgical technic involved in dealing with such lesions. It is along surgical lines that the attack on these tumors and the increased intracranial pressure which commonly accompanies them has been made with the greatest degree of success. And as always occurs in dealing with any problem of living pathology it is through this advance in surgical methods of exposing and removing such tumors that our familiarity with them has increased even to the point where prior to operation it is now possible to venture a shrewd guess, often a positive statement, as to their pathological structure and its bearing on the ultimate outcome of the case.

Since, therefore, grouped as a whole surgical extirpation of the neoplasm is indicated under these conditions, it is of course necessary

to recognize the fact that there are neoplasms in which surgery offers but little or may even be contra-indicated. Among these lesions are the metastatic tumors. A recent experience with an intracranial metastatic lesion from an unrecognized primary cancer of the lung led to a review of similar cases to determine how effective surgery has been in the handling of malignant metastases to the brain.

The history of this case is as follows:

Operative removal of a large vascular infiltrating tumor of the left fronto-motor area. Decompression. Operative recovery. Microscopic examination proved tumor to be metastatic carcinoma. X-ray disclosed primary growth in upper lobe of left lung.



FIG. 1.—Tumor removed from case reported in text. Note that tumor is fairly firm and discrete though unencapsulated.

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April 22, 1925. Admission of Mr. C. D. G., aged fifty-six. Chief complaint: Paresis of right arm and leg, motor aphasia, headache.

Present illness: Patient had been entirely well until March 8, 1925. On this date he had a sudden twitching of the muscles of the right side of his face. This occurred again on March 12. At this time it was noticed that his speech was becoming thick and that he showed a tendency to fumble over words and phrases. Within two weeks a motor aphasia had become pronounced. Weakness of his right face was noted, he was slightly weak in his right hand and a right-sided clonus and Babinski sign appeared. There was no evidence of intracranial pressure. The diagnosis lay between a vascular lesion and tumor. A left cerebral exploration was performed elsewhere March 28 with negative findings. Following this procedure his motor aphasia became complete.

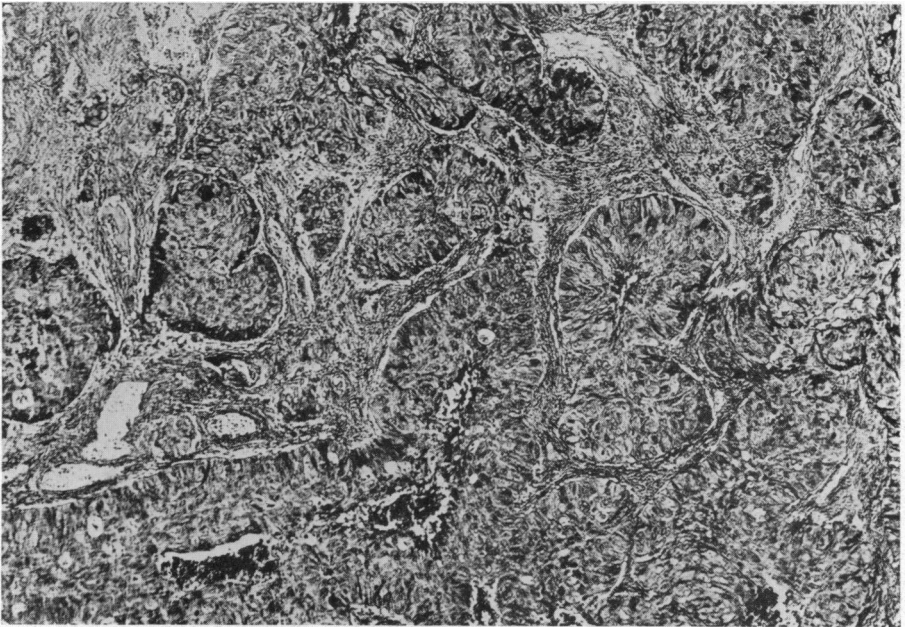


FIG. 2.—Photomicrograph of tumor shown in Fig. 1. Low power H. and E. stain.

A left-sided weakness in face and extremities with sensory hypæsthesia developed. He recovered somewhat from this condition before his admission to this hospital.

Physical examination on admission was essentially negative except for the neurological findings outlined. It is stated specifically that the lungs showed no abnormal physical findings. No evidence of intracranial pressure present. X-rays of the skull showed the pineal shifted to the right suggesting a left-sided tumor. As the case seemed obscure and the tumor if present probably deep-seated, intensive X-ray treatments were given. Just prior to his discharge he had a generalized convulsion beginning in the right side of the face and accompanied for the first time by unconsciousness.

On June 25, 1925, about six weeks after his discharge, he was re-admitted. For a month his condition had continued to improve appreciably, but two weeks prior to this date he had had two generalized convulsions with unconsciousness. Since that time he had rapidly deteriorated, his motor aphasia again became complete, and the paresis of his right extremities increased to paralysis with spasticity. He was semi-comatose and incontinent. The right extremities were spastic and paralytic with increased reflexes, Babinski and a bilateral clonus. A bilateral papillitis with fresh exudate and hemorrhages were recorded.

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In view of the progression of symptoms and desperate condition, Doctor Cushing reëlevated the old flap and identified and extirpated a large vascular tumor lying in the left fronto-motor area which was thought to be a glioma.

The patient made an excellent operative recovery and by degrees regained his speech, and power in his extremities. The tumor proved unexpectedly on microscopic examination to be a metastatic carcinoma, probably, from its structure, primary in the lungs. An X-ray study of the chest revealed a large round tumor in the left upper lobe. After X-ray therapy of the tumor sites in the cranium and chest, he was discharged much improved, and continued to improve for the next four months. On

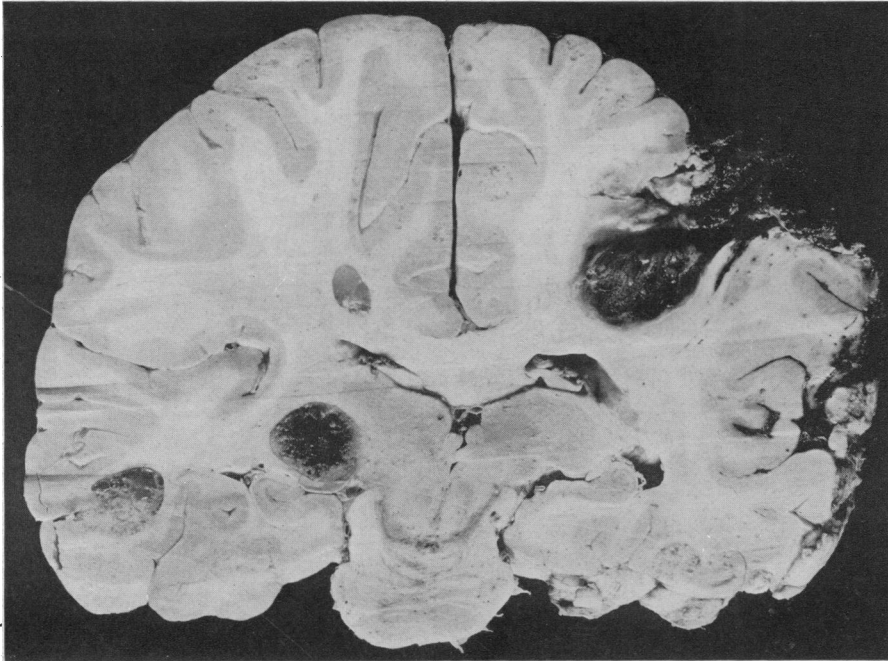


FIG. 3.—Coronal section of brain. Shows multiple carcinomatous metastases throughout cerebral hemispheres. Primary focus in breast.

October 11, 1925, he had a sudden severe general convulsion from which he never fully regained consciousness and he died two weeks later.

That this patient had a metastatic lesion from a primary cancer of the lung was entirely unsuspected. As noted by Craver¹ the diagnosis of pulmonary cancer is rarely made on physical signs alone. Unusually as in this case it is an accidental X-ray finding. Certainly nothing was brought out in the history or by the routine examination to cast suspicion on the chest. Moreover a detailed thoracic examination after the tumor had been radiographically disclosed failed to reveal any physical signs which would have shown its presence even had it been suspected.

But even had the primary tumor in the lungs been disclosed, would operation have been contra-indicated. The prognosis of course would have been utterly bad. But here was a patient with headache, choked disc and other signs of pressure. He was a man of large affairs, cut down in his prime to

whom relief of symptoms, even for a short time, would mean much. A left subtemporal decompression, or as was carried out, a flap with decompression might, as it did, reveal a pathological condition which could be handled. At least pressure symptoms might be relieved. Deep X-ray therapy might have ameliorated his condition, but it had been attempted without avail. Decompression to relieve pressure and to permit of more effective X-ray treatment was indicated in any event. As the patient had already had a flap turned

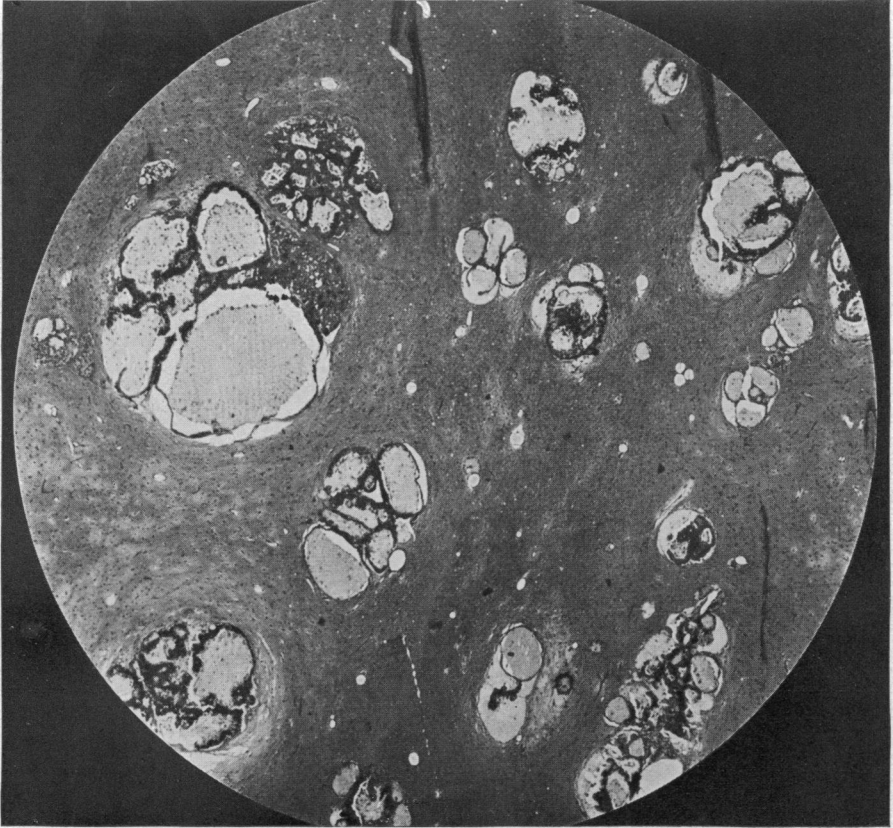


FIG. 4.—Low power photomicrograph showing multiple metastases in brain shown in Fig. 3. $\times 80$. H. and E. stain.

back, its reëlevation was simple. If a similar case appears for treatment it will doubtless be handled in the same fashion. But the clinical history illustrates excellently well the rapidity with which cerebral carcinoma acts and the ultimate hopelessness of the condition even though symptoms may be palliated by surgical measures.

A review of the literature on the occurrence of malignant metastases to the brain gives evidence that this takes place with variable frequency. Krasting² in examining the tissue from 12,730 cases found 1238 (9.8 per cent.) with malignant disease. In this group there were 1078 cases of carcinoma and 160 of sarcoma. In 935 of the 1238 the brain had been examined.

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Of these 817 were carcinomata and 39 (4.7 per cent.) showed a brain metastasis; 118 were sarcomata and 14 (12.4 per cent.) showed a brain metastasis. It is important to emphasize that sarcoma gives a larger percentage of metastases to the brain than does carcinoma, although carcinoma metastases are more frequently encountered since this form of malignant disease is the more common of the two.

Rau³ compiled similar statistics in a series of 10,393 autopsies and identi-

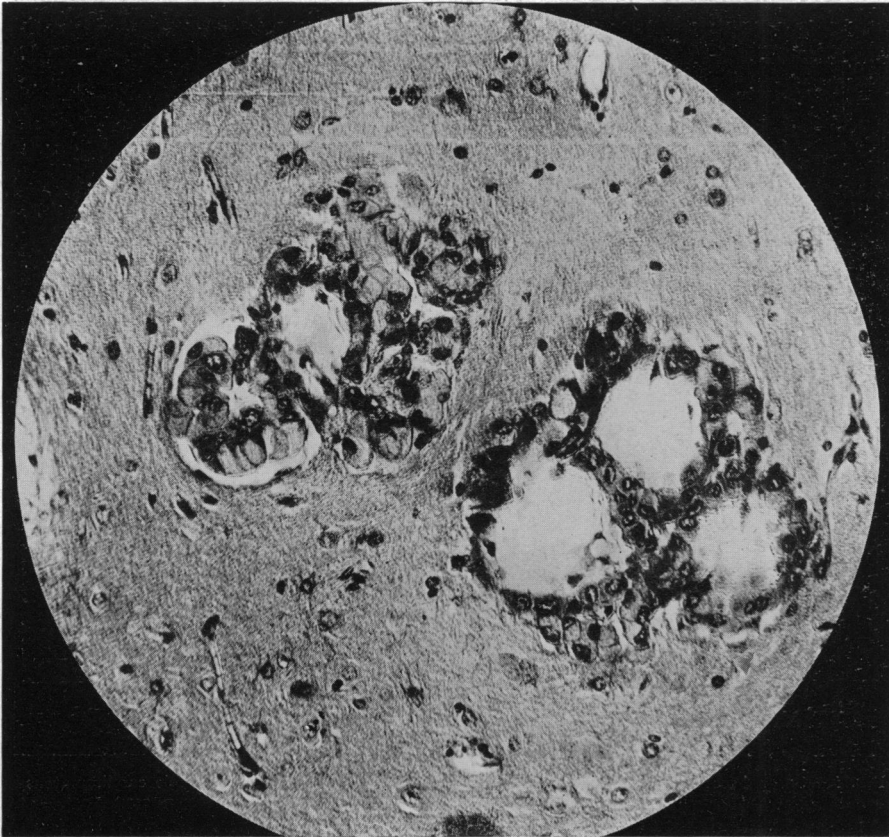


FIG. 5.—High power photomicrograph showing perivascular invasion by carcinoma cells.

fied 1032 examples of carcinoma (10 per cent.) and 90 of sarcoma (0.9 per cent.). Of the carcinoma group 851 had brain sections and 28 (3.2 per cent.) gave evidence of intracranial metastasis, while among the 90 sarcoma cases 68.1 per cent. showed involvement of the brain.

Krasting states on the basis of his own figures and those of Starr,⁴ Gurlt,⁵ and Gallavardin and Varay⁶ that intracranial metastasis follows 18 per cent. of all primary carcinomata. Redlich,⁷ Riechelmann,⁸ Feilchenfeld,⁹ Bejach¹⁰ and Berenczy and Wolff¹¹ in large series of cases show a smaller percentage than either Krasting or Rau of malignant metastases to the cranial cavity, due apparently to the fact that the brain was less often examined.

All authorities agree that sarcoma, though less frequent than carcinoma, is more malignant and gives intracranial metastases in a much larger percentage of cases. Malignant neoplasms in certain situations seem to show a definite predilection to metastasize to the brain, but if the primary focus be located elsewhere such metastases are uncommon. Cancer of the stomach, probably the most frequent primary carcinomatous lesion curiously enough is but rarely followed by intracranial involvement. Rau³ found only three such



FIG. 6.—Coronal section through cerebral and cerebellar hemispheres, showing a single carcinomatous nodule in cerebellum. Primary focus, probably breast.

metastases in 169 cases of gastric carcinoma. The pulmonary capillaries must act as a great filter for tumor emboli in the blood stream. Once past this barrier the pathway for an intracranial implantation is direct. Hence mammary and pulmonary cancer furnish the highest percentage of secondary growths in the cranial cavity. Among 139 cases of secondary cranial malignancy, Krasting² found that 40 followed mammary and 29 pulmonary cancer. Handley¹² records 16 cerebral metastases among 329 primary malignancies of the breast; Rau 7 in 72; the Middlesex Hospital Series¹³ 39 in 470 similar lesions. Dosquet¹⁴ found metastases to the central nervous system in 31.4 per cent. of 165 patients with lung cancer.

Krasting states that 50 per cent. of all melanotic sarcomata metastasize to the brain. Rau identified nearly one-half of his reported sarcoma cases

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as of this type. Erwin¹⁵ quotes Westphal and his own cases as showing that but 8 of 131 verified hypernephromata showed cranial metastases.

Secondary malignant metastases develop two types of lesions within the skull. The first and by far the most common is the single or diffusely scattered discrete nodular lesion more frequently subcortical and apparently only involving the surface of the brain by increase in size and extension of growth. It is evident that these metastases must be blood-borne and embolic in origin from the primary growth (Kaufman,¹⁶ Goldman,¹⁷ Siefert,¹⁸ Schmidt,²⁰ and von Recklinghausen²¹). Krasting holds that the relatively greater frequency of left-sided cerebral metastatic lesions over other areas speaks for metastasis through the arterial tree, for the left cerebral hemisphere being more important functionally than the right receives a larger supply of blood, and the amount of blood passing through the cerebrum is relatively greater than through the cerebellum.

There is another much rarer condition of "meningitis or pachymeningitis carcinomatosa" in which the brain tissue itself may be totally free from cancer elements while the dura and pia arachnoid are so infiltrated as to cause serious pressure symptoms. The infiltration may be of the dura only, causing it to appear thickened and hemorrhagic resembling the so-called hemorrhagic internal pachymeningitis (Hassin²²). A diffuse sarcomatosis or melanosis of the cerebral envelopes has also been described (Boyd,²³ Weaver,²⁴ Weller,²⁵ Ford and Firor²⁶), but this is primarily an intracranial lesion and there is some doubt as to whether the term "sarcoma" for the process is properly used.

All the verified cases in this series showed metastases of the first type, nodular and discrete in character, single or multiple, all presumably due to emboli carried in the blood stream from the primary focus. The diffuse involvement of the arachnoid space which occurred in several instances was always accompanied by and probably secondary to a subcortical lesion. As the subcortical focus grew the cells broke into the perivascular space of adjacent blood-vessels and then passed to and infected the subarachnoid space. Or as the metastatic nodule grew it eventually broke into the subarachnoid space by direct extension.

Among the cases admitted to the neurosurgical service of the Peter Bent Brigham Hospital in the thirteen years up to March 1, 1926, 49 were diagnosed as having a metastatic intracranial lesion, 26 of them having been verified at operation or autopsy. Among the 23 histologically unverified cases, the nature of the primary focus or of its glandular metastases had been assured here or elsewhere in all but three instances. In these unverified cases the clinical symptoms pointed so definitely to an intracranial metastasis that in most cases surgical intervention was not recommended. But since microscopic evidence of the nature of the lesion within the brain is lacking, such lesions are classed as unverified.

From an examination of the statistical tables (Table I), based on this series of 49 cases, it will be seen that carcinoma occurs almost twice as

TABLE I.
Intracranial Metastases—Summary

Primary malignant focus	Carcinomatata							Sarcomata					
	Breast	Lung	Mouth and sinuses	Generative organs	Liver and intestines	Primary focus unknown	Total	Skin and retina	Hypernephroma	Generative organs	Myeloma	Total	Total all cases
Number of cases	15	6	4	4	2	5	36	7	4	1	1	13	49
Verified	6	6	2	1	1	4	20	3	2	1	0	6	26
Unverified	9	0	2	3	1	1	16	4	2	0	1	7	23
Initial symptoms													
Psychosis	5	4		2		1	12			1		1	13
Headache	9	2	3	3	2	3	22	5	1	1	1	8	30
Vomiting	5	1		1	1	1	7	3	1		4	4	11
Loss of vision	4		1	1		1	7	2	1		3	4	10
Sensory	4			1		3	8	1	1		1	1	9
Motor	5	4	1	2	1	3	13	3	2		5	5	18
Average period from initial symptoms to admission to hospital	15 cases, 67 mos. aver. 4½ mos.	6 cases, 21 mos. aver. 3½ mos.	4 cases, 32 mos. aver. 8 mos.	4 cases, 47 mos. aver. 12 mos.	2 cases, 6 mos. aver. 3 mos.	5 cases, 31 mos. aver. 6 mos.	36 cases aver. 5½ mos.	7 cases, 25 mos. aver. 3½ mos.	4 cases, 16 mos. aver. 4 mos.	1 case, 3 mos.	1 case, 10 mos.	13 cases, 54 mos. aver. 3½ mos.	49 cases, aver., 5½ mos.
Osteoplastic flap	3	5	1	1	1	3	14	3	1			4	18
Operation	2		1	1		1	5	3	1			4	9
Decompression							6	2	2			4	10
Improved													
Operation	3	2	2	1		4	13	4	2		4	4	17
Average period from operation or admission to hospital to death	5 op. cases, aver. 2½ mos.; 10 unop. cases, aver. 4½ mos.	5 op. cases, aver. 3 mos.; 10 unop. cases, lived 3 mos.	2 op. cases, aver. 1½ mos.; 2 unop. cases, aver. 1½ mos.	2 op. cases, aver. 3 mos.; 2 unop. cases, aver. 4½ mos.	1 op. case, 5 mos.; 1 unoper. case, 1 mo.	4 op. cases, aver. 5 mos.; 1 unop. case, aver. 2 mos.	10 op. cases, aver. 3½ mos.; 1 unop. case, aver. 3 mos.	6 cases op. aver. 3 mo. 1 unop. case lived 7 mos.	1 op. and rec. 1 op. and died 2 mos. 2 unop. cases av. 4 mo.	1 mo.	1 mo.	7 op. cases aver. 2½ mos.; 5 unop. cases op. cases aver. 3½ mos.	26 op. cases aver. 2½ mos.; 3 unop. cases op. cases aver. 3½ mos.
Average period from initial symptom to death	6+ mos.	6 mos.	9 mos.	14 mos.	5½ mos.	9½ mos.	7+ mos.	7 mos.	5 mos.	3 mos.	10 mos.	6½ mos.	7+ mos.
Average period from initial focus to death	52 mos.	Uncertain	11 mos.	28 mos.	38 mos.	Uncertain	11+ mos.	59 mos.	107 mos.	11 mos.	12 mos.	63½ mos.	29 mos.
Single	7	3(?)	2	1(?)	?	3(?)	16	1	2			3	19
No. of metastases	6	3	?	?	1	2	12	2		1		3	15
Multiple	15		2	3	1	1	22	5	3			8	30
Diagnosis of malignancy made? Yes													
. No		6	2	1	1	4	14	2	1	1	1	5	19

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frequently as sarcoma and that in almost one-half of the carcinomas the primary focus was in the breast. In the sarcoma group the melanotic type and hypernephromata predominate. Considering examples of verified carcinoma (Table II), the tumor is recorded as single in ten instances, five in the left hemisphere, two in the right, and three in the cerebellum. However, in only three of these was an autopsy performed, the lesions being verified at operation. When compared with the 10 cases in which multiple tumors were found, all verified at autopsy, it seems most probable that had a more thorough examination been possible, many of those cases recorded as single would have been found to be multiple. Three of the sarcoma metastases were multiple, three single. Of the latter but one was verified at autopsy, two tumors being removed at operation. The three instances of multiple metastatic sarcomatous lesions were confirmed at autopsy. The evidence seems definite that in the great majority of instances, unless the tumor spreads by direct extension as may happen following a malignancy in the

TABLE II

Number and distribution of metastases	
A. Carcinoma—20 verified cases 10 cases multiple tumors—10 autopsies. 10 cases single tumor—3 autopsies 5 left cerebral hemisphere 2 right cerebral hemisphere 3 cerebellum	B. Sarcoma—6 verified cases 3 cases multiple tumors—3 autopsies 3 cases single tumor—no autopsies 2 left cerebral hemisphere 1 right cerebral hemisphere

accessory sinuses, secondary malignant metastases to the brain are multiple.

Aside from a careful and thorough history and physical examination to determine whether they have or have not had any lesion suggesting a malignant focus, is there any striking feature in the clinical picture of these patients that might lead to a suspicion of its presence? Unfortunately the symptoms seem to be those which accompany any other intracranial growth causing increased intracranial pressure. Headache predominates as an early complaint, with vomiting and loss of vision less frequently noted. Motor and sensory changes depend largely on the position of the metastasis in the brain. It is curious how much more common motor symptoms are than sensory. There is one clinical fact that has been recorded by other observers (McCarthy,²⁸ Heyde and Curschman,²⁹ Löhe,³⁰ Barrett,³¹ Binswanger,³² Crouzon, Behague and Bertrand,³³ Lewis,³⁴ and Toulouse, Marchand and Pezé³⁵) and which appears sufficiently often in this series to be significant, namely, the sudden development of a psychosis. In thirteen patients dispositional changes and dulled mentality were observed. Ten of these thirteen cases were women. Twelve occurred following a carcinomatous implantation. Whether as suggested by Hassin²² the cause of the mental clouding is a general toxic encephalitis set up in the brain as a reaction to the malignant foci is not clear. But it is evident that if a woman of middle age develops a sudden psychosis with asthenia and signs of intracranial pressure, a primary focus of malignancy from which cerebral metastases may have occurred should be most

carefully sought. And the two most reliable methods for determining this diagnosis are a painstaking detailed history and a thorough physical examination.

It is satisfactory to record that in 31 of these 49 cases the true condition of affairs was surmised. In 22 out of the 23 unverified and in 9 among 26 verified cases a diagnosis of metastatic tumor was made. In 10 of this last series the finding of a malignant neoplasm was unexpected, it being supposed that a primary brain tumor was present. In all of the 15 instances of mammary carcinoma, in 3 of 5 cases of melanotic sarcoma and 2 in 4 of hypernephroma the proper diagnosis was made. In none of the 6 subjects harboring metastases subsequent to a primary pulmonary malignant focus was a proper conception of the pathology obtained prior to operation or necropsy.

That neither radical nor palliative surgery is of any permanent avail under these conditions is certain. The average length of life from time of

TABLE III

Operative results	
Operated cases—25 (2 cases still alive)	
Osteoplastic flap—16 cases lived 50 months, average 34 months.	
Decompression—9 cases lived 25 months, average 3- months.	
Non-operated cases—22	
Verified—4 lived 3- months.	
Unverified—18 lived 3 months.	

admission to this hospital to death in both verified and unverified cases, whether operated or non-operated, whether radical extirpation or palliative decompression was performed, was less than four months (Table III). It will be noted that these figures are based on 47 cases. One case in which the tumor extirpated was believed to be a metastatic hypernephroma returned with a recurrence. Following a second successful removal the pathological diagnosis was changed to chordoma. He is alive and well 30 months after the second operation. Aside from a temporary hæmaturia no signs of a renal growth were present, either before or after his stay in the hospital and the actual diagnosis remains in doubt. One other patient who has been lost sight of had a cerebral tumor enucleated in April, 1925, which resembled a metastatic carcinoma of pulmonary origin.

The results published by Tooth,³⁶ giving the survival period following operation for malignant metastases to the brain, confirm our opinion as to the ultimate hopelessness of surgery in dealing with these conditions. Following operation, 13 patients with metastatic sarcomatous lesions in his series lived two and one-half months; 8 with carcinomatous tumors lived an average of one and one-half months. Except for these statistics of Tooth, the literature contains few references to the survival period following cranial operations for malignant nodules. Lower and Watkins³⁷ report a case following carcinoma of the bladder which survived the extirpation of a single large evident that if intracranial metastases have occurred, the cancer cells evident that if intracranial metastases have occurred that the cancer cells

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are free in the blood stream, the bodily resistance to the neoplasm is broken down and that other organs beside the brain must be involved. The most that the surgeon is justified in attempting is a decompression to relieve pressure headaches. In this way the last days of the sufferer may be made more comfortable. Our conclusions are these:

CONCLUSIONS

1. About 4 per cent. of all brain tumors are malignant in origin.
2. Carcinoma is found more frequently than sarcoma, but a higher percentage of sarcomatous tumors metastasize to the brain.
3. Malignant metastases to the brain are in the great majority of cases multiple.
4. The commonest primary foci for carcinoma metastases are the breast and lungs; for sarcoma the skin and kidneys.
5. A suddenly developing psychosis when a history of a primary malignant focus is present is extremely suggestive of metastases to the brain.
6. Surgery, whether radical or palliative, is of no ultimate benefit to these patients insofar as prolongation of life is concerned. But surgical intervention for the relief of intracranial pressure is frequently indicated and may go far toward relieving suffering in the last few months of life.

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