

B R A I N .

PART II., VOL. 35.

Original Articles and Clinical Cases.

SOME OBSERVATIONS ON THE GROWTH AND SURVIVAL-PERIOD OF INTRACRANIAL TUMOURS, BASED ON THE RECORDS OF 500 CASES, WITH SPECIAL REFERENCE TO THE PATHOLOGY OF THE GLIOMATA.¹

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THE following observations form part of a general inquiry into the history, progress, treatment, fate, and, in many cases, the *post-mortem* findings of persons suffering from intracranial new growths who have come under observation at the National Hospital during the period of ten years, 1902-1911 inclusive.

I have here to make grateful acknowledgment of the permission of my colleagues to use the notes of their cases, and the ready help given me on all occasions, especially in the difficult matter of tracing the after-history of patients. As the numbers are large, and the notes in most cases voluminous, many being models of medical note-taking, it may not be out of place to say a word upon the method employed, especially as the value of some of the tables submitted depends entirely upon the accuracy of interpretation of the recorded clinical details, and the information received from the patients themselves, both of which constitute the main difficulty in an inquiry of this nature.

A careful abstract of the clinical features has been made upon a card under an index number, a running card-index of clinical points being made at the same time. This card also receives all other information that can be obtained, namely: (1) An account of operation, and further course of the case; (2) an abstract of the *post-mortem* examination—no small part of the task, which has been undertaken by my colleague

¹ Presidential Address (Section of Neurology), Royal Society of Medicine.

Dr. Howell, then pathologist, to whom I offer my best thanks; (3) an examination of the microscopical appearances; (4) all patients who have left the hospital have been written to—a circular letter with a short series of easily answered but sufficiently searching questions on the fly-sheet, and on the whole the answers have been intelligent, and of use in forming an opinion of the present state; 346 of these letters have been sent out, and 177 answers returned from patients or their friends; the remainder have not been answered, or the letters have been returned through the post. In forming tables of results, therefore, it has been necessary to assign a column of “No reply.”

My junior colleagues, who have in the last ten years served on the Resident Staff, have kept in touch with some of these “No reply” cases to fairly recent dates, so this group affords some information of value. These facts are entered upon the cards.

During the ten years there have been in hospital 566 cases diagnosed as new growths, or as gummata. The gummata, 40 in all, have been rejected as requiring separate consideration. On close consideration, also, 26 cases have been eliminated for various reasons, not the least being the absence of optic neuritis. These rejections leave 500 cases of practically certain intracranial tumour, and it is from these that the facts and conclusions which follow have been gathered.

Table I presents the distribution of these tumours according to the regions of the brain involved. The larger number have been verified by operation or *post-mortem* examination. Many, of course, have been subjected to neither of these tests, but from the clinical details one may have little hesitation in accepting the diagnosis as correct, and these have been used for the estimation of the period of growth of tumours, whether still alive or since dead, without verification *post-mortem*.

To show how difficult is this question of rejecting or retaining cases in the absence of verification, I must refer to two cases amongst the rejections. The first, a woman, aged 43 (Dr. Beevor), who had suffered nineteen years before from severe fits, ten years torticollis, and frequent faints, five months posterior headache, five weeks a Jacksonian convulsion, left hand and arm preceded by an aura in the same situation. On admission she presented the picture of right precentral tumour: mental levity, intense optic neuritis, blurred vision, left hemiplegia, exaggerated left deep reflexes. The brain was explored by Sir V. Horsley over the region indicated, and nothing was found. There was much bulging afterwards, but the neuritis subsided to pallor, and she

became almost blind. Six weeks after operation she had a series of fits, beginning with purposive movements of the right arm, becoming clonic later, and, as the fit subsided, similar movements on the left side,

TABLE I.—REGIONAL CLASSIFICATION OF CASES OF ALL TUMOURS, WHETHER VERIFIED OR NOT.

Region	SEX		Total	Per cent.	
	M.	F.			
(1) Frontal	60	40	100	21·7	Fore-brain : 239. 52 per cent.
(2) Central pre- and post. Parietal	43	20	63	13·7	
(3) Temporo-sphenoidal ...	24	25	49	10·6	
(4) Occipital	8	6	14	3·0	
(5) Corona radiata; corpus callosum, &c.	4	6	10	2·1	
(6) Lateral ventricle	2	1	3	0·6	
(7) Pituitary	10	4	14	3·0	Mid-brain : 30. 6·5 per cent.
(8) Optic thalamus	4	2	6	1·3	
(9) Mesencephalon	18	8	26	5·2	
(10) Pineal	4	—	4	0·8	
(11) Choroid plexus; III and IV ventricles	4	1	5	1·0	Cerebellum and pons : 160. 34·2 per cent.
(12) Cerebellum	44	33	77	16·7	
(13) Extra-cerebellar	19	21	40	8·7	
(14) Pons	19	24	43	9·3	
(15) Medulla	—	1	1	0·2	
(16) Base	1	3	4	0·8	
Total	264	195	459		
(17) Not localized	24	17	41		
Grand total	288	212	500		

followed by coma. Nearly five months after she became alternately stuporose and noisy, again a series of right-sided fits, coma, and death from respiratory failure. *Post-mortem* no tumour was found, but great general rise of intracranial pressure, so as to force the posterior part of

the cerebellar lobes down into the foramen magnum—so-called pressure-cone. Dr. E. F. Buzzard made some 500 sections of the brain, and failed to find any cause for the symptoms. This may not be a rare case—in fact, there have been three similar cases—but if the *post-mortem* findings were not to hand it would have come into my table as a tumour of the Rolandic area.

The second case was of optic neuritis with swelling without localizing symptoms. This was rejected as a case of family optic neuritis. Her sister had been in hospital one year before with the same symptoms, and eventually quite recovered. Both had suffered from severe headache, parietal and frontal, and both had been diagnosed as tumor cerebri. Again, there may be many such.

Therefore the group "Not localized" has little value, and is placed by itself in this table. It has been used in Table II, age-incidence, but in the other tables in which it occurs it is taken by itself on its own merits.

There can be little doubt that a fair number in this group are Frontal and Temporo-sphenoidal cases, latent or of slow growth; some may be deeply seated subcortical growths in the Corona radiata or ventricles, regions of indefinite symptomatology. It will be seen that the two most vulnerable regions are the Frontal and the Cerebellum. But if we take the Frontal and Parietal together, which, considering the great tendency to overlapping, is a reasonable thing to do, and for the same reason we link together the Cerebellum and Pons, it is remarkable how closely in the respect of vulnerability these two antipodal regions correspond—i.e., Fronto-parietal 163 cases, Ponto-cerebellar 160—making together more than half the total of all growths, whether verified or not, for all regions.

In the Fore-brain, which includes the first six regions in Table I, and which claims 52 per cent. of the whole number, the Frontal group heads the list with 100 cases, 21·7 per cent. of the total, and 41·8 per cent. of the Fore-brain. We have much exact knowledge both of localization, and of the characters, of the growths of this region, by reason of the fact that operations have been performed in 74 per cent. of the cases. The Central group is smaller, 63, but owing to the comparatively clear and definite symptomatology of the motor region, operations have been performed in a yet larger percentage of cases—i.e., 52 out of 63, or 82·5 per cent.

Of tumours of the Temporo-sphenoidal region we have a fair number, 49. The diagnosis of lesions of this region is among the most difficult,

TABLE II.—AGE AT APPEARANCE OF FIRST SYMPTOM FOR ALL GROWTHS, VERIFIED OR NOT.

Region	SEX		Total	1—20 YEARS		21—30 YEARS		31—40 YEARS		41—50 YEARS		51—60 YEARS		61—70 YEARS	
	M.	F.		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
(1) Frontal	60	40	100	9	9.0	30	30.0	39	39.0	14	14.0	7	7.0	1	1.0
(2) Central (parietal) .. .	43	20	63	9	14.2	12	19.0	19	30.0	16	25.3	6	9.5	1	1.5
(3) Temporo-sphenoidal .. .	24	25	49	10	20.4	14	28.5	18	36.7	5	10.2	2	4.0	—	—
(4) Occipital .. .	8	6	14	2	14.2	4	28.5	1	7.1	3	21.4	4	28.5	—	—
(5) Corona radiata, corpus callos., &c. .	4	6	10	1	10.0	3	30.0	—	—	2	20.0	4	40.0	—	—
(6) Lateral ventricle .. .	2	1	3	1	33.3	—	—	2	66.6	—	—	—	—	—	—
(7) Pituitary .. .	10	4	14	2	14.2	6	42.8	4	28.5	2	14.2	—	—	—	—
(8) Optic thalamus .. .	4	2	6	1	16.6	1	16.6	2	33.3	2	33.3	—	—	—	—
(9) Mesencephalon .. .	18	8	26	12	46.1	9	34.6	3	11.5	1	3.8	1	3.8	—	—
(10) Pincal .. .	4	—	4	1	25.0	2	50.0	—	—	1	25.0	—	—	—	—
(11) Choroid plexus, III and IV ven- tricles .. .	4	1	5	1	20.0	2	40.0	—	—	2	40.0	—	—	—	—
(12) Cerebellum .. .	44	33	77	47	61.0	14	18.1	10	14.2	3	3.8	3	3.8	—	—
(13) Extra-cerebellar .. .	19	21	40	5	12.5	7	17.5	19	47.5	6	15.0	2	5.0	1	2.5
(14) Pons .. .	19	24	43	23	53.4	7	16.2	8	18.3	5	11.6	—	—	—	—
(15) Medulla .. .	—	1	1	1	—	—	—	—	—	—	—	—	—	—	—
(16) Base .. .	1	3	4	1	25.0	—	—	—	—	1	25.0	2	50.0	—	—
(17) Not localized .. .	24	17	41	13	31.7	12	29.2	12	29.2	2	4.8	2	4.8	—	—
Totals .. .	288	212	500	139	—	123	—	137	—	65	—	33	—	3	—

yet a large number, 32, or 65.1 per cent., have come to operation and with a lower mortality than in the two preceding groups. The occipital group is much smaller, only 14, and as the localization is not difficult owing to the rather sharp symptomatology referable to the optic radiations and angular gyrus, it may be inferred that tumours in this region are comparatively rare. Operations have been performed in seven cases—i.e., 87.7 per cent. The Mid-brain group includes 26 cases, to which may be added the Pineal cases, making together 30, or 6.5 per cent. of the whole. The diagnosis of these lesions has been made more practicable by the work of Head and Holmes, and probably in the future the percentage of this group will be higher, but I fear surgery offers little hope of help in dealing with such cases.

The Cerebellum proper offers 77 cases, 16.7 of the whole, and as the clinical indications are fairly well marked, this is probably a true figure; 36, or 46.7 per cent., have been verified by operation.

Of the Extra-cerebellar group, 5 are Gliomata and 13 Fibrogliomata, and therefore primary in the Cerebellum, but as their line of growth was almost entirely in the lateral recess, I have included them in this group. There were 40 in all, and 32, or 80 per cent., came to operation.

Of tumours of the Pons there were 43, or 9.3 per cent.; they require no comment in this connexion.

Growths of the Medulla must be very rare. I find record of only 1, an infiltrating Glioma.

Table II: Age at appearance of first symptom.—This, of course, is not necessarily a true indication of the age of the tumour, which may have existed in a latent state for any length of time. The table requires little comment. Its value is regional only. Of tumours of the Fore-brain generally, 142, or 59.4 per cent., made their first manifestation between the ages of 21-40; 32 only, or 13.4 per cent., between 1-20; 63, or 26.7 per cent., between 41-60; and only two in the last decennium, one of which was strictly 72.

Of the Mid-brain group 21, or 80.7 per cent., appeared first between ages 1-30, 12 of these falling between 1-20. Of the Ponto-cerebellar tumours (excluding Extra-cerebellar; in 70 cases, or 58.3 per cent., symptoms appeared first between 1-20, 21, or 17.3 per cent., between 21-30, 18, or 15 per cent., between 31-40, and only 8, or 6.6 per cent., between ages 41-50.

But the Extra-cerebellar group more nearly resembles in age-incidence the Fore-brain tumours, in that the larger number, 19, or 47.5 per cent., fall between ages 31-40.

To sum up briefly, it would appear that tumours of the Fore-brain tend to appear more frequently in middle age, but no age is exempt. Those of the Mid-brain, on the other hand, appear first predominantly in the early or adolescent period, and the same may be said of the Cerebellum and Pons; comparatively few occur after 30.

Table III has perhaps more interest than the last, and though the figures are smaller they include verified cases, and are therefore of more value. The Gliomata come first, 127, or 49·2 per cent., and it is seen that the numerical age-incidence for each decennium to 50 is fairly similar, but the largest number falls between 21-40. The Fibrogliomata are few, but they conform in this respect with the last.

The same may be said of the Endotheliomata: the largest number, 16, or 43·2 per cent., of the group falling between 31-40.

The Sarcomata show practically the same age-incidence.

Carcinomata, as might be expected, appear in later periods, 31-60, but they are few.

Tuberculomata also are few, 14 only; of these 9 appear between 1-20, and only 1 between 30-40. The remaining growths are too few to base any conclusions upon.

Heredity.—In the records of cases heredity receives due attention. The class of patients at this hospital, generally speaking, is perhaps somewhat above that of general hospitals, so that diseases so striking as tumour of the brain, or cancer, might be expected not to be overlooked by the patient or friends. Yet among the 500 cases I find a cancerous heredity in no more than 37 cases, or 7·2 per cent. Of these 13 were in the father and 2 others on his side, 15 in the mother and 2 others on her side, 1 brother, 3 sisters, 1 aunt. In 10 the growth in the patient was Glioma, in 2 Fibroglioma, in 4 Fibroma, in 2 Endothelioma, and in 1 Tuberculoma. In 17 the nature of the growth was not known.

In no case is there any family history of tumor cerebri. We may assume, then, that heredity is a negligible factor.

Table IV: Regional incidence of growths verified on operation or *post-mortem* examination.—The accuracy of this table depends upon the correct interpretation of the microscopical appearances of the section preserved, and some of them are so puzzling that their proper place in this table is almost a matter of opinion. With this reservation the table may be considered for practical purposes a true statement.

Glioma.—It is evident that of all growths the Glioma is the largest in number and the most universal in its incidence. Of the total 258

TABLE IV.—REGIONAL INCIDENCE OF GROWTHS VERIFIED ON OPERATION OR POST-MORTEM.

Region	No. of growths in each region	GLIOMA		FIBROGLIOMA		FIBROMA		ENDO- THELIOMA		SARCOMA		CARCINOMA		TUBERCU- LOMA		CYST		PAPILLOMA		CHOLESTEA- TOMA		PITUITARY		PINEAL ADENOMA	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
(1) Frontal ...	68	38	55.8	—	—	—	—	21	30.8	4	5.8	4	5.8	1	1.4	—	—	—	—	—	—	—	—	—	—
(2) Central ...	43	25	58.1	—	—	—	—	10	23.2	3	6.9	5	11.6	—	—	—	—	—	—	—	—	—	—	—	—
(3) Temporo- sphenoidal ...	27	17	62.9	—	—	—	—	4	14.8	2	7.4	2	7.4	2	7.4	—	—	—	—	—	—	—	—	—	—
(4) Occipital ...	6	4	66.6	—	—	—	—	—	—	1	16.6	1	16.6	—	—	—	—	—	—	—	—	—	—	—	—
(5) Corona radiata, corp. callos., &c.	8	6	75.0	—	—	—	—	—	—	1	26.5	1	26.5	—	—	—	—	—	—	—	—	—	—	—	—
(6) Lateral ventricle	3	1	33.3	—	—	—	—	—	—	2	66.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(7) Pituitary ...	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(8) Optic thalamus	3	1	33.3	—	—	—	—	—	—	2	66.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(9) Mesencephalon	8	4	50.0	—	—	—	—	—	—	1	12.5	—	—	2	25.0	1	12.5	—	—	—	—	—	—	—	—
(10) Pineal ...	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(11) Choroid plexus, III and IV ven- tricles	4	—	—	—	—	—	—	—	—	1	25.0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(12) Cerebellum ...	34	18	52.9	—	—	1	2.9	1	2.9	3	8.8	1	2.9	6	17.6	4	11.7	—	—	—	—	—	—	—	—
(13) Extra-cerebellar	32	5	15.6	13	40.6	11	34.3	1	3.1	—	—	—	—	—	—	—	—	—	—	2	6.2	—	—	—	—
(14) Pons ...	12	7	58.3	1	8.3	1	8.3	—	—	—	—	—	—	3	24.9	—	—	—	—	—	—	—	—	—	—
(15) Medulla ...	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(16) Base crus, &c. ...	3	1	33.3	—	—	—	—	—	—	1	33.3	1	33.3	—	—	—	—	—	—	—	—	—	—	—	—
Totals ...	258	127	49.2	15	5.8	13	5.0	37	14.3	21	8.1	15	5.8	14	5.4	5	1.9	3	1.1	2	0.7	2	0.7	4	1.5

growths, 127, or 49·2 per cent., were Gliomata. Grouping the regions as before, we find there are 91 Gliomata, or 58·7 per cent. of all growths in the Fore-brain. Again, in the Mid-brain this class of tumour predominates to the extent of 50 per cent., but the numbers are few. In the Cerebellum and Pons, including the Extra-cerebellar growths, there are 30 Gliomata out of a total of 78, or 38·4 per cent.

Fibroglioma and fibroma.—These are peculiar to the Cerebellum and Pons and the one Medulla case. The Fibroglioma is a growth which presents the features of Glioma and Fibroma, and I cannot yet say whether it is a distinct pathological entity or a true Glioma in which the conditions of growth are in some way modified by its surroundings. I am inclined to think the latter, and if so it should be included among the Gliomata.

In the peripheral parts of some of the Gliomata in the Fore-brain a tendency to the formation of fibrous stroma with elongation of nuclei is frequently seen, even to the extent of rough capsulation.

Endothelioma.—Endotheliomata are much less common, and they occur practically only in the anterior fossæ of the skull. The regions involved are therefore the Frontal 21, Central 10, and Temporo-sphenoidal 4. Two only affected the posterior fossæ, one in the lateral recess and the other compressing the vermis. To these must be added two Cholesteatomata, which were Extra-cerebellar. This is a curious and interesting point, and it is difficult to explain why the endothelium of the falx, and only the anterior part of it, should be affected to the exclusion almost of all the rest of the great dura mater sheath. There were 35 Endotheliomas of the three regions named, or 25·3 per cent. of all growths for those regions.

Sarcoma.—This group presents some difficulty in classifying, for, as will appear later, there are stages in the growth of the Glioma which, if universal in the section, may be almost indistinguishable from some of the recognized forms of Sarcoma. In any case the group is not a large one. Twenty-one cases only, or 8·1 per cent. of the whole. Six were undoubted round or spindle-celled Sarcomas, 3 of them secondary growths, 1 to suprarenal, 1 to kidney, and the other, melanotic, to the eye. The remainder were primary, and no part of the brain can be said to be exempt.

Carcinoma.—Primary carcinoma is interesting from its comparative rarity. Of the total (15) 1 only is undoubtedly primary, and, from its peculiar appearance, of the Choroid plexus. Seven may have been primary, that is, no growth was found elsewhere, but in one or two only

the brain was allowed to be examined. The remaining 7 were secondary—the primary growth being mammary in 3, ovarian, suprarrenal, pancreatic and rectal in the other 4.

Tuberculoma.—Verified cases are surprisingly few. It is often diagnosed, but deaths are few. The age-incidence is so young that no doubt large numbers of these patients go to children's and general hospitals. It is also probable that many recover, and I suspect that many of the long survival-periods may include this class of tumour.

Cyst.—The simple cyst deserves attention. I can find record of only 5 in which the true character was verified. All were thin-walled, apparently structureless bags containing clear fluid. One was found *post-mortem* in the mid-brain lying ventrally to the Sylvian aqueduct. The patient died unrelieved by a cerebellar decompression. The others were in the cerebellum, and three came to operation. Two of them were successfully drained and the patients were known to be alive and well six or seven years after ; in the other, by a mistake in localization the exploration was made on the wrong side and the patient died seven days after. The fifth case presented an uncertain symptom picture, though a Mid-cerebellar growth was suspected ; no operation was attempted and the patient died fifteen months after the first symptom in the London Hospital. The Medical Registrar has kindly sent me an abstract of the autopsy, at which was found a very thin-walled cyst, of the size of a golf-ball, lying between the two lobes of the cerebellum and pressing down upon the floor of the fourth ventricle. Here is a case that must fill one with regret ; operation might reasonably be expected to have been quite successful. If simple cysts were common, that in itself would almost justify exploration in any cerebellar case indiscriminately, but 5 in 258 is 1·9 per cent., and if this is anywhere near the truth simple cyst is a rare condition. Many gliomas, one may say most of the more chronic forms, develop cysts containing semi-gelatinous fluid, the drainage of which often affords more than temporary mechanical relief, but there is little evidence that the ultimate growth of the tumour is to any extent modified.

Papilloma.—Papilloma of the Choroid plexus is a rare condition ; it occurred in 3 cases only. In one the growth was felt in the middle peduncle of the right lobe of the Cerebellum, and as much as possible was removed, but the patient died ten days after. Another patient died of pneumonia, and the third died outside, but Dr. Holmes made an autopsy and found a Choroid plexus tumour undergoing colloid degeneration. These growths present the appearance of simple adenomatous overgrowths

of the normal tissue, but clinically they are as dangerous to life as any malignant growth, and their situation is such as to be out of the range of successful operation, even if they could be diagnosed with certainty.

The only case of undoubted primary carcinoma, alluded to above, presented the general features of a Choroid plexus tumour, but the columnar cells of the papilloma are swollen into great round cells undergoing active multiplication. In this case also there were many small islands of secondary growth, mostly cortical, the largest being in the left Rolandic region. This region was explored and a cyst punctured, with the escape of 1 c.c. of colloidal fluid. The patient died of respiratory failure on the table. A papilloma, then, may take on highly malignant features.

Cholesteatoma.—One undoubtedly presented the characteristics of this class of tumour. It was Extra-cerebellar in situation, found on operation in the right lateral recess, and removed successfully, but unfortunately the patient died seventy-five days after of sepsis. The tumour was encapsuled, and on incision exuded white, glistening, pulsataceous matter consisting largely of cholesterin, and also some large epithelial cells. It proved impossible to preserve the crystals and the section now shows a structureless network with some granular detritus in its meshes. The other was also Extra-cerebellar deeply in the right lateral recess. It was removed successfully piecemeal. The patient was seen a year after, but was in a very poor condition, with all the old symptoms, severe vertigo, and ataxia, with mental enfeeblement and a large hernia. The tumour was described as white, hard, and encapsuled, but no cholesterin was noted at the time of operation. The section now is strikingly like the last.

It is probable that these growths are highly degenerate endotheliomata, and it is perhaps an unnecessary refinement of classification to place them in a group apart.

Pituitary.—The clinical features of pituitary tumour referable to pressure on the Chiasma are so marked that the number 14, or 3 per cent. of the whole, probably represents the true percentage, though only 4 have been verified, all by operation. In 3 of these the tumour was removed more or less completely, and in the fourth partially only, the state of the patient becoming so bad that operation had to be suspended and the patient died nine hours after without recovering consciousness. Of the 3 that survived 2 died in about six months and the third survived three and a half years. It is probable that recurrence took place, and therefore a considerable degree of malignancy

must be ascribed to these growths, at any rate if disturbed by operation. This result should be compared with the long survival of pituitary tumours considered below.

Pineal.—Clinically these tumours are undiagnosable as such, the symptoms being referable to Mid-brain and internal hydrocephalus. There have been 4 cases in the ten years, 3 of which have been reported by Howell. The growth, which is of the nature of adenoma or adeno-sarcoma, tends to fill the third ventricle and to extend down the aqueduct of Sylvius to the fourth ventricle, infiltrating more or less widely the surrounding structure.

THE SURVIVAL-PERIOD OF TUMOURS FROM THE APPEARANCE OF THE FIRST SYMPTOM TO DEATH.

I now come to a most interesting part of the subject, an inquiry into the life-history of such tumours as have been verified *post-mortem*, untouched by surgery, which therefore may be assumed to have run a natural course, for it is idle to suppose that, in the present state of knowledge, any therapeutic agent can modify, to any extent, the growth of any of the tumours now under consideration except the tuberculomata. And yet it must be within the experience of every physician that in many cases an extraordinary change for the better occurs during the period of rest and observation in the wards, so that important symptoms, pain, vomiting and the like, disappear, and even optic changes regress. This adds another difficulty in deciding upon the advisability of operative interference.

Table V includes patients who died in the wards and on whom a *post-mortem* examination was made. There were 65 of these, and the average in months of survival from the first symptoms is given for the regions and growths.

In the last column, "Not verified," is given the same average for patients in whom the diagnosis was reasonably certain, but who died outside, or on whom autopsy was not allowed; they number 43.

These periods are of sufficient significance to justify some consideration in detail, especially as the survival-period after operation is of paramount interest, which must be enhanced by comparison with these. The results of operations in this respect will form part of a report to the International Congress of Medicine in 1913.

Glioma.—If we take the 22 gliomata of the Fore-brain as a whole, we find that the patients survived for all sorts of periods from six

weeks to nine years, and if we strike a rigid average for all these periods it is found to amount to 16·2 months. But among these 22 is one most exceptional survival-period, nine years, so much so that it seems justifiable to exclude it, and strike an average of the remaining 21. The result of this is to bring the average survival-period down to 10·1 months, and I think this is probably not far from the truth. It may be in excess somewhat because there were three other rather exceptional periods, namely, of four, four and a half, and three years, but on the other hand more cases to deal with might show still more of these long periods.

It will be noticed that the survival-period in cases of tumour of the Frontal region is the longest; the Temporo-sphenoidal region comes next with fewer figures, and the Corona radiata last with still fewer. The Central and Occipital are too few to be considered separately.

The Mid-brain, Ponto-cerebellar and Base (interpeduncular space) may be fairly taken together, though the number of cases is small, 11 in all. The shortest survival-period was twenty-four days, a case of glioma of the Pons, and the longest was two years, also of the Pons. The average survival-period for the 11 cases was 9·4 months, not much less than that for the Fore-brain.

Fibroglioma and fibroma came to operation in all cases but the two on this table.

Endothelioma.—There are too few to base conclusions of any value, 4 in the Fore-brain and 2 in the Cerebellum. These 6 give an average survival of 20·2 months. A rough estimate of the period of growth may be arrived at by averaging the period from the first symptom to the time of operation, in the operation cases, disregarding the result, whether good or evil. Perhaps this may give truer results than at first appears likely, for in some of the cases a fatal issue in any case could not have been long deferred. Thirty-one cases are available for this purpose with very variable survival-periods, for instance, 1 of twenty years or more, another of eighteen years, 3 of ten years, and the rest of all periods from seven years to six months, 1 only of two months. A strict average for all these gives four years as the average survival-period for this class of tumour, and on the whole this may not be far from the truth, though probably it errs on the side of under-estimation.

Sarcoma.—The figures again are few, only 5. The survival-period averages 11·2 months. One patient, however, with a sarcoma of the Optic thalamus, survived four years, which must be an extreme time for

TABLE V.—AVERAGE SURVIVAL PERIOD IN MONTHS FROM FIRST SYMPTOM TO FATAL TERMINATION. NATURE OF GROWTH VERIFIED POST-MORTEM.

Region	GLIOMA		FIBROGLIOMA		FIBROMA		ENDOTHELIONA		SARCOMA		CARCINOMA		TUBERCULOMA		CYST		PAPILLOMA		NOT VERIFIED		Totals
	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	No.	Average in months	
(1) Frontal...	9	16	—	—	—	—	2	10:72	—	—	2	8	—	—	—	—	—	—	6	39	19
(2) Central...	2	7:108	—	—	—	—	1	4	1	2.5	1	7	—	—	—	—	—	—	3	6	8
(3) Temporo-sphenoidal	6	9	—	—	—	—	1	9	—	—	1	8	—	—	—	—	—	—	2	—	10
(4) Occipital	1	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	19	2
(5) Corona radiata	4	7	—	—	—	—	—	—	1	5	1	5	—	—	—	—	—	—	1	5	7
(6) Lateral ventricle	—	—	—	—	—	—	—	—	1	1.7	—	—	—	—	—	—	—	—	—	—	1
(7) Pituitary	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	48	1
(8) Optic thalamus	—	—	—	—	—	—	—	—	2	6:48	—	—	—	—	—	—	—	—	1	30	3
(9) Mesencephalon	1	5	—	—	—	—	—	—	1	1.5	—	—	2	1:1:6	—	—	—	—	2	10:18	6
(10) Choroid plexus	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	7:24	—	—	2
(11) Cerebellum	2	12	—	—	1	7	1	3	—	—	1	10	2	13:108	1	15	—	—	7	20	15
(12) Extra-cerebellar	2	6:18	—	—	—	—	1	12	—	—	—	—	—	—	—	—	—	—	2	12:33	5
(13) Pons	5	9	1	10	—	—	—	—	—	—	—	—	3	7	—	—	—	—	11	21	20
(14) Base	1	2	—	—	—	—	—	—	1	12	1	24	—	—	—	—	—	—	1	22	4
(15) Not localized	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5	48	5
Totals	33	—	1	—	1	—	6	—	7	—	7	—	7	—	1	—	2	—	43	—	108

Where the number is more than two, averages are given. If only two, the survival-period for each is given, unless the two periods are almost equal.
Decimal points omitted, except in single cases.

sarcoma. If we drop this, the remaining sarcomas give a period of 5·1 months, which perhaps is an under-statement.

Carcinoma.—Seven cases give an average survival-period of 10·1 months, probably an over-statement.

Tuberculoma.—In any case verified Tuberculomata are few, 14, 7 of which came to operation. The 7 that remain give a strict average survival-period of 21·5 months, but in one case the growth had been in existence nine years; without this the survival falls to seven months. However, taking the survival-period to the time of operation, as was done in dealing with the endotheliomata, we find an average survival-period of 17·4 months. The probable explanation of these varied results is that tuberculomas present in their development periods of activity and of quiescence, determined by varying degrees of constitutional resistance, and it is not too much to assume that such periods of latency may ultimately become permanent. This must surely be the explanation of some of the results shown in Table VI. The importance of an early tuberculin test need scarcely be urged, in view of medical treatment, for the results of surgical interference are far from encouraging.

Simple cyst.—One might expect a simple cyst to be associated with a long survival-period. Only one is forthcoming as fatal without interference, and that had given symptoms for fifteen months (*vide supra*). Mechanical pressure on the floor of the fourth ventricle no doubt was the immediate cause of death. But one can form no conception of how long this cyst had been in existence before making itself felt, and this, of course, applies to all growths. Four came to operation, and in them the survival-period averaged 12·3 months. Apparently these cysts, though rare, are progressive in their enlargement, and their progress is fairly rapid.

Papilloma.—Two cases ran a natural course and, as shown in Table V, survived seven months and two years respectively. Two came to operation and had shown symptoms six months and twelve months to the time of operation. One of these patients was alive four and a half years after. No conclusion can be arrived at in so few instances.

The column "Not verified" includes 43 cases in which the localization was sufficiently clear to justify placing them in the regions named. For various reasons operation was not thought advisable, or in a fair number of cases was refused by the patient. All these patients left hospital alive, and having been written to, the information has come to hand that they have since died, and generally a date has

been given. Some died in hospital, but an autopsy was refused. Of course, we have no idea of what class these tumours were, but nevertheless the survival-period is worthy of note. Averaging the 43 cases, we arrive at a survival-period of 24·3 months, a little over two years. The largest number of these, 20, are of Cerebellum and Pons.

TABLE VI.—AVERAGE SURVIVAL-PERIOD IN YEARS FROM FIRST SYMPTOM FOR PATIENTS ALIVE OR FROM WHOM NO INFORMATION HAS BEEN RECEIVED. NATURE OF GROWTH NOT KNOWN.

Region	ALIVE TO DATE		NO REPLY		Total
	Number	Average in years	Number	Average in years	
Frontal	2	2 : 6	5	1·3	7
Central	—	—	3	2·6	3
Temporo-sphenoidal	2	4·6 : 6	5	2·4	7
Occipital	2	18	3	5·2	5
Corona radiata	—	—	—	—	—
Lateral ventricle	—	—	—	—	—
Pituitary	7	9·7	2	2·5 : 0·5	9
Optic thalamus	1	9	1	3	2
Mesencephalon	6	6·5	7	3·4	13
Choroid plexus	—	—	—	—	—
Cerebellum	13	5·7	13	1·4	26
Extra-cerebellar	—	—	3	2·5	3
Pons	5	6·9	12	1·5	17
Base	—	—	—	—	—
Not localized	13	5·2	19	2·8	32
Totals	51		73		124

There remains for consideration Table VI, which seems to me to be of some interest in spite of many weak points. It concerns a total of 124 cases of more or less clinically certain tumours of the Brain, 22 in the Fore-brain, 9 Pituitary, 20 in the Mid-brain, 46 in the Cerebellum and Pons, and 32 not localized at all. These cases fall in an

"Alive to date" column, 51, and of these I have certain information as to their survival and some idea as to their present condition, and a "No reply" column, 73; letters to the patients have been returned through the post.

A glance at the first column suffices to show a remarkably long survival-period. The average, excluding the Pituitary group which deserves special notice, is 6.3 years. Grouping the regions as in former calculations, we find the Fore-brain gives the long survival-period to date of 9.5 years, but this is exaggerated by 2 Occipital cases of eighteen years, 1 probably a tuberculoma.

The Mid-brain and Optic thalamus together, 7 cases, give an average of 6.9 years, and the Cerebellum and Pons, 18 cases, in the same way give a survival-period of six years to date.

The Pituitary groups seem to possess special significance examined in this manner, because the symptomatology of these tumours is so distinctive. It includes 7 cases. All had more or less intense optic atrophy, with progressive loss of sight, and at some time characteristic hemianopsia, though one patient replies that his sight has improved. The average survival-period for all of these is 7.5 years to present date. All of them had been diagnosed as pituitary cases, 2 seem doubtful, but their removal does not appreciably affect the average. Even if this is a gross over-statement it would appear that the growth of these tumours is naturally a slow one, and this is significant in view of the tendency to recurrence after operative treatment (*vide supra*).

In the "No reply" column the survival-period is naturally less striking, because it has to be calculated to the date at which the patient left hospital. It is therefore of little value, but the average survival to that date is 28.4 months. Many of these, of course, may not be alive.

Now I give these figures for what they are worth and they must be received with great caution; but they are sufficiently large to arrest attention and provoke speculation, too large, I think, to be ignored. Probably a certain number are gummata without a history of syphilis, many no doubt are tuberculomata, but it is quite possible that among them are quiescent or latent gliomata or endotheliomata. This is pure speculation, but I would recall the not infrequent instances of a long survival-period among the verified cases, proving that glioma even, and endothelioma certainly, may run very long courses. It is also significant that the cerebellum should supply a proportionately large number of the cases, namely, 26, 13 of which are alive still with an average sur-

vival of five and a half years; an equal number from whom no reply has come give an average of 1·4 years to the time of leaving hospital, which perhaps might safely be doubled or even trebled, but equally, of course, some may not be alive. The symptomatology of cerebellar tumours is sufficiently distinctive so that the margin of error in diagnosis can scarcely be very great. The obvious objections to a table of this kind are the initial possibility of error in diagnosis, and ignorance of the nature of the lesion; so much has to be taken on trust, and the danger is that it may be taken too literally.

AN INQUIRY INTO THE LIFE-HISTORY OF THE GLIOMA FROM THE HISTOLOGICAL STANDPOINT.

Of all the growths that affect the brain the glioma stands first both in frequency and importance.

As shown above, of 258 cases in which the nature of the growth was verified 127, or 49·2 per cent., were of this class. Most of these I have examined myself, thanks to the labours of our pathologists during the last ten years, and they present a bewildering variety of histological appearances, and the difficulty of placing some of them seems almost insurmountable. This difficulty is rendered all the greater from the fact that the same tumour may present, sometimes within the compass of an ordinary section, grades of change of great variety, so that at one end of the section we are looking at an apparently innocent growth, and at the other a richly cellular mass, more like a malignant sarcoma, or in another place an area of necrosis. On the whole, this variety of appearances seems to be distinctive of the gliomata, and occurs more often, and in a higher degree, among them than in any other of the intracranial growths. To arrive at a just estimate of the malignancy of a glioma it is really necessary to make sections from the periphery to the centre, and this of course, is not always possible.

The original conception of a glioma is that of a simple overgrowth of the connective tissue element of the brain. It is not common to find a tumour which presents this simple character throughout; the nearest approach to a typical instance is:—

Case 1.—This is from T. H., a man aged 42 (Sir W. Gowers), who had presented symptoms referable to the left Frontal region of eighteen months' duration. Unfortunately the operation notes have been mislaid, and one can only find that the left Frontal region was explored (Sir V. Horsley), and some part of the tumour removed, from which this section was made. The patient died at home not very long after, but the reply is very indefinite. (Fig. 1.)

The noteworthy histological features (fig. 1) are¹:—

- (1) A fine, loose-meshed glia reticulum.
- (2) Delicately stained, barely visible glia-cells, with three or more branching processes, which divide into a fine reticulum which forms the stroma or connective tissue basis of the tumour. To show these elements a counter-stain, such as Van Gieson's, is necessary.
- (3) Scattered over the section in not excessive numbers are the glia-nuclei, always deeply stained by hæmatoxylin. I call these "glia-

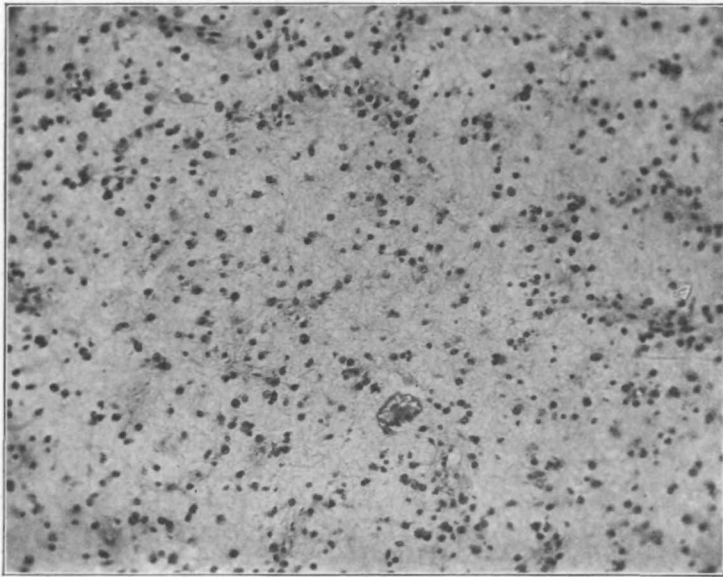


FIG. 1.—Case 1. Section of a glioma of a low degree of malignancy. Frequent arrangement of nuclei in circles or semicircles of very varying diameters, also in places in almost straight lines.

nuclei" to distinguish them from the more histologically definite "glia-cells." Possibly they also are cells with an invisible cytoplasm. The term is provisional only. They should be fairly uniform as to size and not grouped, but even in this apparently innocent quiescent picture these cells tend to show an arrangement in circles or segments of circles, a feature to be referred to later when considering the more malignant types.

(4) The blood-vessels are few and their walls lined internally by a single layer of flattened endothelial cells.

¹ In preparing the photomicrographs throughout a Zeiss D. objective has been used without correction. This has the advantage of giving sufficient magnification, without requiring great illumination, but at the expense of complete flatness of field.

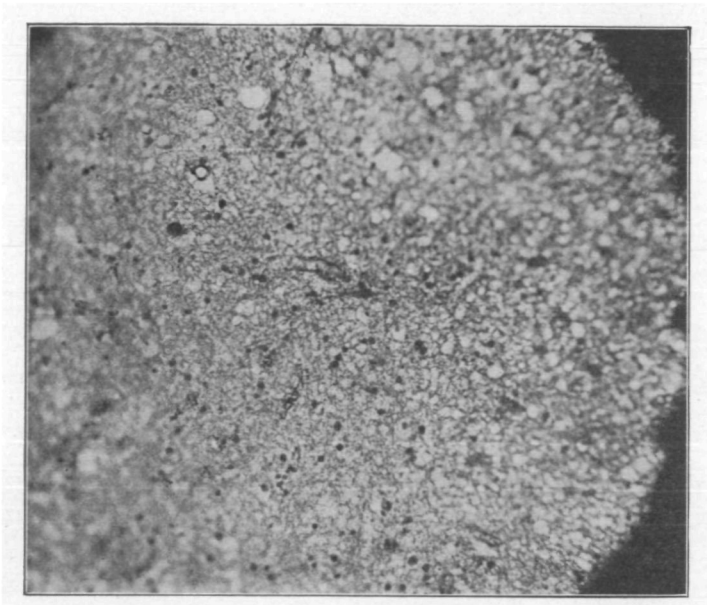


FIG. 2.—Case 2. Quiescent glioma. Very few glia-nuclei. Some cyst formation.
(Section not flat.)



FIG. 3.—Case 2. From another part of the same tumour as fig. 2. Hæmorrhages in the centre of the field.

These are the characteristic features of the simple (?) non-malignant phase of a glioma.

There is reason to suppose that a glioma may retain these apparently innocent characters for an indefinite period; in fact, the clinical history of many cases can be explained in no other way. It is conceivable that in such a phase the growth may be no more malignant than a lipoma. Moreover, rarely, it may be removed successfully without recurrence.

In confirmation of this statement is the following case:—

Case 2.—A girl, E. B., aged 19 (Dr. Bastian), admitted in 1904 with marked clinical evidence of cerebellar tumour. First symptom one and a half years before. Operation (Sir V. Horsley) disclosed a tumour the size of a hen's egg, occupying the left lobe, vermis, and part of the right lobe, which was removed. The patient is still alive, eight years after, and in excellent health. There is no bulging of the wound, so probably no tendency to recurrence. But owing, no doubt, to considerable permanent destruction of cerebellar tissue, she still presents many of the symptoms—ataxia and paresis of the legs—of a cerebellar lesion. She is so well that she is about to join her father in Canada. (Figs. 2 and 3.)

Sections of the tumour removed (figs. 2 and 3) show a rather thickly felted stroma, so much so as to hide the glia-cells; small cavities are seen all over the section, indicating cyst formation so common in all gliomas. The glia-nuclei are relatively few, another suggestion of quiescence. Hæmorrhages may be seen, but possibly these may be due to operative manipulation.

Unfortunately this is a rare result, much too often the sequel is recurrence.

Now, assuming that there is such a thing as an innocent, latent, quiescent glioma, in what elements of the growth do the changes occur which constitute malignity, and what are those changes? The physiological process in action would appear to be that of active proliferation; this has its seat in: (1) The normal glia-nuclei of the stroma; (2) the glia-cells; (3) the blood-vessels.

(1) *The nuclei.*—The number of these may be variable within limits which may justify our considering the appearance as of an innocent type. But one evidence that these nuclei may be sharing in the awakening of proliferative activity is their arrangement into circles or even lines, as has already been hinted in fig. 1. To what extent they share in the ultimate richly nucleated and cellular growth of the malignant glioma I am unable to say.

(3) *The glia-cells.*—The evidence that the glia-cells play a most, if

not the most, important part in malignant activity seems to be quite clear. The alteration from the normal consists in: (a) Enlargement of the glia-cells; (b) increase in their number, though still retaining their morphological character, dendritic processes for instance; (c) multiplication of their nuclei; dislocation of these to the periphery of the swollen cell; (d) disappearance of the original cell, and independent existence of nuclei, which now resemble round sarcoma cells in a state of active multiplication.

This, I think, must be the sequence of events in many, if not all, of the malignant types. But it is possible that new cells, having some resemblance to altered glia-cells, may have a different origin, and the resulting growth may then more nearly resemble a true large-celled sarcoma. This is a difficult point, and it may be that the glia-nuclei may bear a larger share in this process than has been suggested above. It must not be forgotten that all these changes, in varying degree, may be seen going on in the same growth.

In illustration of the foregoing remarks are the following cases:—



FIG. 4.—Case 3. Glioma of innocent appearance. Glia-nuclei small and few. Glia-cells difficult to see; one large one to right of centre.

Case 3.—A man, W. E. T., aged 50 (Dr. Buzzard); symptoms of ten months' duration. A fit followed by right hemiplegia and partial aphasia.

Operation (Sir V. Horsley), left Central, discovered a large subcortical tumour, a cyst the size of a hen's egg, was drained, and part of the wall excised, from which the section was taken. A considerable hernia resulted, and later sepsis showed itself. Five weeks after, another operation was performed, but the notes are here defective. A febrile condition set in; he became quite aphasic, and died three months after admission. (Figs. 3, 4, 5, 6.)

Fig. 4 shows a simple, sparsely nucleated, somewhat cystic reticular stroma with only one doubtful glia-cell in the field. No evidence of active growth.

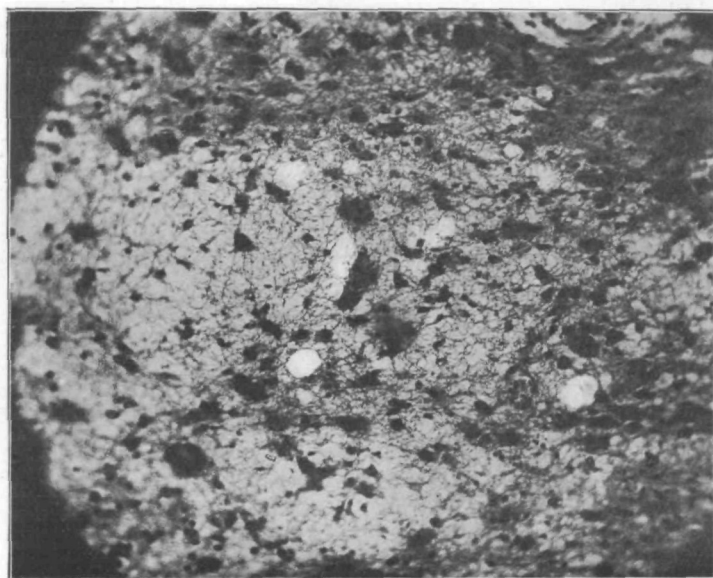


FIG. 5.—Case 3. Evidence of activity. Glia-cells enlarging, their nuclei multiplying, shown in two cells in centre of field.

Fig. 5, the same stroma, but a considerable, not excessive, number of large glia-cells variable in size, some containing more than one nucleus. Glia-nuclei more abundant. General appearance of activity.

Fig. 6 from another part of the section; the stroma is more condensed, and glia-nuclei are in greater abundance than in the last two fields. The glia-cells are also here in some number, and of very variable size. Their proliferated nuclei are situated in rings round the periphery of the smaller cells; in places these rings are all that remain.

Case 4.—T. W. A., a man, aged 47 (Dr. Taylor); symptoms dated only fifteen weeks before admission; paræsthesia of the left arm and leg in attacks

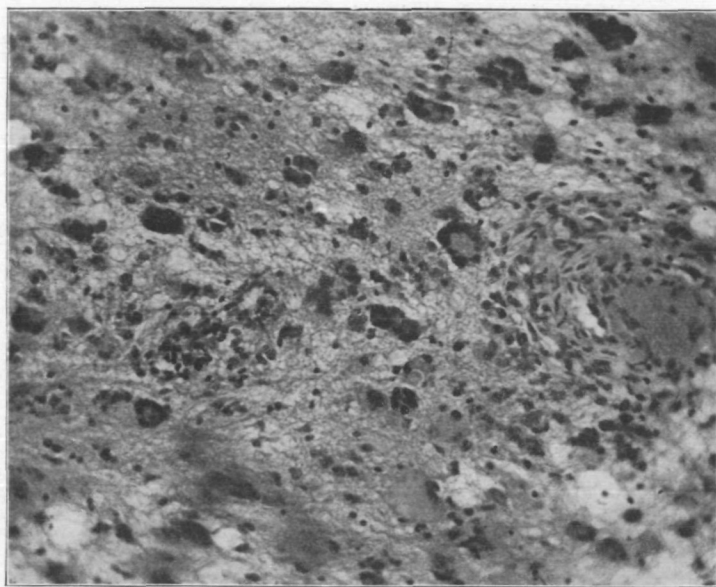


FIG. 6.—Case 3. From a more active part of the same glioma as figs. 4 and 5. Proliferation of nuclei of glia-cells, disappearance of cells, leaving rings of nuclei.

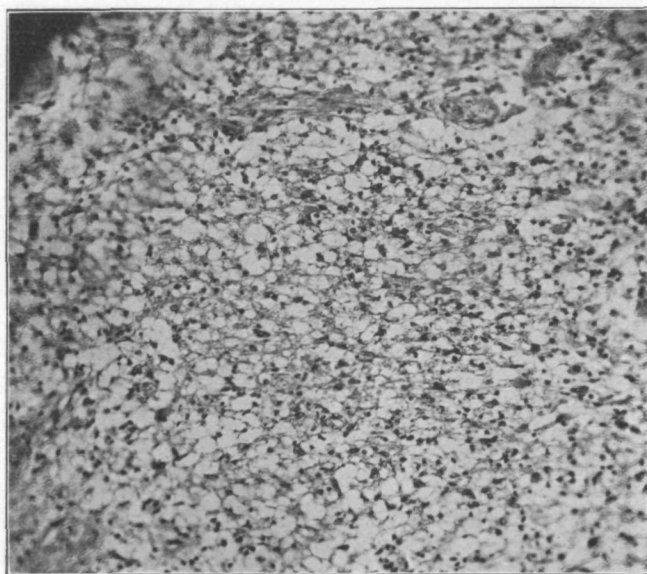


FIG. 7.—Case 4. Glioma. Stroma finely reticular and cystic. Nuclei small, but in considerable numbers. Glia-cells of normal appearance and number.

of three months' duration. Left hemiparesis and anæsthesia on admission. Double optic neuritis and left hemianopsia. Operation (Sir V. Horsley) four days after admission. Right Parieto-temporal not much bulging at first stage, but this was more evident at the second five days after. A large tumour sub-cortical to the right post-central region was found extending to the descending horn of the lateral ventricle, forward to the lower part of the precentral convolution, and back to the supra-marginal region. It was removed as far as possible. The patient made a fair recovery, but considerable bulging resulted, and there remained a left spastic hemiplegia. I hear from his wife that he died five and a half months after operation outside the hospital. (Figs. 7, 8, 9.)

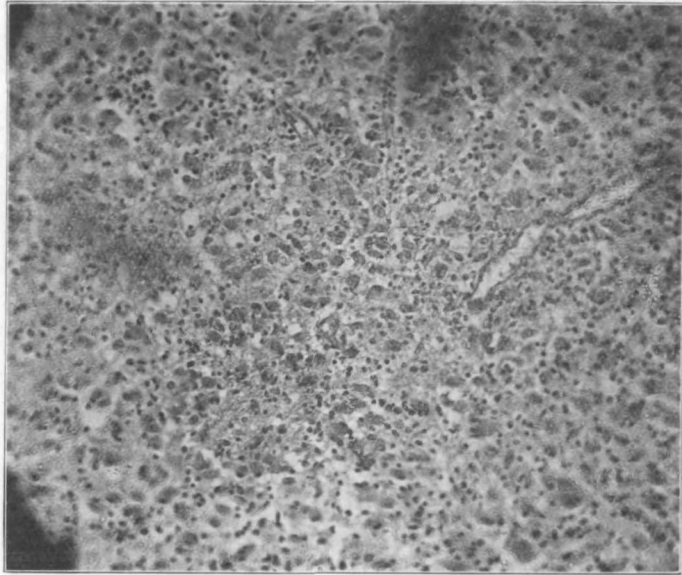


FIG. 8. —From same as fig. 7. Richly cellular, but glia-stroma retained.
Cells mostly oval with a nucleus at one pole.

Fig. 7 shows a fine specimen of the simple type of glioma. The glia-nuclei are fairly abundant, but small, and with little evidence of proliferation. The stroma, however, has a cystic appearance, and the glia-cells are few and of normal character.

Fig. 8.—Here is a centre of activity, many definite cells of various size, some possessing glia-cell characteristics, others barely recognizable as such. Some with more than one nucleus, others with only one, but at one pole of the cell. I am doubtful of the true interpretation of this appearance, which is a common one. The cells are almost too small for

swollen glia-cells, they are mostly uni-nuclear. They may be swollen "glia-nuclei" and not glia-cells. Here and there the tendency to ring arrangement of nuclei is also to be seen in places.

Fig. 9.—In another part of the section is an area of necrotic degeneration, and in the neighbourhood of these areas one repeatedly finds thrombosed vessels; this will be referred to later.

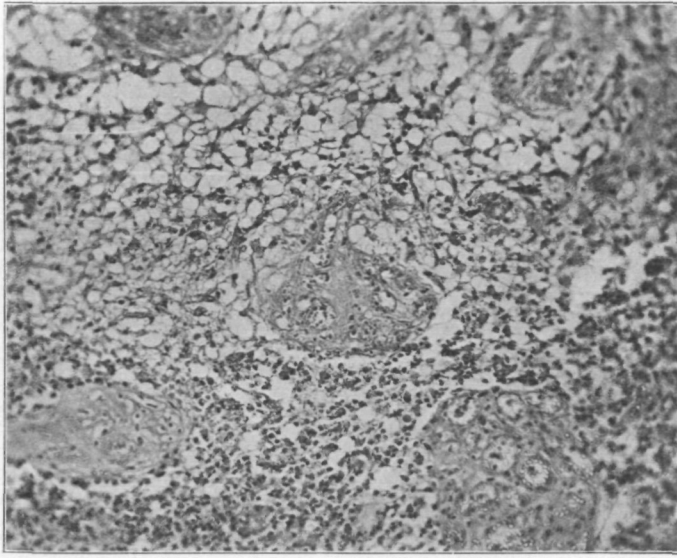


FIG. 9.—Case 4. Vessels thrombosed, on the border of an area of necrosis.
Lower half of section.

Case 5.—T. J., a man, aged 38 (Sir W. Gowers), was admitted in March, 1904, with a seven months' history of failing memory, fits, development of the dull, lethargic mental state of a frontal tumour, and intense double optic neuritis. A month after admission the right frontal region was explored (Sir V. Horsley), and a cystic tumour was found presenting as a small patch 1 in. in diameter in the middle of the right middle frontal convolution. On incision this proved to be the wall of a large cystic cavity; this was removed as much as possible, the area of removal reaching to the lateral ventricle. He made a good recovery, and left hospital, with some bulging of the wound, optic neuritis much subsided, and mental state natural, two months after. The hernia, mostly fluid, increased, and it was tapped with some relief three months after operation. The subsequent history of the case will be considered later under the head of "Recurrence." (Figs. 10 and 19.)

Fig. 10.—A section of the tumour removed at the first operation. The glia-stroma presents no greatly abnormal appearance, it is somewhat condensed and cystic, and the glia-nuclei are not excessive in number. But what I take to be the glia-cells are in great numbers, large and swollen, yet with in many instances their dendritic processes retained. In some the nucleus seems to have disappeared, in others it is displaced to one pole of the cell, or in others there is more than one. This seems to me a more convincing illustration of the part played by the glia-cells than any I have yet shown. In some parts these cells have multiplied to the extent of obscuring all the other features of the original glioma.

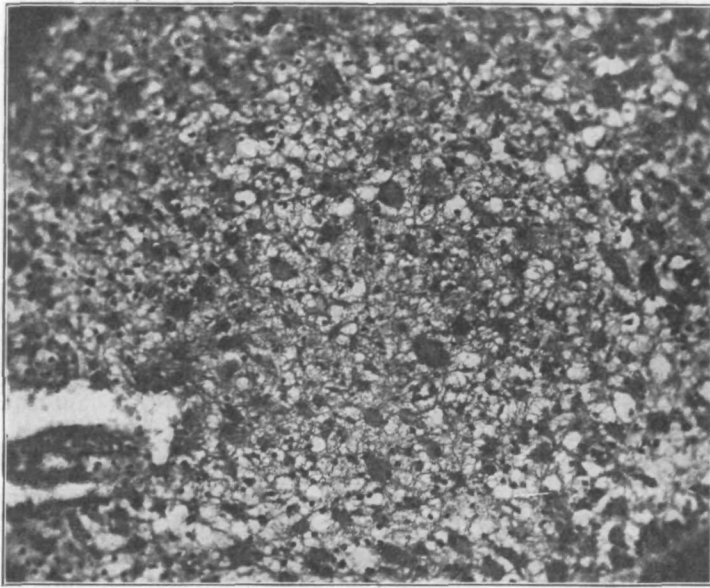


FIG. 10.—Case 5. General glia-cell enlargement and multiplication, suggesting considerable malignant activity. The cells retain their processes, many are still uni-nuclear, or devoid of nuclei. The stroma is denser than in the last case, and cyst spaces are numerous.

The following is yet another instance. In spite of the very malignant appearance of the growth, this patient is still alive.

Case 6.—F. B., a man, aged 35 (Sir W. Gowers), admitted July, 1908, with a six months' history of failing memory, faints, headache, vomiting, diplopia, and failing vision. His mental state, defective memory, "dreamy states," were suggestive of a Temporo-sphenoidal tumour, and two months after admission a large cystic tumour was removed (Mr. Armour) from the left Temporo-sphenoidal

lobe. After operation he was quite aphasic for a time, but this improved, so that four months after he could talk well and get about. But he remained emotionally unstable, and a large hernia cerebri developed. He was readmitted three years after operation with an enormous hernia. Mental condition vacant and stupid, memory and attention very poor. Right hemiplegia. Vision: right, blind; left, $\frac{3}{80}$. Optic disks: right, consecutive atrophy with + 4D. of swelling; left the same, but to a less degree. From the reply I have received I judge that he is in much the same condition, perhaps worse, than when last seen. (Figs. 11, 12, 13, 26.)

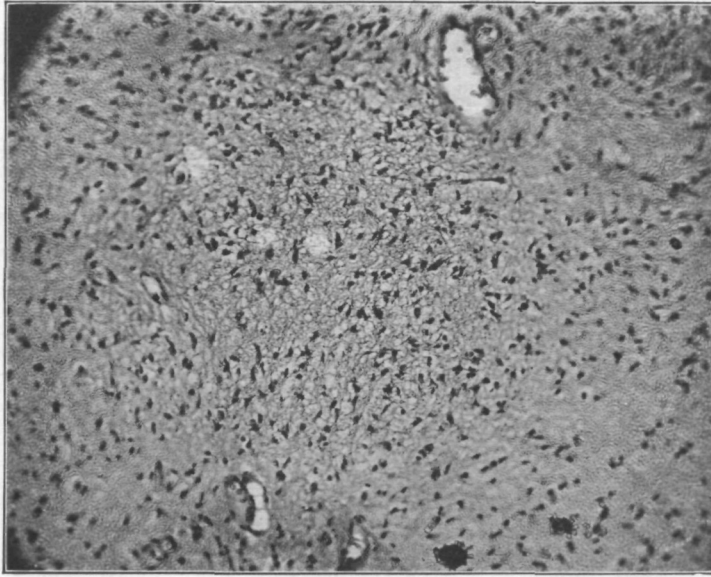


FIG. 11.—Case 6. Glioma. Stroma rather dense. Nuclei present a shrunken angular appearance. No marked evidence of activity.

Fig. 11.—All parts of the growth show some evidences of its gliomatous nature, and this part has almost an innocent appearance, but the glia-nuclei, if such they are, present an unusually angular appearance.

Fig. 12 shows a great multiplication of glia-cells, less convincingly glia-cells perhaps than in the last case, but still retaining in many of them the multipolar form, and more closely packed. Multi-nucleation is also well shown. But some of the cells are oval and uni-nuclear, as in fig. 8.

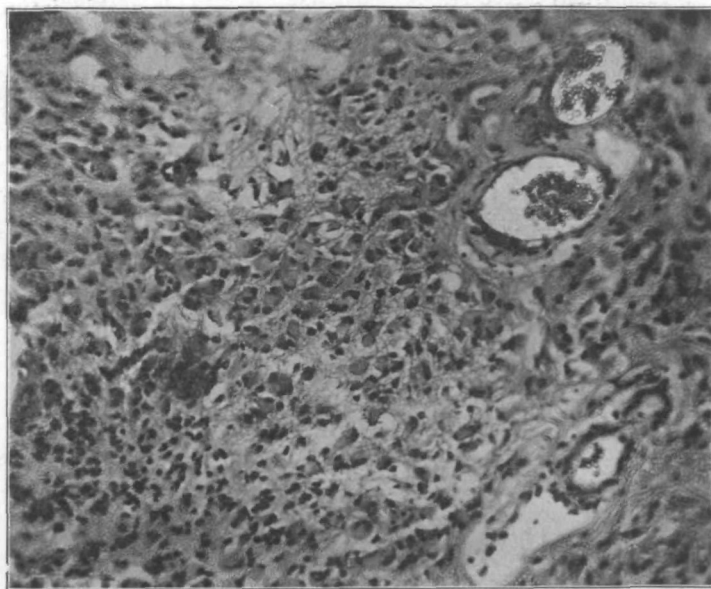


FIG. 12.—Case 6. From an active part of the growth. Many swollen multinucleated glia-cells. Some oval with single nuclei, as in fig. 8.

Fig. 13 shows the same characters considerably enlarged.

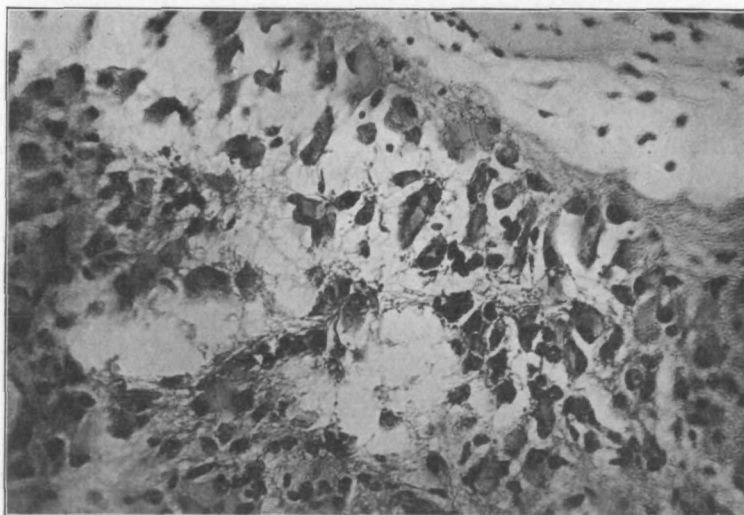


FIG. 13.—Case 6. The same appearances as in fig. 12 enlarged.

Case 7.—H. C., man, aged 31 (Sir W. Gowers). The first symptom, sudden failure of vision and memory, dates only six months before death. He presented the typical mental state of a frontal growth, disorientation in time and space, jocular mania "Witzelsucht," anosmia, double optic neuritis passing to atrophy, with great amblyopia. An operation was arranged for, but he died the day before, eight days after admission. This is one of the most rapid cases. *Post-mortem* a tumour was found involving the median and orbital surface of the left frontal lobe extending into the right. (Fig. 14.)

Fig. 14.—The field is packed with large cells of varying sizes, and containing one to six nuclei, generally peripherally disposed. The cells

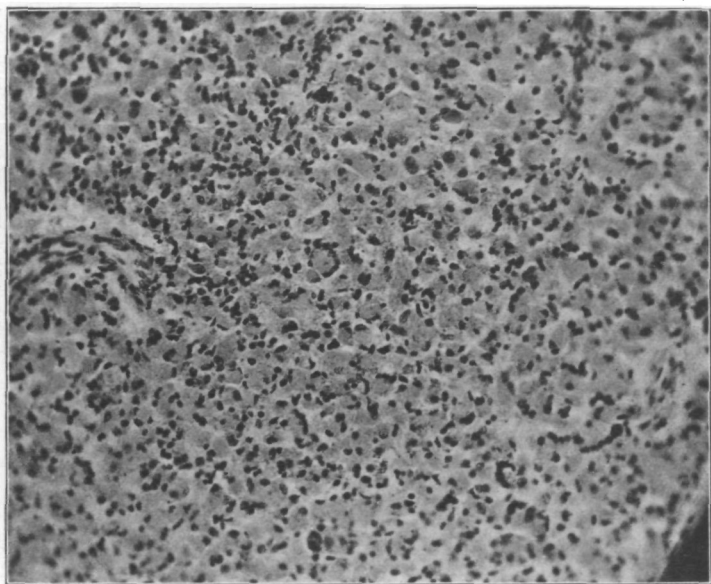


FIG. 14.—Case 7. Closely packed large cells; cytoplasm faintly stained; multinucleated; nuclei peripherally disposed. Disappearance of parent cell, leaving a ring of nuclei.

contain a faintly staining granular cytoplasm and some are angular, but the original glia-stroma is very little in evidence. The annular arrangement of the escaped nuclei is well seen and within their circles may be seen the remains of the parent cell. This picture I regard as the extreme result of glia-cell proliferation. If not viewed by the light of the preceding cases it might well be regarded as a large cell sarcoma.

Gliomas are not commonly multiple, and metastasis is almost non-existent. The following is a case of two tumours, one of which was a glioma and the other probably an angio-sarcoma.

Case 8.—W. E. G., aged 51 (Dr. Taylor). Another very rapid case, five months from first symptoms to death. He gave a history of left hemianopsia and rapidly failing vision to complete blindness. He was in hospital under a month, during which he became more and more stuporose and died. *Post-mortem* a large tumour was found occupying most of the right occipital and temporal lobes, and another small one was in the right marginal gyrus, about 1 in. in diameter, hard and deeply congested. (Figs. 15, 16, 22.)

Fig. 15 from the large occipital tumour is obviously a glioma. In spite of the rapid history this section shows little evidence of great

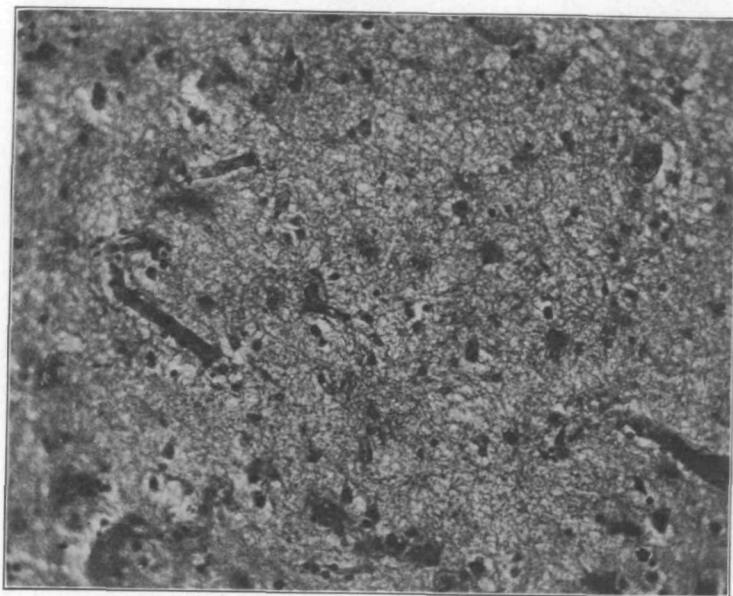


FIG. 15.—Case 8. Occipital glioma. A densely reticulated stroma with large and not very many glia-cells; a few glia-nuclei.

activity. Probably sections from other parts of the growth would discover appearances of malignancy similar to those in the preceding cases.

Fig. 16 is a spindle-celled growth with many vessels, an angio-sarcoma.

I do not suggest any pathological connexion between the two growths, but the case is interesting from its comparative rarity.

The next stage in this moving picture of proliferative growth that demands attention is that concerned in the further progress of the nuclei

liberated by the disappearance of the parent glioma-cells, by which an appearance is produced different from that hitherto described in this account.

Malignant activity is plain enough in some of the sections figured above, but to my mind it is still more so in the stage to which we have now arrived; in fact, the histological picture is that of forces suddenly brought to a standstill when in full play. In illustration of this—

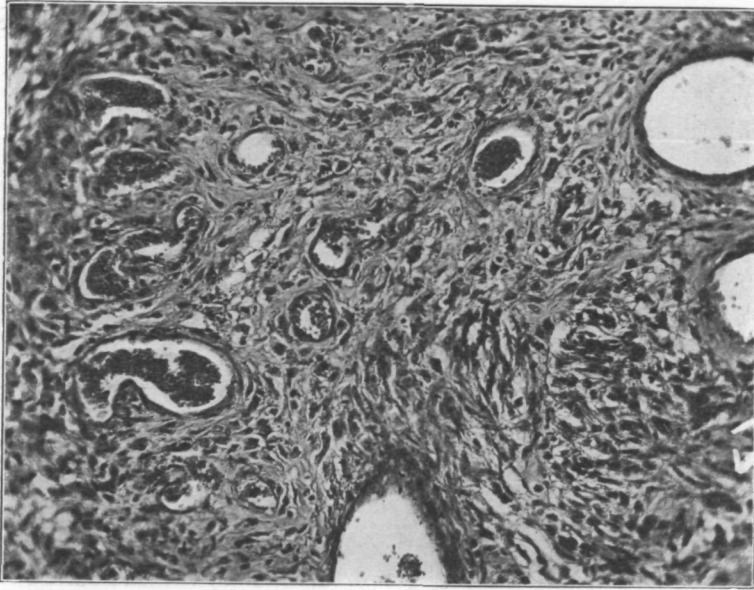


FIG. 16.—Case 8. Second small, hard, vascular tumour in straight marginal gyrus; an angio-sarcoma.

Case 9.—A. M., aged 37 (Dr. Beevor), admitted July 1, 1904, with a long history, two years, of fits, no details given; ten months, visual symptoms suggesting left hemianopsia, which was confirmed on admission; four months, fits beginning in the left foot. No hemiplegia, no optic neuritis. Readmitted in December, 1904, seven months afterwards; two months after this optic neuritis appeared, a post-central growth was diagnosed, and operation followed (Sir V. Horsley), February, 1905. A large cystic tumour, cyst within cyst, was shelled out. The patient made a good recovery and was discharged as "cured." He was readmitted in June, 1906, four months after operation, with progressive left hemiplegia and hemianæsthesia, but the optic disks were clear and showed no evidence of past neuritis. I heard from his widow that he died in September, 1906—i.e., nineteen months after operation. (Figs. 17 and 18.)

Fig. 17.—Section of the growth, which includes a piece of cortex, under which the growth lies. This is a cellular glioma, rich in large swollen cells, but with their processes yet retained, and some of the gliastroma reticulum between, also rings of nuclei, many of small diameter, showing within their circumference the remains of the parent cell.

Farther away from the cortex the large cells are in still greater abundance, packed closely and also crowded with nuclei round about them.

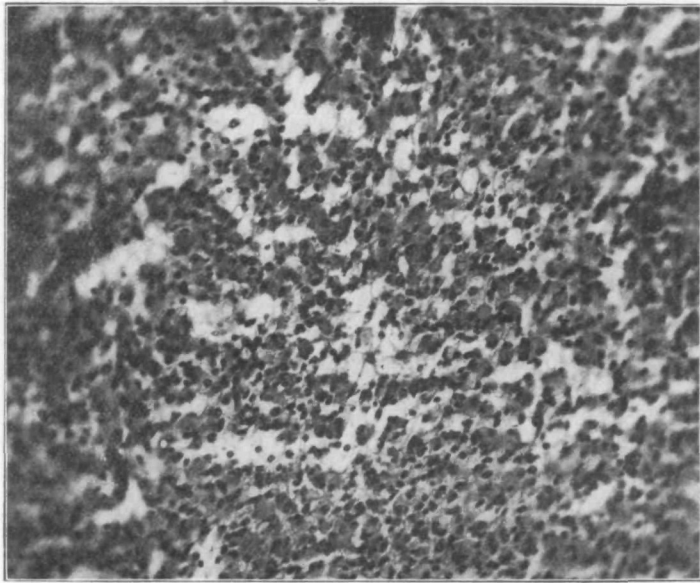


FIG. 17.—Case 9. Richly cellular and nuclear glioma. Of the large cells many are multinuclear, and many are disappearing, leaving a ring of nuclei.

Fig. 18.—Farther still we find the nuclear elements in such numbers as to obscure the parent cells or their remains, though by careful focusing many may be seen. The picture now is that of a small round-celled sarcoma, but by no effort of focusing can one see any cytoplasm surrounding these nuclei. Possibly recent special stains may show that these are the nuclei of new cells, but I have not yet had the opportunity of seeing the result of their use.

The arrangement of these nuclear elements of the growth is also characteristic; in all parts of the field are circles or half-circles, rarely straight lines, presumably in whatever plane the section is made. The circles may be small, no larger than the circumference of the parent

cells from which they come, but they show a tendency to an ever widening radius, suggesting lateral division of neighbouring nuclei. The semi-circles of course suggest a slight tilting of the plane of that circle, so that half is in one section and the other half in the next above or below. So frequent are the rings in any given plane that one is tempted to conclude that every nucleus all over the field is one of a little circle of its own in another plane. This annulation, as representing independent centres of growth infinite in number, bring home to the mind of the observer the intensity of the exuberant activity that constitutes high malignancy. No doubt this annulation has been seen often enough by other observers, for it can be seen in all these richly cellular growths.

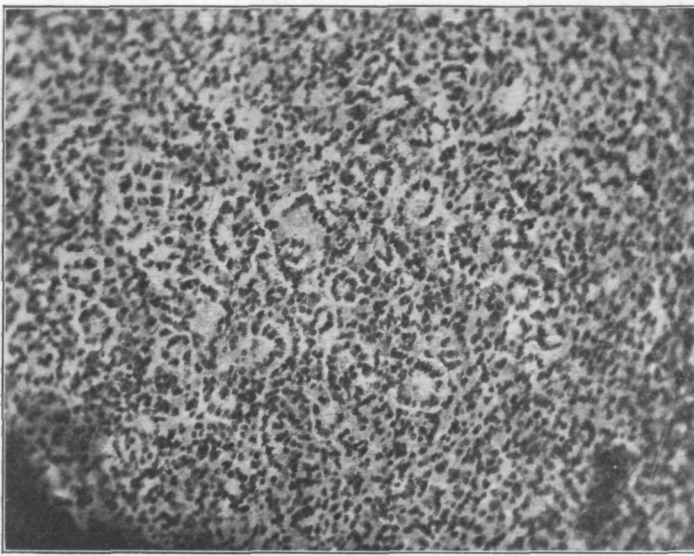


FIG. 18.—Case 9. Illustrating ring formation, or annulation. In a thick section underlying features tend to confuse a photograph; therefore in this figure some of the details immediately adjacent to the most obvious rings or semi-circles have been blocked out.

Annulation has been demonstrated as occurring in a greater or less degree in many of the preceding figures. In fig. 1 even it is seen, and in this also can be seen the tendency to formation of straight lines, which may be a common arrangement, but it would naturally be less evident in a crowded picture. A similar grouping of nuclei may be seen in the growing brain (see the article on the "Cyto-architecture of the Cerebral Cortex," by Bolton and Moyes, in this volume of *Brain*, p. 14, fig. 7).

From the foregoing observations one seems to be justified in conceiving an ascending scale of malignity from the slow-growing or quiescent overgrowth of glia-tissue to an anatomical picture resembling grossly malignant sarcoma. These may be, and are, called glia-sarcoma, but I have avoided using the word; it seems unnecessary and perhaps misleading to have another word for what would appear to be a phase of growth only, if that is the right reading of these changes.

Recurrence.—In several cases an opportunity has been afforded of examining the growth removed by operation and subsequently the recurrent growth at a second operation, or *post-mortem*. The two cases following are the simplest, the others present such complicated appearances and would require so many photographs to bring out all their features that I have thought it wiser to omit them.

Case 5.—Sequel (*vide supra*, p. 87). Three months after removal of a large cystic frontal tumour a large resulting hernia was tapped with some relief. The histological appearances of the growth removed at operation are shown in fig. 10. He was readmitted five months after operation and stated that he had been practically well until six weeks before, since when he had had two to four fits a week and he became mentally dull and lethargic. He was in hospital for a month, and left much improved mentally but with a large fluid hernia as before. During stay in hospital he had one general convulsion. He was readmitted for the third time nine months after operation with a progressive left hemiplegia and much mental dulness and apathy. His condition not improving, the flap was reopened nine days after admission and a large quantity of clear fluid was found in a cavity, the site of the original tumour. At the bottom of this cavity a mass of growth was seen and removed. He did not recover consciousness and died the next day, the temperature rising to 104° 8' F. (Fig. 19.)

Fig. 19 shows very similar appearances to those of the last case, fig. 18. No glia-cells can be seen at all. Annulation is quite distinct and there is no superficial resemblance to the original growth. It shows every appearance of rapid recurrence and would no doubt eventually have filled the cavity left by the old tumour.

Case 10.—This is a more doubtful illustration of recurrence than the last, because the time which elapsed between the removal of the growth and the *post-mortem* is so short, eleven days only. But the time element in pathological events is always an almost unknown factor.

W. O., a man, aged 42 (Dr. Batten), admitted November 4, 1910, with an eighteen months' history of frontal headache and frequent faints, eight months failing vision and memory, and slight sphincter weakness. He showed some of the mental symptoms of frontal tumour, which became more definite later, and intense optic neuritis and swelling, rather more pronounced on the right side.

Twenty-five days after admission the right frontal region was explored by

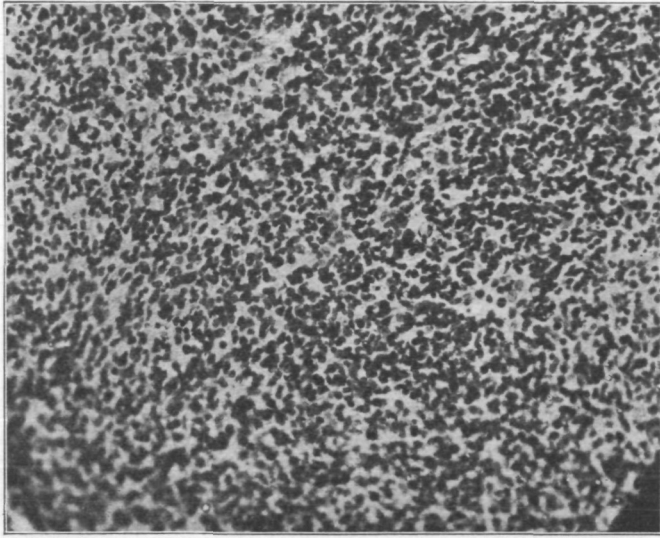


FIG. 19.—Case 5. Section of mass of recurrent growth, resembling closely fig. 18. Annulation is obvious, also a tendency to arrangement in lines more or less straight.

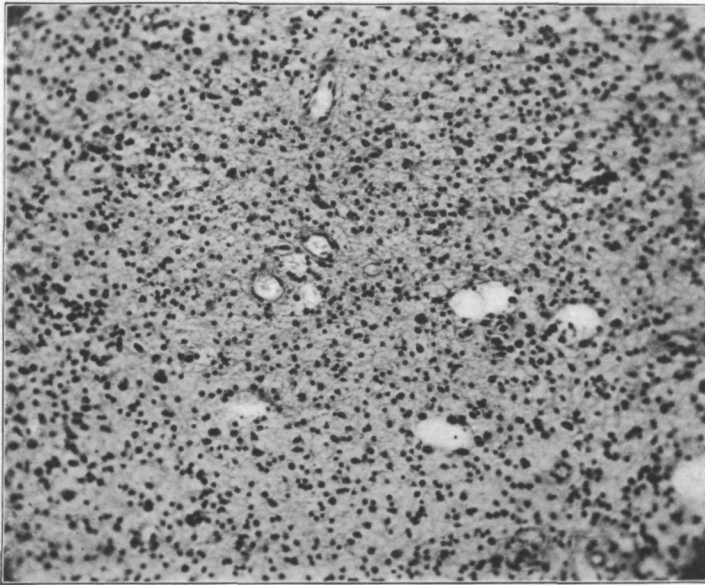


FIG. 20.—Case 10. From the glioma removed at the second operation (the first was exploratory). The stroma is finely and normally reticular, and the glia-cells few and almost invisible. But the nuclei are in great number, and annulation well shown all over the field. Two normal vessels are seen on each side of an annulus, to the left of the centre.

incision (Sir V. Horsley); the substance was thought to be abnormally firm and nothing was done. The patient made a good recovery and the neuritis subsided rapidly. He was discharged to the Convalescent Home, but was readmitted four months after operation, with headache again, mentally emotional and slow cerebration. There was an increasing hernia, and a renewal of the optic disk swelling. Another operation was then performed. On exposing the frontal lobe a large cyst burst, which was partly removed. There was no relief this time, the temperature fluctuated between 100° and 104° F., and patient died eleven days after. At the autopsy the main tumour was found in the mesial side of the right frontal lobe extending over to the same side of the left frontal and forward to within 1 cm. of the frontal pole and back to the anterior horn of the lateral ventricle, involving the genu of the corpus callosum, from which it may have originated. (Figs. 20 and 21.)

Fig. 20.—A section of the tumour removed eleven days before death is a fine example of a glioma in which the glia-cells seem to be little affected. The reticular stroma also is fairly normal and also the vessels. But the field is richly nucleated and annulation is evident. The nuclei are variable in size and in places still more numerous than in this figure. This is a good example in illustration of a probable share taken in proliferation by the simple glia-nuclei.

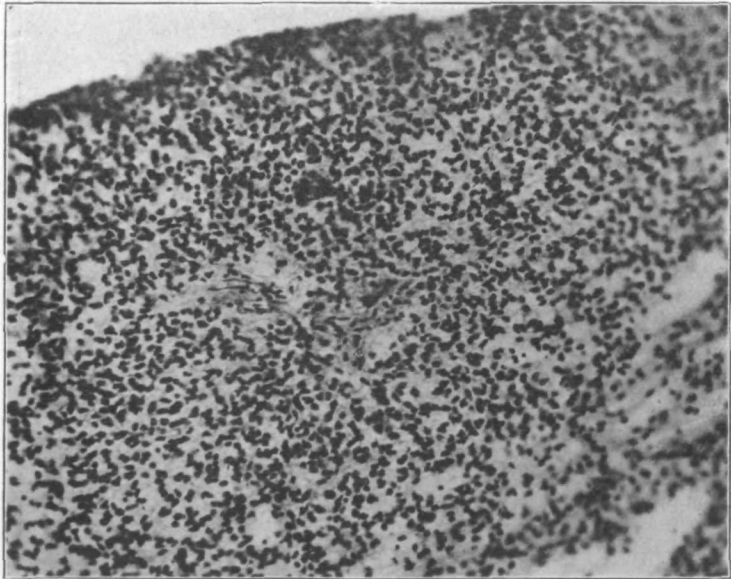


FIG. 21.—Case 10. Recurrence. From the growth removed (*post-mortem*) eleven days after the second operation. The appearances are almost exactly similar to those of fig. 19.

Fig. 21.—A section of the growth removed *post-mortem*. Unfortunately most of the section is of altered brain substance, but there is one portion of it sharply delimited, and evidently growth which resembles in every respect the recurrent growth of the last case; little if any gliastroma is to be seen, but somewhat irregular annulation is visible all over the field.

If these appearances are to be accepted, and I offer them with the greatest possible diffidence, one is forced to infer, on pathological grounds alone, that surgical interference, exploration, or manipulation, with few notable exceptions, is liable to awake into greater activity a tendency to exuberance which perhaps may be almost latent at the time.

The Rôle of the Blood-vessels.

What part do the blood-vessels play in the growth and progress of the glioma?

In vascularity these growths show wide variations, from one or two small thin-walled vessels to the field, of which the endothelial lining is marked by a few nuclei at regular intervals, to the development of numbers resembling an angioma.

The larger vessels should present the natural appearance of an arteriole, but sometimes one finds, especially in the more angiomatous forms, a thickening and condensation of the glia-tissue round about the large vessels as in fig. 22, belonging to Case 8, in which the second tumour was an angio-sarcoma.

But in many cases the small vessels show great swelling and proliferation of the endothelial intima. Fig. 23 is from another case of recurrence after removal. The recurrent growth was more vascular than in the cases above mentioned, and the stroma presents a fibro-sarcomatous appearance, which was absent in the original growth. This section illustrates the swelling and proliferation of the endothelial intima. The vessel may remain pervious, but if the process continues the ultimate result is complete blocking of the lumen and a picture that is almost unrecognizable as a vessel at all may result.

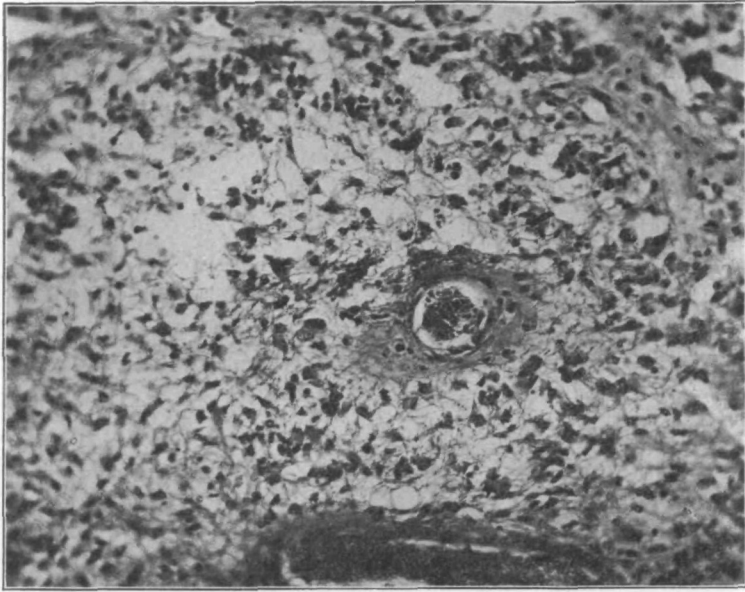


FIG. 22.—Case 8. Detail from the smaller tumour, of which fig. 16 gives the general characteristics of angio-sarcoma. A vessel surrounded by condensed, almost fibrous tissue. In this particular situation the stroma somewhat resembles that of coarse glioma, but it is exceptional, and probably a necrotic effect.

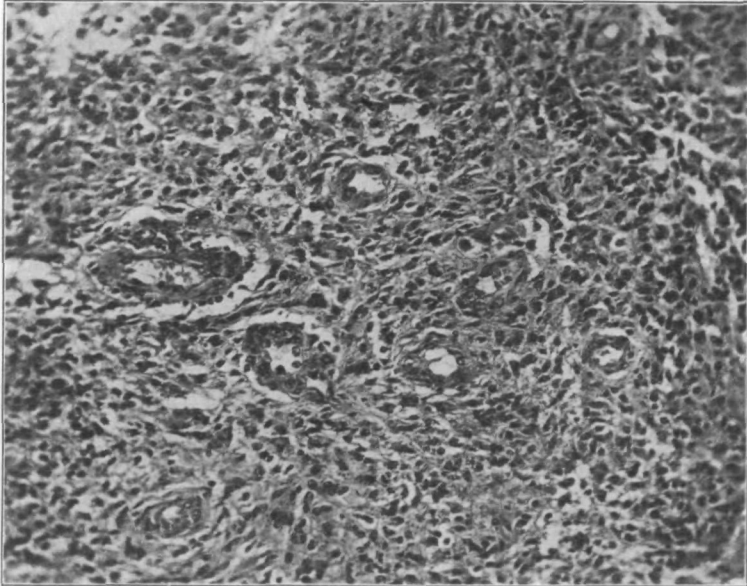


FIG. 23.—From a recurrent growth after removal of the original tumour from the post-central area. The small vessels show swelling and proliferation of the intimal endothelium, but many are still pervious.

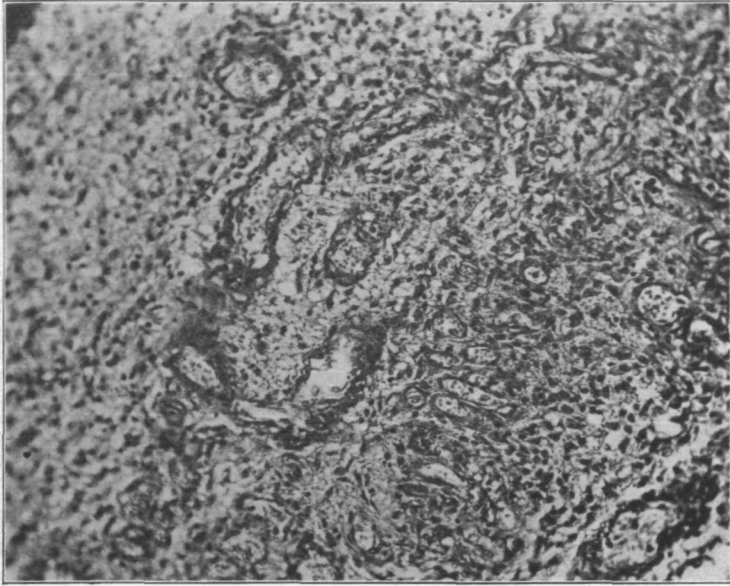


FIG. 24.—Case 11. From a large glioma of the centrum ovale. Great vascularity, but intimal proliferation is not shown in this section.

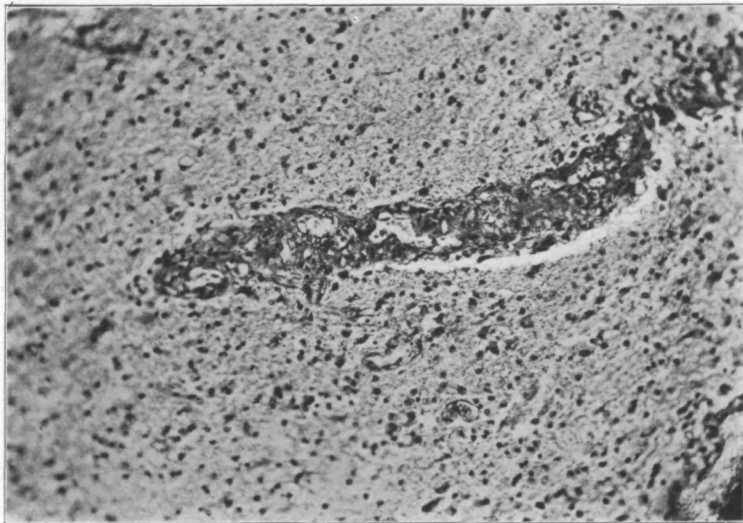


FIG. 25.—Case 11. A longitudinal section of a vessel, showing an extreme effect of endothelial proliferation.

Case 11.—H. B. (Dr. Tooth), a large glioma of the right centrum ovale. The patient died seven years after the first symptom. (Figs 24 and 25.)

In places (fig. 24) the angioma formation only is seen. In others the intimal proliferation is very striking (fig. 25). A similar instance is taken from Case 6 (fig. 26).

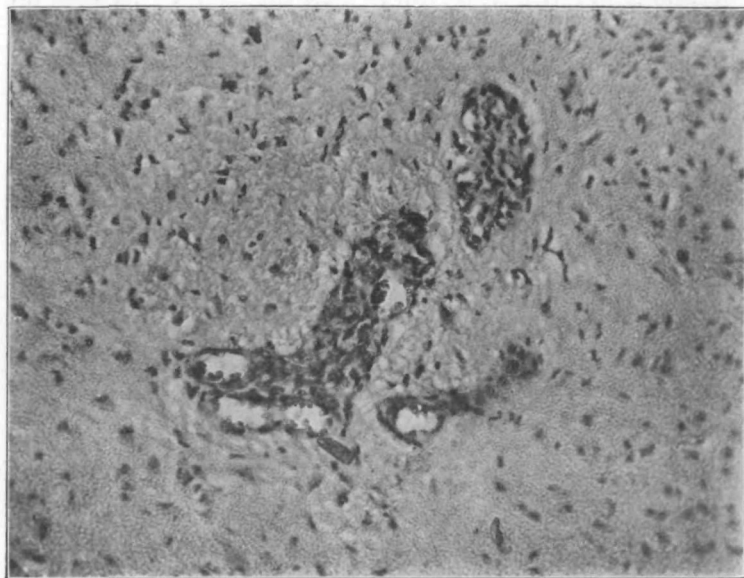


FIG. 26.—Case 6 (*vide supra*). A longitudinal and almost transverse section of (?) the same vessel. Showing complete obstruction of the lumen.

The following illustrates some of the features of vascular change very well.

Case 12.—W.H., a man, aged 47 (Dr. Jackson). Two months before admission he fell on the back of his head and immediately after his left leg became weak and this progressed. The connexion between the blow and the onset is so obvious that one must suppose that the tumour was in existence in a latent form and that traumatic influences either woke up malignant activity or caused a small hæmorrhage. However that may be, the case ran a rapid course from this time, and a left hemiplegia with gross optic neuritis resulted. Two months after the first symptoms he came to operation and the arm-area was found involved in growth, a richly cellular glioma of ill-defined margin extending deeply to the lateral ventricle; as much as possible was removed. He made a good recovery, and all symptoms improved; hemiplegia less, and optic neuritis subsiding. He wrote four weeks after discharge that he was still improving, but I learn that he died later, ten months after the first symptom. (Figs. 27, 28, 29, 30, 31.)

Fig. 27 shows an intensely richly nuclear part of the growth; annulation marks its activity. Tiny vessels can be seen ramifying in all directions. They are quite primitive, little more than channels with a thin limiting membrane and no endothelium can be seen.

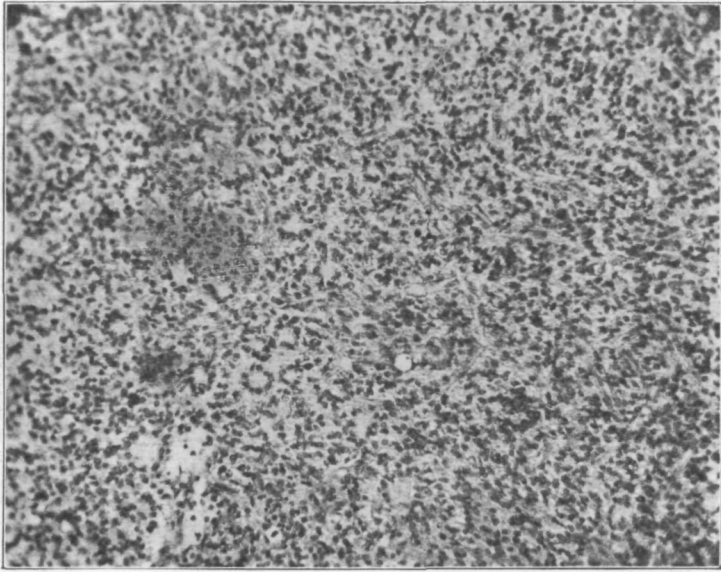


FIG. 27.—Case 12. From a highly active part of the growth. Fine vascular channels can be seen with a glass in the right central part of the field.

Fig. 28.—On the border of an area of necrosis; the small vessels are in great plenty, as indeed they are everywhere in all the sections, and the intimal proliferation can be seen in all degrees from the single layer of swollen cells to complete blocking of the lumen. The photograph is wanting in distinctness on this point.

Fig. 29 shows two bunches of vessels somewhat like a renal glomerulus. Some of the constituent vessels are pervious, and many are blocked.

Fig. 30.—In a necrosed area, a large vessel in the centre of the field, pervious, and containing blood corpuscles. Its wall presents a meshed appearance, which may be due to necrosis of proliferated intima, very much resembling on a small scale the structureless meshwork of a cholesteatoma. A neighbouring vessel appears to be thrombosed, full of fibrinous fibrils.

Fig. 31.—A vessel on the border of a necrosed area, probably containing organized thrombus.

In some of these pictures it is difficult to say how much the appearance is due to intimal proliferation—because the endothelium tends to degenerate with the other elements of the growth—and how much is due to organized clot. Both may be present; probably the sequence of events is—blocking of the smaller vessels which have an endothelial lining, by the multiplication of the cells composing it, and a subsequent thrombosis backwards to the larger vessels, and so starvation of blood to an area of the tumour.

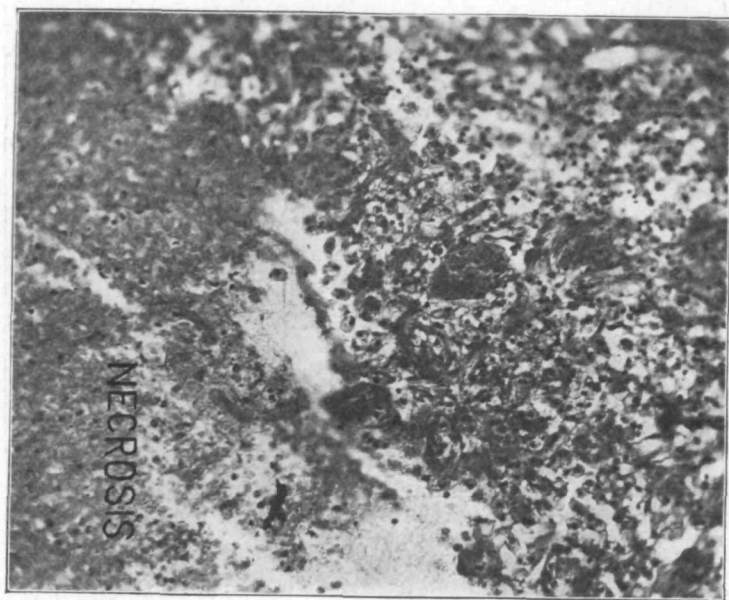


FIG. 28.—Case 12. Vessels on the border of an area of necrosis (left half of section). The central right half of the field shows a group of small vessels the endothelium of which is proliferated; but the photograph fails to bring out their features owing to obtrusion of other nuclear details.

Necrosis.—This brings us to the last stage in the life-history of the glioma—necrosis, a process which is going on *pari passu* with vigorous vitality elsewhere in the growth. Moreover, it is not too much to say that the more evidence existing in a given tumour of active growth, the more certainly will be found parts in which necrosis is in progress. Fig. 32 is a good picture of such an area taken from another case. There is an appearance of the calm of death about it—dissolution rather. The last remaining nuclei have still some chromatin, but it is fast disappearing; so they present a shrunken appearance very

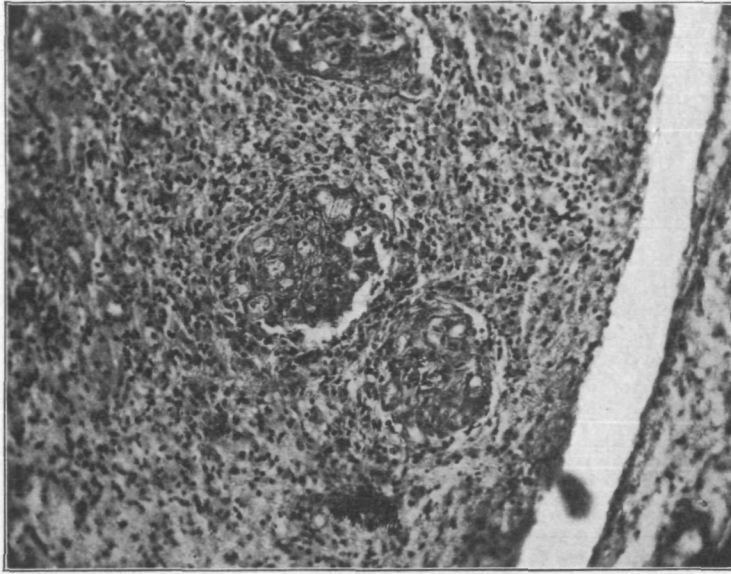


FIG. 29.—Case 12. Glomerular multiplication of vessels on the border of an area of necrosis.

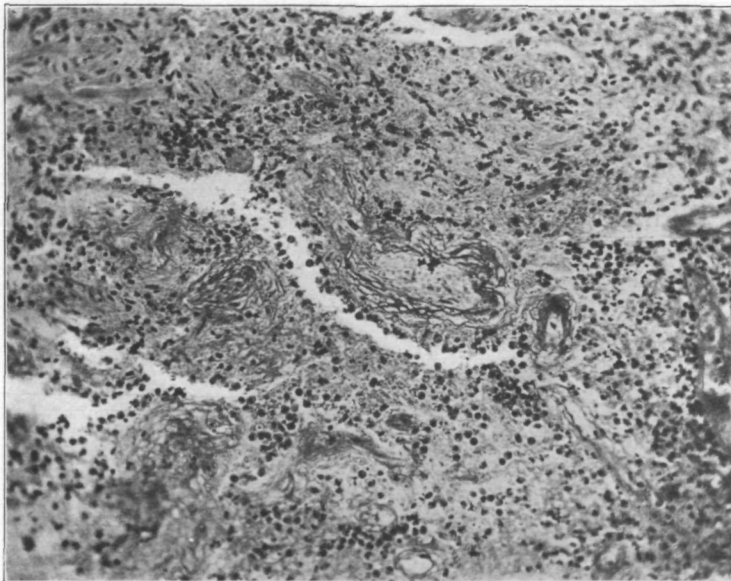


FIG. 30.—Case 12. In a necrosed area. In the centre of the field is a large vessel, pervious, containing blood. Its wall is meshed by degeneration. To the left is another in the same condition but probably thrombosed.

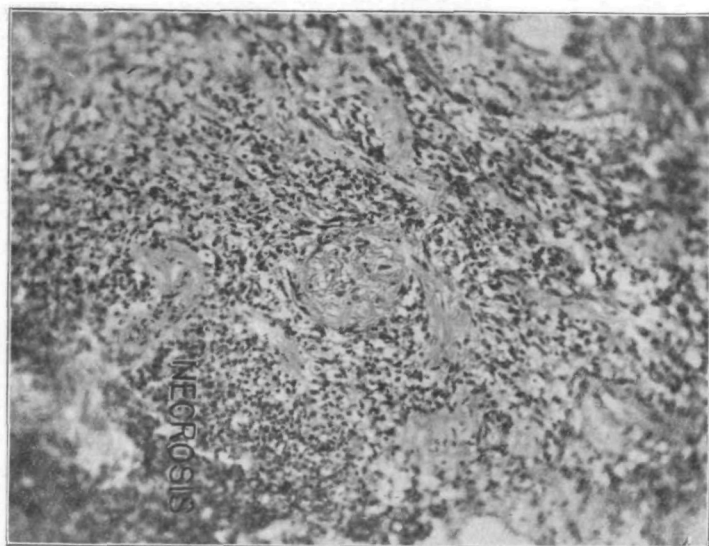


FIG. 31.—Case 12. A vessel on the border of a necrosed area. The appearance may be produced by organized thrombus.

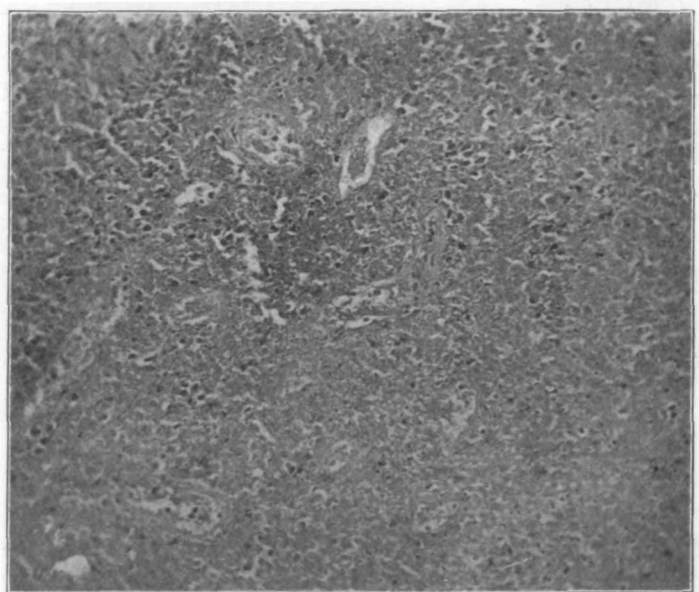


FIG. 32.—Necrosis. Granular amorphous ground substance with only a few nuclei remaining undergoing chromolysis.

different from the full, round bodies shown in so many of the active growths above. The rest of the field is made up of feebly staining amorphous débris, with here and there the remains of a blood-vessel also bearing evidence of decay.

Cyst formation.—The glioma shows the tendency to cyst formation perhaps more often than any other group. Pathologically this may be considered as a degenerative process, but clinically it may be as disastrous as the more malignant forms. Glioma cysts, which are sometimes single but more often multiple, may certainly be drained with temporary and even prolonged benefit, but it is doubtful whether the growth of the surrounding or underlying tumour, if of the active kind, is modified to any extent, and there is always the fear that by interference latency may awake to activity. This is, however, a risk that must be taken, in the event of operation disclosing an obvious cyst.

The simplest and earliest evidence of cystic tendency is shown in the rarefaction of the glia-stroma which may be seen in so many apparently innocent-looking growths. In its full development it presents a superficial resemblance to an emphysematous lung.

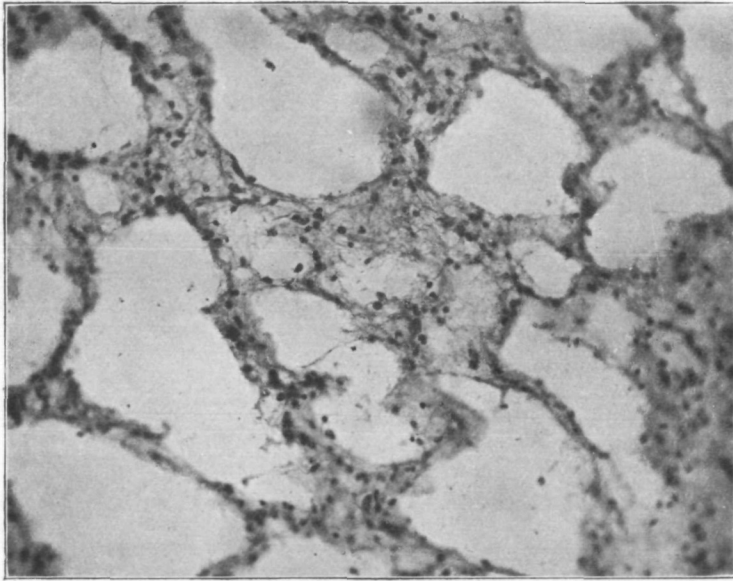


FIG. 33.—Case 13. Cyst formation, in a glioma of long duration. The glioma tissue presents no appearance of activity.

Case 13.—E. W. H., a man, aged 30 (Dr. Ormerod), gave a long history commencing with a fit, general convulsions, three years before admission, general drowsiness a year before that; but the fit has been reckoned as the first symptom—sixteen months, vomiting attacks, two months, weakness right leg. Vision: right, $\frac{6}{38}$; left, $\frac{6}{9}$. Consecutive atrophy of the right optic disk and intense neuritis of the left. A frontal growth of a quiescent type was suspected. He improved in hospital, and was discharged to report progress later. He died one year after. Dr. Stewart made a *post-mortem* examination outside, and found a large right frontal tumour and a small left frontal, one of the few multiple gliomata. (Fig. 33.)

Fig. 33.—The cysts occur in the midst of simple glioma structure and the section shows no evidence of malignity; but of course if cysts continue to enlarge by increase of their fluid contents, such a growth, however innocent pathologically, is clinically malignant from simple mechanical increase in bulk.

Cyst formation, in fact, would appear to be an evidence of long life, from the pathological standpoint, and the process rather one of atrophy than of activity.

In conclusion, it is evident that the glioma, when it enters upon an active stage, by the very exuberance of its activity carries on within itself a process of self-immolation. Also that this aspect of the question centres round the blood-vessels, which may increase vastly in number—an angiomatous stage; become blocked—an intimal proliferative stage; thrombosis spreads backwards into larger vessels—a thrombotic stage; and lastly there results necrosis of the area concerned. If this is the true sequence and proper interpretation there may be some hope of treatment in the future by some application of ultra rays after removal of the bone, such as has given results in some other vascular growths.

But this is only one side of the matter. The larger question still remains, how to meet the forces that are seething within the rapidly growing tumour. Complete recovery of the diffuse forms is practically impossible. One may almost assume that the earliest possible stage of growth, when the tumour might conceivably be removed completely, is undiagnosable in most parts of the brain. A removal as complete as possible seems to be followed by increased activity, and recurrence, or, worse still, a relatively latent growth, may be awakened into malignity. It seems that in the present state of our knowledge we must be content with relieving pressure by decompression in all gliomata, lest worse befall.