Malignant intrinsic brain tumours are relatively common intracranial neoplasms and they form the major preoccupation of most neurosurgeons in the United Kingdom. They have captured the attention and engaged the energy of many neurosurgeons. Despite the improvements in operative technique and more powerful sources of radiation, they remain as major problems, little changed in the last 30 or 40 years.

The distressing and almost invariably rapidly progressive character of these neoplasms has led some neurosurgeons to abandon all attempts at treatment once the diagnosis has been made. Others have investigated new techniques in attempts to improve the apparently dismal results of conventional treatment. Thus intracavitary radiation, radioactive isotopes and numerous chemotherapeutic agents have been tried. Attempts have also been made to increase the radiosensitivity of these tumors by producing hyper- or hypo-oxygenation and by other, possibly more complex, methods such as the administration of thyroid hormone, at present on trial in this Unit.

Many of these methods are reported as achieving “encouraging results.” In our opinion, these often are attributable to the selection of patients. It is not reasonable to assess the results of a particular treatment in a series comprising both relatively benign astrocytomas and highly malignant gliomas. The variable course of gliomata, even without treatment, is well known, and clearly it is important to assess the results of treatment for each group of neoplasms. All cerebral gliomas are malignant in that they are intrinsic tumours of the brain, and it is rarely possible to excise them completely. Speaking of “benign gliomas” we refer to cases with material obtained by burr-hole biopsy or at operation, although other areas of the same tumour may have malignant features. Similarly, material from an area with malignant features results in the histological diagnosis of “malignant glioma.” Although the over-all behaviour of a particular tumour is determined by the most malignant part, the presenting symptoms and signs may be caused by the larger mass of the “benign glioma.” In such cases survival may exceed that for other cases of malignant glioma.17 One of the difficulties is the so-called “malignant change” presumed to have occurred in growths previously regarded as “benign.” Not all this clinical malignancy has histological confirmation. Even in a slowly growing tumour such as a meningioma, a stage is reached when the vital centres are invaded and no further increase in size can be tolerated.

But there is a group of cases satisfying the histological criteria of malignancy, and the biological criteria as well. The effects of treatment in such cases may be assessed more reliably and the influence of different treatments compared. The present investigation was made in order to produce a basis for the comparison of conventional methods of treatment with new methods.

There have been a number of studies of the course of gliomas, many of which have included glioblastoma multiforme.1,3,10,17,19 Surveys restricted to glioblastoma multiforme have also been made.5–7,9,13,15,18,21

Selection of Cases

The notes of all cases indexed as cerebral glioma were examined for the period 1950–1960. Approximately 500 of these were diagnosed as malignant gliomas. Cases for the 11 years up to 1950 have already been reported by Pennybacker et al.17 The criteria for ac-
ceptance in this series was a progressive history of less than 1 year and histological confirmation, either at operation or at autopsy, if the latter was performed within 1 month of admission. All other cases, including those with probable but doubtful histology, were excluded, as were patients when the date of death or ultimate fate was unknown. Only 225 of over 500 patients examined satisfied these criteria.

Age Incidence
Fig. 1 presents the ages of patients on admission. The ages ranged from 9 months to 80 years but the peak for both sexes is in the 6th decade. Eight-six per cent were over 40 years old. These findings are in agreement with those of most authors.

Sex Incidence
Of 225 cases 137 were male (61 per cent), a relationship of 1.5 to 1. Roth and Elvidge found 78 per cent were in men, although Frankel and German and Netsky et al. had figures approximating ours.

Duration of History
Sixty per cent (133 cases) had a history of less than 3 months, 24 per cent (55) less than 6 months, and 16 per cent (37) less than 1 year. The preponderance of patients with a very short history agrees with most authors and accords well with clinical experience.

Site and Extent of Tumour
It is not always possible to determine the site of origin of these tumours, but in considering the parts of the brain involved most commonly, the parietal lobe was involved in 49 per cent (111 patients), the frontal lobes in 45 per cent (102 patients), temporal lobe in 40 per cent (91 patients), and the occipital lobes in only 12 per cent (27 patients).

Basal ganglia, thalamus or corpus callosum was involved in 38 per cent (85 patients), and 11 per cent (24 patients) had bilateral involvement.

Of 201 (89 per cent) of patients with unilateral involvement, 140 (70 per cent) had tumours of the cortex or subcortical white matter without encroachment on deep structures. Both deep and superficial structures were involved in 55 patients (27 per cent) and 6 patients (3 per cent) had tumours in deep structures only. In 73 (52 per cent) of 140 patients with unilateral superficial tumours, only one lobe was involved, in 62 (44 per cent) two lobes, and in 5 (4 per cent) three lobes. These findings agree with those of Davis et al. although Maxwell, using necropsy material, had 75 per cent of patients with bilateral involvement as compared to our 11 per cent. Matsukado et al. also found 47 per cent were bilateral. This difference between the clinical and autopsy findings illustrates the great difficulty in determining the potential resectability of lesions on a purely clinical basis as well as on the findings at operation.

We found no relation between age and extent of a tumour, although Roth and Elvidge found that involvement of multiple lobes was most frequent in the elderly and involvement of basal ganglia in the younger age group.

Cystic and Solid Tumours
We assessed the incidence of cystic tumours in this series on the basis of operative and autopsy findings. Obviously some tumours with cystic changes escaped inclusion in the cystic group because a cyst was not found at operation and no autopsy was done,
but since the same diagnostic and therapeutic methods were used for all age groups, comparison between them appears valid. Of 225 cases, 149 (66 per cent) were solid and 76 cystic (34 per cent). Frankel and German\(^8\) had similar results with 59.5 per cent solid and 40.5 per cent cystic. It is interesting that Davis et al.,\(^8\) describing cases of cerebral fibrillary astrocytomas, found 47 per cent solid and 53 per cent cystic. They regarded the solid astrocytomas as more actively proliferative, with the patients having shorter survival. We found no difference between the survival rates for cystic and solid tumours.

There was a marked difference, however, between the incidence of cystic and solid tumours in the two age groups (Fig. 2). Thus 49 per cent (16) of tumours in the group aged under 40 were cystic, as compared with 51 per cent (60) in the group aged over 40. Whether a tumour was cystic or solid appeared to exert no influence over the type of symptom produced although the time relationship may be affected—that is to say that the development of a cyst may lead to a rapid accentuation of a pre-existing neurological deficit.

**Local and General Effects**

The local and general effects of gliomas were investigated for the two age groups. As regards the general effects, 81 per cent of the young age group showed evidence of increased intracranial pressure as compared to 59 per cent of the group aged over 40. The local effects of tumour, on the other hand, were more apparent in the older age group, 93 per cent compared to 70 per cent of the group aged under 40.

These findings indicate that in the younger age group symptoms caused by increased intracranial pressure are more likely than symptoms resulting from infiltration. This obviously has some bearing on surgical possibilities, as will be seen presently.

**Factors Influencing Survival after Surgical Intervention**

**Age.** Frankel and German\(^8\) noted that the oldest age group had a slightly more rapid course which they attributed to their being poor surgical risks. However, in this series, excluding operative death, the over-all survival rate for the two age groups, irrespective of treatment (Fig. 3), shows a marked difference in survival rate over the first year, although little difference thereafter. The median survival rates for patients aged over 40 was just over 1 month as compared to 6 months for those under 40 years old. Netsky et al.\(^15\) also noted longer survival in the 24- to 42-year-old patients.

**Extent.** We compared the survival rates for various degrees of unilateral superficial involvement. Although there was little difference between one- or two-lobe involvement, the involvement of three or more lobes markedly affected the survival rate. For both single- and double-lobe involvement the median survival rate was nearly 3 months, as compared with 1 month for three-lobe involve-
ment. All these latter patients died within 3 months, although 15 per cent of those with single- or two-lobe involvements were alive at the end of 1 year. The effect of deep extension upon survival is shown in Fig. 4 in which superficial and deep involvement, unilateral or bilateral, is graphed against survival. It is clear that the effect of deep extension is to shorten markedly the survival period. Thus for superficial lesions the median survival rate was nearly 3 months but for deep involvement less than 1 month. These findings indicate that superficial extension has less effect on survival than deep extension. According to Scherer,20 markedly infiltrative and destructive growths pass all barriers, such as the basal ganglia and internal capsule, whilst less infiltrative and more expansive growths tend to follow fibre tracts. In the latter form of extension nerve fibres may be preserved and thus extensive superficial growths have relatively fewer clinical manifestations than less extensive but more destructive growths involving the deep structures. Roth and Elvide18 concluded that the location and extent of tumour influence the survival rate. The average survival for two-lobe involvement was 11.8 months, as compared to 10.4 months for three-lobe involvement. Patients with tumours of the basal ganglia and thalamus had a survival rate of only 0.8–1.7 months. However, Net-sky et al.16 concluded that location did not influence survival.

Symptoms. The effect of symptoms on survival irrespective of methods of treatment showed only that patients with no increase of intracranial pressure survived a little longer than those with increased pressure. The median survival rates of patients with increased pressure was about 1 month, but for patients without was about 3 months. Roth and Elvide18 found that patients with confusion, stupor or coma had a poor prognosis. Of the whole series of 225 patients, only 2 are still alive. One patient with a partial removal of a tumour of the right temporal lobe with subsequent deep roentgen-ray treatment is still alive over 4 years post-operatively, and another with partial removal of a large left posterior parietal cystic tumour and subsequent irradiation has now survived over 11 years.

Treatment

Many factors influence the choice of treatment of the individual patient with malignant glioma. The patient's age, site and extent of the tumour, symptoms and signs, the wishes of the relatives and philosophy of the neurosurgeon all influence the final choice. There was a tendency toward more extensive procedures in the younger age group than in the older. Thus in the former only 18 per cent (6 patients) had burr-holes only, whilst 43 per cent (14 patients) had radical operations as compared to, in the older group, 65 per cent (126 patients), with burr-holes only and 21 per cent (39 patients) with removals. The reason for this is partly because of the higher incidence of increased intracranial pressure and less evidence of infiltration in the young as compared to the older age group.

The extent of the tumour exercised a definite and not unexpected influence on the choice of intervention. It was apparent that less radical operative procedures were used more frequently in more extensive lesions. Thus 48 per cent (35) of 73 patients with single-lobe involvement had burr-holes only, 59 per cent (36) of 62 patients with two-lobe involvement, and 100 per cent (5) of the 5 patients with three lobes involved. Of the 85 patients with deep involvement, 65 per cent (56) were treated with burr-holes only. Cor-
respondingly, major procedures became less frequent as the lesions became more extensive.

For the whole series, 58 per cent (132) had burl-holes only, 13 per cent (29) had external decompression only, and 23 per cent (53) had removals. Five per cent of the patients had other treatment, usually ventriculocisternostomy, and in 1 case ventricular drainage.

Nine patients were readmitted for further treatment. Seven of these had removals of tumour following a previous admission with burl-hole only, and 6 had subsequent irradiation. One had re-aspiration of a cyst and 1 had irradiation. Only the initial treatment was used in the analysis of choice of treatment.

The tendency for radical procedures to be used appears to be greater in American centres than in this country where less extensive procedures are more usual. Seventy per cent (148) of the 211 cases reported by Davis et al.7 had removal of the tumour, and 82 per cent (404) of 495 cases reported by Roth and Elridge15 had removal of the tumour. In this centre there has been a gradual increase in the number of cases with radical procedures. Pennybacker et al.,17 reporting 282 cases of spongioblastoma multiforme, had 89 cases (32 per cent) with major interventions ranging from decompressions to complete removals. This compares with the 51 per cent having a radical procedure in the ensuing decade.

The over-all operative mortality was 19 per cent (43 of 222 cases). An operative death was arbitrarily defined as any occurring within 3 days of operation. Thus, many patients already moribund at operation are included and heavily weight the operative mortality. Frankel and German9 had an operative mortality of 18.5 per cent, including deaths within 7 days of operation. The operative mortality for all major procedures including ventriculocisternostomy was 6 per cent as compared to 10 per cent for the preceding 11 years.17

The highest mortality was with burl-hole biopsy (27 per cent), external decompression in the form of a flap came next with an operative mortality of 10 per cent; and the most radical procedure, partial or apparently complete removal, had the lowest operative mortality at 4 per cent. These figures are in general agreement with other authors in indicating that the more radical procedures have the lowest mortality rate. Frankel and German9 had an operative mortality of 40 per cent for the burl-hole biopsy, 22 per cent for partial removal, and 5 per cent for total removal of tumours.

Patients with superficial tumours treated with burl-holes had a 20 per cent operative mortality as compared to deep involvement when the mortality was 37 per cent.

The older age group had a higher mortality, 21 per cent (39 of 190) compared to 13 per cent (4 of 36) in the younger group.

The operative mortality was directly related to the extent of the tumour and to the location. In the superficial group 11 per cent of those with single-lobe involvement died, 16 per cent with two-lobe involvement, and 20 per cent with three lobes involved. The over-all operative mortality for superficial involvement was 14 per cent, as compared to 29 per cent for deep involvement. Davis et al.7 had an operative mortality of 27 per cent for single-lobe involvement, 44 per cent for multiple-lobe involvement, and 50 per cent for bilateral involvement. Patients with evidence of increased intracranial pressure had a higher operative mortality rate than those who did not have increased pressure, 23 per cent compared to 6 per cent. This must be attributed to the inevitable swelling occurring after needling an already swollen brain. Of the 108 patients with increased intracranial pressure treated with burl-holes, 35 died, an operative mortality of 32 per cent. In 24 patients without evidence of increased intracranial pressure also treated with burl-hole biopsy only 1 died, an operative mortality of 4 per cent.

Neither the duration of symptoms nor the cystic or solid nature of the tumour had any significant effect on the operative mortality. Patients chosen for particular treatments were highly comparable and errors because of
The selection of patients can be ignored. Fig. 5 shows clearly that the survival was profoundly influenced by treatment. Patients who survived burr-hole biopsy, but without aspiration of cyst, were described as non-treated. The median survival rate for untreated patients was less than 1 month, and for treated between 3 and 6 months. However, at the end of 6 months all the non-treated patients were dead, but approximately 40 per cent of those who were treated were still alive.

Aspiration of a cyst often produced immediate improvement and to some extent influenced survival, especially if repeated aspirations were done.

**Effect of Radiation Therapy**

In general, patients with crippling dementias or aphasias tended not to have irradiation and in this respect the remainder may be considered "good cases," but dementias or aphasias had no significant influence on survival and in respect to survival the groups of cases may be considered comparable. The over-all median survival for nonirradiated patients was about 1 week and for irradiated patients about 9 months.

To avoid the argument that only "good patients" had irradiation we excluded those dying within 7 days of discharge, as clearly such patients had no opportunity either to have irradiation or to complete a reasonable course. Thus the survival of those untreated with irradiation is slightly improved. Despite this there is a considerable and statistically significant difference between the two groups.

Bloor et al., Davis et al., Frankel and German, Roth and Elvidge, and Taveras et al. all found that irradiation made a significant difference to survival. Netsky et al. thought the effects of irradiation were slight and that patients living longer had more opportunity to be irradiated rather than that irradiated patients lived longer. By excluding patients unable to receive irradiation, however, we have shown that in this series irradiation significantly affected survival.

We found no difference between the response of cystic and solid tumours to irradiation. The only outstanding feature was the improved survival rates of patients treated with irradiation as compared to those untreated (Fig. 6).

**Comparison of Various Treatments**

Fig. 7 shows the survival rates for various methods of treatment. More extensive procedures produced better survival rates. In the group without irradiation and subjected to burr-hole biopsy only the survival was short (median survival about 1 month), although patients who had external decompressions and tumour removals had somewhat better chances of survival (median survival about 3 months). All patients with burr-hole biopsy died within only 6 months of operation, but those with irradiation had survival rates comparing favourably with those who had a flap or removal without irradiation.

There was no significant statistical differ-
ence between decompression followed by irradiation, and tumour removal followed by irradiation, in which the median survival rate of both lay between 9 and 12 months. This is a most important finding for it suggests that an external decompression without any removal of brain, and therefore without the same risk of producing further disability, produces as good results as partial removal, provided irradiation is given. Thus simple decompression and irradiation may be suitable for lesions of the left hemisphere at present regarded as inoperable, although the operative mortality (10 per cent) is greater than for removal (4 per cent).

Quality of Survival

There is a quality as well as a quantity to life, and although these results indicate that survival may be prolonged, such survival may produce great distress to both patient and relatives. We investigated, therefore, the postoperative life of 66 patients surviving more than 3 months from operation. Information was obtained in 44 cases. We defined the term “useful life” on the basis of ability to lead a relatively normal life with the exception of being unable to work. Thus such patients were able to dress and eat unaided, read newspapers or watch television, and go for walks. Some were also able to have gainful employment, usually at their old place of work, and this we defined as “working life.” Patients with profound aphasia, bedridden or mentally disorganised, were regarded as having a “useless life” (Fig. 8).

Of the 44 patients, 76 per cent (33) had “useful life” of at least 6 months, 32 per cent (14) for at least 1 year, and 12 per cent (5) for more than 3 years. Of these, 49 per cent (16) could return to work. The “working life” is also shown in Fig. 8. Of 44 cases, 28 per cent (12) were able to work for at least 6 months, 21 per cent (9) for at least 1 year, and 9 per cent (4) for more than 3 years.

On the whole, these results are discouraging and the number of patients able to return to work is small. However, about a third of patients surviving longer than 3 months postoperatively had some period of useful life, although the duration of this was often short.

The value of such survival is a matter for the philosophy of the neurosurgeon and more importantly the feelings of the relatives. We cannot certainly prognosticate the survival of the individual patient nor can we always tell what sort of survival will result. The preoperative condition of the patient is some guide to the quality of survival and we see no moral or economic advantages in a patient surviving with a profound aphasia and hemiplegia.

Radical Excision

The ideal treatment for many neoplasms is complete excision, perhaps followed by irradiation. In other parts of the body excision of part or even the whole of an organ is feasible. In the brain, however, although it is
technically possible to excise large areas, we are restricted by the disastrous effects of injury to vital areas. The effects of such excision on the motor and sensory systems, and especially upon intellect and speech, are such that in practice we must restrict excision to certain areas.\textsuperscript{11}

The excision of a whole or part of one side of the visual pathways, as in occipital lobectomy, does not result in gross incapacity. Tumours restricted to one occipital lobe are thus ideal for radical removal. Unfortunately the occipital lobe is less commonly involved than other lobes, and indeed in this series there were no cases with involvement of the occipital lobe only.

Similarly, one or other frontal lobe may be excised often without gross disability. The need for a wide excision in these infiltrative tumours is such, however, that excision must be limited to only one lobe and often in only the nondominant hemisphere. Of single frontal tumours there were 27 clinically limited to one lobe.

The temporal lobe may also be excised, but the risk of disturbance of speech in tumours of the dominant hemisphere is such that only the anterior or inferior part of the dominant lobe may be resected. Rarely does the malignant glioma limit itself to such a small area and, although partial removal may be permissible, we have excluded such cases from resectable lesions in this survey. Thus of 24 temporal tumours 12 were restricted to the right temporal lobe.

Excision of the parietal lobe is, we feel, contraindicated, although some would advocate it on the nondominant hemisphere. Partial removal as part of an excision of a right frontal or right temporal tumour is, however, often justifiable.

Deep tumours, with evidence of involvement of basal ganglia, thalamus or corpus callosum, we regard as inoperable at the present time, although Arseni\textsuperscript{2} and Tolosa \textit{et al.}\textsuperscript{22} have presented a case for excision of primary tumours of the basal ganglia and thalamus.

Bilateral involvement generally is a contraindication to radical treatment but there may be cases in which a unilateral subtotal removal is justifiable;\textsuperscript{16} we have excluded such cases from resectable lesions.

The total resectable tumours in this series by our criteria is therefore 27 frontal tumours and 12 right temporal, making 39 cases in all, but of these 39 patients, 9 were aphasic and this again we considered a contraindication to radical surgery. There may be occasions when partial removal is justifiable in such cases if the tumour is not primarily in the speech area and the aphasia is mild; such cases are uncommon and thus we exclude them, making 30 cases without aphasia and involving single frontal or right temporal lobes. The patients with clinically resectable lesions are thus 30 of 225 (13 per cent), and we must emphasise that this assessment is a clinical one and it is probable that the true extent of many of these lesions is much greater. As we mentioned earlier, clinical evidence of infiltration is less common than evidence of increased intracranial pressure in the younger age group, while the reverse holds for the older group. In the younger patients we might therefore expect greater opportunity for resection. Indeed, 9 of 33 patients under 40 years of age (27 per cent) satisfied our criteria for resection as compared to 30 of 192 patients over 40 (16 per cent). Radical resection does not therefore hold much hope in the treatment of these tumours although partial removal will benefit many.

\textbf{Indications for Treatment}

The treatment given will vary with the philosophy of the neurosurgeon and radiotherapist. However, when the patient's condition justifies prolonged survival, \emph{flap} or \emph{external decompression} should be reserved for patients with increased intracranial pressure and should be followed by irradiation. Obviously there will be patients having flaps as part of an exploratory operation for suspected benign lesions.

\textbf{Partial or “complete” removals} should be restricted to patients with increased intracranial pressure caused by tumours invading single ineloquent sites. Again irradiation is indicated.

In other cases either a \emph{biopsy only} or
biopsy and irradiation is available. Although many factors are involved in the decision as to the correct treatment for these tragic cases, in our opinion profound disturbances of speech are absolute contraindications to therapy, but if the patient’s condition justifies survival irradiation should be given.

Finally, we must emphasise that every patient with suspected malignant glioma should have a biopsy, and equivocal or negative biopsy demands a reassessment and possible exploration.

Conclusions

Malignant gliomata are relatively common intracranial tumours and the results of conventional treatment are not impressive. Despite this, radical procedures may greatly lengthen survival and, more importantly, irradiation has been shown to be the most effective single factor influencing survival. Useful palliation may be achieved and the results of this survey indicate that a more aggressive attitude in therapy is frequently justifiable.

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