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THE TREATMENT AND PROGNOSIS OF MEDULLOBLASTOMA IN CHILDREN*

A STUDY OF 82 VERIFIED CASES

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IN 1925 Bailey and Cushing[2] identified the medulloblastoma as an entity, distinguishing it from the sarcomas and other posterior fossa gliomas. They described its natural history, and gave it the name by which it is known today. For nearly 50 years it has been appreciated that medulloblastomas are highly radiosensitive and that following postoperative irradiation, life is prolonged to a greater extent than after surgery alone. Coupled with this knowledge, however, has been an almost universal pessimism concerning the ultimate outcome. Most authors, even in recent years, regard the diagnosis of medulloblastoma as tantamount to a death sentence, with a life expectancy generally measured in months.

It is the purpose of this paper to report on early and late results of treatment in children under 15 years of age with cerebellar medulloblastoma, to evaluate factors influencing prognosis, and to consider the quality of life in long-term survivors. We hope to show that not only can a proportion of children with this tumor be cured by postoperative cerebrospinal axis irradiation, but that cure, in the majority of such cases, can be accomplished without serious radiation sequelae.

ETIOLOGY

During the development of the cerebellum, proliferation of neuroepithelial cells occurs in the posterior tip of the roof of the fourth ventricle to form the germinal bud: from here, undifferentiated cells migrate over the outer surface of the cerebellum as the external granular layer. Persistent foci of these primitive cells may be found in the region of the posterior medullary velum in children and even in adults.[43] It is postulated that under certain conditions in the fetus or later in life, these cells may undergo proliferation to form a medulloblastoma. The stimulus could be provided by a neurotropic virus or chemical carcinogen, both of which can pass the placental and blood-brain barriers in the fetus. Druckery *et al.*,[22] for example, have recently reported that a single injection of ethylnitrosourea to pregnant rats resulted in tumors of the nervous system in the offspring, but not in the mothers.

Medulloblastoma constitutes approximately 4 per cent of all tumors of the central nervous system (Table 1), and some 20 per cent of intracranial neoplasms in children (Table II). In practice it is a rare tumor, and we have estimated that in England and Wales there are only about 60 new cases per annum.*

PREVIOUS SERIES

Following a vast surgical effort in 61 cases, and with a case mortality of 32 per cent, Cushing[17] was left with only 1 patient alive at 3 years. Half his cases received limited postoperative irradiation. It soon became clear that radical surgery alone was not enough to control medulloblastoma; that irradiation of the whole ventricular

* This figure is based on the reported annual incidence of cases of brain tumor in children 0–14 years of age supplied by 4 national cancer registration regions (population 0–14 years = 10.7 million) in England and Wales. From these statistics we estimated that there are rather less than 300 new brain tumor cases per annum in the country as a whole, of which some 20 per cent are medulloblastomas (*i.e.*, 60 cases).

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TABLE I

INCIDENCE OF MEDULLOBLASTOMA IN ALL INTRACRANIAL TUMORS

Author	Total Cases	Medulloblastomas	
		No.	Per Cent
Cushing (1932)	2,023	86	4.3
Zülch (1965)	6,000	230	3.8
Berger and Elvidge (1963)	2,443	109	4.5
Total	10,466	425	4.1

system and spinal cord was necessary to prolong life appreciably, and that better results followed higher doses given in a single course. In spite of these observations, very few long-term survivors were subsequently reported, such cases being regarded as rarities.[28,41]

Lampe and MacIntyre[30] searched the literature between 1925 and 1948 and were only able to find a total of 27 3 year survivors, of which 12 were alive 3 to 9 years after treatment. These authors had 21 personal cases under 15 years of age, 6 of whom (28 per cent) were alive more than 3 years after treatment.

TABLE II

INCIDENCE OF MEDULLOBLASTOMAS IN CHILDHOOD INTRACRANIAL TUMORS

Author	Age Group	Total Intracranial Tumors	Medulloblastomas	
			No.	Per Cent
Cushing (1927)	Preadolescent	154	24	16
Zülch (1937)	<20	120	23	19
Bailey *et al.* (1939)	≤15	100	19	19
Craig *et al.* (1949)	<15	427	86	20
Bodian and Lawson (1953)	<13	129	25	19

After Crue (1958).

In the 1950s, very poor survival rates for medulloblastoma continued to appear in the literature, although two encouraging reports concerning a small number of cases were published in England in 1953. Paterson and Farr[39] were able to claim 7 of 13 children, and Richmond[46] 7 of 14 alive 3 years after treatment. During the past decade 5 year survival rates beyond all previous expectations have been reported from England by Paterson[37] (41 per cent of 27 cases), from the United States by Smith *et al.*[52] (28 per cent of 38 cases), and from Canada by Bouchard[8] (27 per cent of 37 cases). These results must be compared to the hopeless background of a life expectancy of 8 or 9 months from the clinical onset for untreated cases.[17] In reports concerning radiotherapy for medulloblastoma, the number of cases has usually been small and details of possible case selection have often been incomplete.

ROYAL MARSDEN HOSPITAL SERIES

Between 1950 and 1964, 108 cases of histologically verified medulloblastoma were referred to the Radiotherapy Department of the Royal Marsden Hospital (Table III). Of these, 3 were located in the supratentorial region, 2 had been previously treated, and 5, for domestic reasons, were referred for treatment to centers nearer their home. A further 16 cases were older than 15 years. After excluding these 26 cases, there remained for evaluation 82 children under the age of 15 years with medulloblastoma of the cerebellum.

TABLE III

ROYAL MARSDEN HOSPITAL MEDULLOBLASTOMA 1950–1964

Total Cases Referred		108
Supratentorial	3	26
Treated Previously	2	
Referred Elsewhere	5	
Adults (≥15)	16	
Cerebellar Medulloblastoma in Children (<15)		82

The diagnosis in all 82 cases has been based on histologic material seen by 2 or 3 pathologists at London Teaching Hospitals. Dr. N. F. C. Gowing (Director, Department of Morbid Anatomy, Royal Marsden Hospital) was able to obtain the histologic sections of 72 of the 82 cases for further review; the diagnosis in all 72 was confirmed once again.

Cerebellar medulloblastoma constitutes approximately one-third of all intracranial tumors in patients under the age of 15 years referred for irradiation to this hospital. Brain tumors in children occur with equal frequency in boys and girls. The medulloblastoma, however, is twice as common in males (Table IV). Eighty per cent of all medulloblastomas occur under the age of 15 years. The age distribution in the present series (Fig. 1) was comparable to that in 400 cases collected from the literature by Crue.[16] Our youngest child was 11 months of age. Two minor peaks can be seen around the ages of 3 to 4 years, and 8 to 9 years.

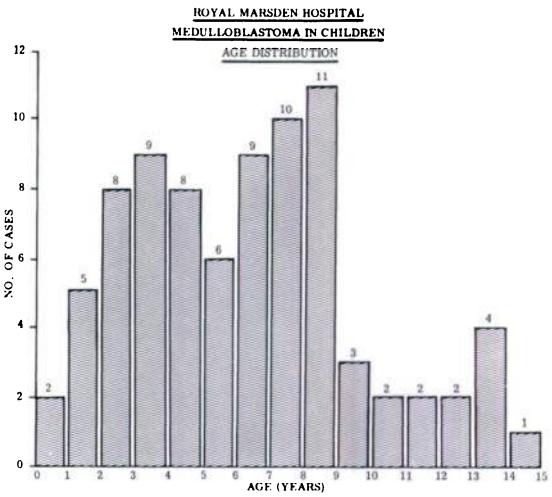

Fig. 1.

Techniques of Radiotherapy

There is now general agreement that the entire cerebrospinal axis must be irradiated in cases of medulloblastoma. We have not, however, adhered to the principle of uniform dosage throughout the treated volume, which has been the practice in some centers. We believe that it is essential to concentrate on the primary site and the region of immediate direct tumor extension, since in practically all of the children that we have failed to cure, there has been evidence of persistent or recurrent tumor in the cerebellum and brain stem region. In 14 cases subjected to autopsy in the present series, 13 were found to have tumor at, or in the vicinity of, the original primary growth. For this reason, the maximum dose is directed to the infratentorial region and to the third ventricle. We aim to complete treatment to the head before starting on the spine because of the risk of leukopenia, which may cause irradiation to be suspended.

Table IV

Royal Marsden Hospital
Intracranial Tumors in Children <15 Referred to Radiotherapy Department
(1950–1964)

	Cases	Males	Females	♂ : ♀ Ratio
Medulloblastoma	82	56	26	2.2:1
Other Intracranial Tumors	178	91	87	1:1

At the Royal Marsden Hospital prior to 1959 several radiotherapy techniques were employed for medulloblastoma. All but 2 of the cases had cerebrospinal axis irradiation, but in most patients part of the brain, the frontal poles and, in some, the vertex, were outside the planned treated volume. There was much variation in dosage but the cerebellum and the upper cervical cord, in continuity with the brain-stem, generally received a tumor dose of 4,000–5,500 r in 5–8 weeks from 250 kv. roentgen rays (half value layer, 3.4 mm. Cu). The spinal skin dose was usually 3,000 r in 6–8 weeks. This resulted in a tissue dose of approximately 1,900 r (phantom measurements) to the remaining part of the cord. The full dose range varied between 1,000 and 3,900 r to the spinal skin, and between 2,000 to 6,700 r at depth in the posterior cranial fossa.

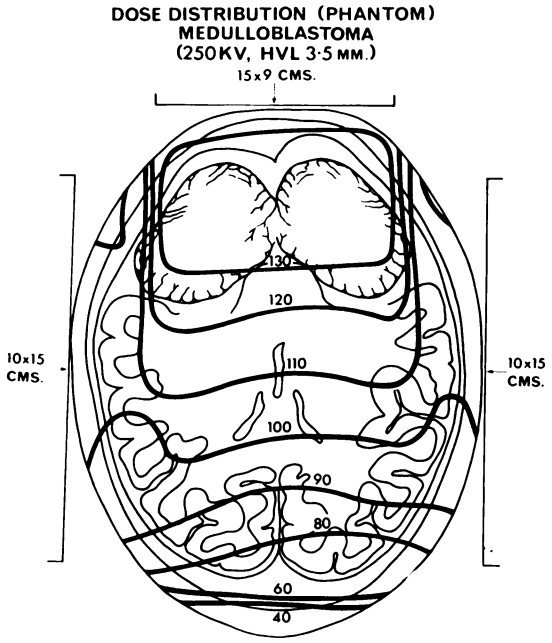

FIG. 2.

Since 1959, a more uniform technique has been employed, the purpose of which has been to treat the entire intracranial cavity and spinal theca. The skull was irradiated

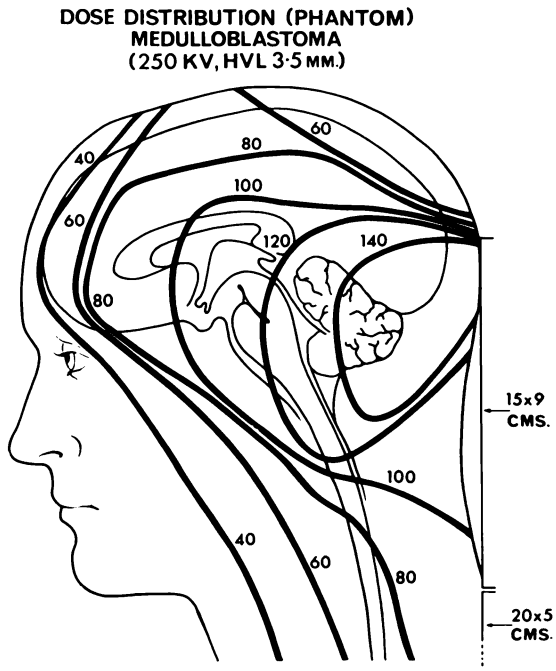

FIG. 3.

with a posterior and two opposing lateral fields (Fig. 2 and 3). The posterior fossa generally received a maximum dose of 4,500–5,000 r in 6–7 weeks; the dose to the mid-portion of the brain was 3,500–4,000 r, and to the frontal poles 2,500–3,000 r. The skin dose over the spine was 3,000 r in 5–6 weeks using contiguous fields of unequal length which were changed around after every 1,000 r to avoid "hot" and "cold" areas at junction zones. With older children we are now using 6 mev. roentgen rays from a linear accelerator, the maximum dose to the brain being 5,000 rads. The spine is treated with a single field and the cord dose is 3,000 rads.

RESULTS

Radiotherapy results in medulloblastoma are necessarily based on selected cases, and the over-all picture regarding outcome in this disease will not emerge until an account is taken of the substantial operative mortality, (presently, approximately 20–25 per cent) and of the cases that die before irradiation is started or completed. Our results are based on operative survivors. Eight children (10 per cent) who were in very poor condition on admission for radiotherapy, and in whom treatment was not completed because of their further deterioration or early death, have *not* been excluded from the series.

During the first 2 years following treatment there is a rapid decline in survival, after which the "force of mortality" appears to decrease. At 3 years, 35 per cent of 77 children are alive; at 5 years 32 per cent of 68 cases; and at 10 years 26 per cent of 34 cases (Table v).

CASES COMPLETING TREATMENT

Five of the 82 children in the present series died during treatment, and in 6 irradiation was abandoned—in 3 because of deterioration, in 1 at the request of the parents, and in 2 because of some doubt regarding the diagnosis which, however, was subsequently confirmed at autopsy. These 11 cases may be excluded to show the re-

sults in 71 patients who completed the prescribed treatment. Practically 40 per cent of such cases survived 5 years, and 30 per cent 10 years (Table VI; Fig. 4).

FACTORS INFLUENCING PROGNOSIS

AGE

It is generally believed that the prognosis in medulloblastoma is more favorable for teen-agers and adults than for young children. Sixteen adult cases treated at the Royal Marsden Hospital appeared to fare better than the children during the first 5 years after treatment; the ultimate prognosis, however, is more promising for children, in whom there is a 10 year survival rate of 26 per cent (Fig. 5).

The results for children by age group are shown in Table VII and Figure 6. Most deaths are seen to occur during the first 2 or 3 years following treatment. The steepest part of the declining survival curve is reached at 1 year for the children under 5 years, at 2 years for those aged 5–9 years, and at 3 years for the oldest group, 10–14

TABLE V

ROYAL MARSDEN HOSPITAL, 1950–1964
MEDULLOBLASTOMA IN CHILDREN (<15)

Interval (yr.)	Cases	Alive	
		No.	Per Cent
2	82	37	45
3	77	27	35
5	68	22	32
7	58	13	22
10	34	9	26

TABLE VI

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN (1950–1964)
SURVIVAL IN PATIENTS COMPLETING TREATMENT

Interval (yr.)	Cases	Alive	
		No.	Per Cent
3	66	26	39
5	58	22	38
10	29	9	31

years. By this time the proportion alive in all 3 age groups is practically identical. *Compared with adults, the tempo of the disease is faster in children, and the younger the patient the quicker will unsuccessful cases die.*

SEX

The possible influence of sex on prognosis does not appear to have received attention from previous authors other than Paterson,[37] who remarked that "treatment is more successful in girls than in boys." In the present series the outlook was appreciably better for girls, as judged by the 3, 5 and 10 year survival results (Table VIII).

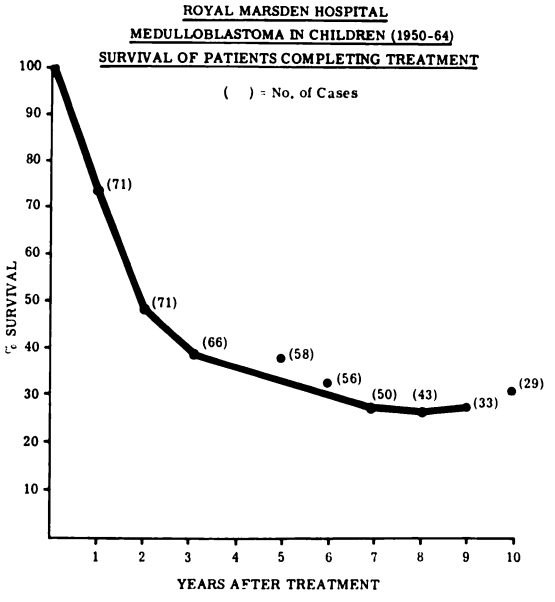

FIG. 4.

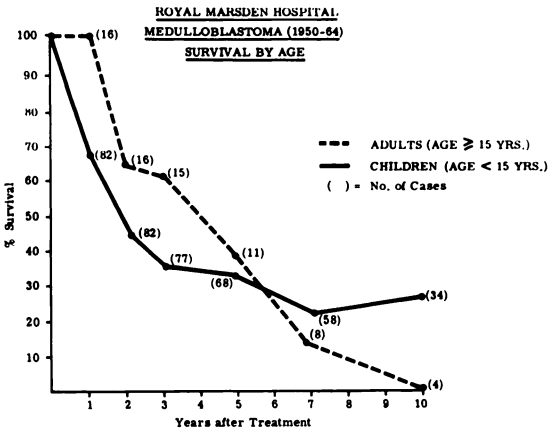

FIG. 5.

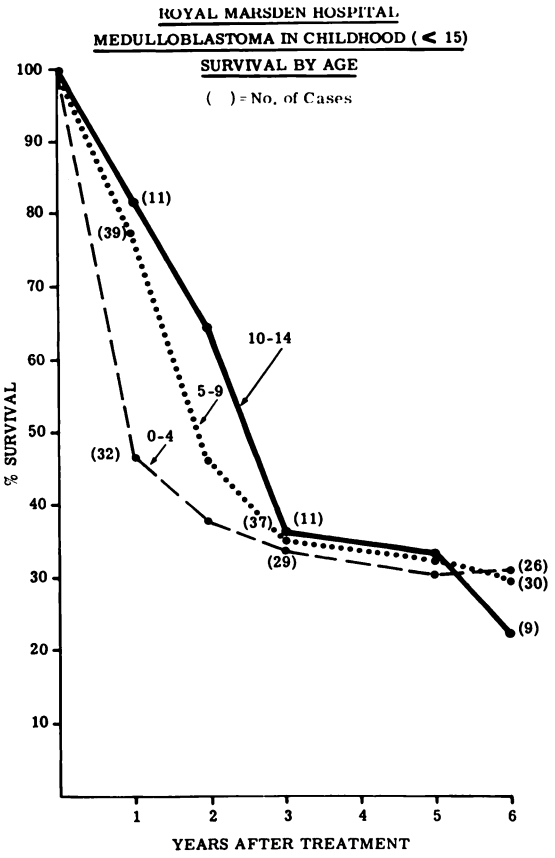

FIG. 6.

EXTENT OF DISEASE

It was possible to assess the presence or absence of brain-stem involvement from the surgical notes in 77 of the 82 patients. Radiotherapy appears to control even locally advanced disease for a considerable time, the influence of brain-stem invasion and probably other lines of local extension becoming evident only after the passage of more than 5 years (Table IX). Ultimately, only 2 of 12 cases with spread to the floor of the fourth ventricle were alive at 10 years, compared with 7 of 18 children in whom this complication was not present.

DELAY IN TREATMENT

No consistent correlation between prognosis and duration of symptoms could be demonstrated in the present series. The mean delay for 45 cases dying within 2 years of treatment was 3.2 months, compared with 3.6 months for 22 cases surviving 5 years, and 2.8 months for 9 cases

TABLE VII

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
SURVIVAL BY AGE

Interval (yr.)	Age 0–4 years			Age 5–9 years			Age 10–14 years		
	Cases	Alive		Cases	Alive		Cases	Alive	
		No.	Per Cent		No.	Per Cent		No.	Per Cent
1	32	15	47	39	30	77	11	9	82
2	32	12	38	39	18	46	11	7	64
3	29	10	34	37	13	35	11	4	36
5	26	8	31	33	11	33	9	3	33

alive at 10 years. On the other hand, in patients with more advanced disease, as judged by the presence of brain-stem involvement at operation, there was a mean delay of 4.7 months, compared with 3.0 months for those without this complication.

HISTOLOGIC TYPE AND GRADE OF TUMOR

The so-called "cerebellar arachnoid sarcoma" is regarded by many pathologists as being merely a desmoplastic variant of the classical medulloblastoma, and this is supported by the finding of transitional forms between the two types.[20,49] The term "desmoplastic medulloblastoma" has been suggested for this variant because of the conspicuous connective tissue elements present which are ascribed to a marked leptomeningeal reaction secondary to tumor invasion. There appears to be little difference in the natural history of both types of tumor and treatment is the same. Nevertheless, they should be distinguished, as far as results are concerned, because of the somewhat better prognosis claimed for the desmoplastic variety in older children and adults. Dr. Gowing considered that only 3 of the 72 cases he reviewed in the present series could be classified as distinct examples of this type of tumor, but because of the small number involved we have not separated them from the main series. All 3 cases died within a year of treatment.

Unsuccessful efforts have been made in the past to correlate prognosis with histologic grade of malignancy in medulloblastoma.[19,50,53] Gowing has attempted to grade the cases in the present series according to degree of tumor differentiation, nuclear pleomorphism, frequency of mitoses and the amount of reticulin present, but no correlation could be demonstrated between any of these factors and survival.

TABLE VIII

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
SURVIVAL BY SEX

Interval (yr.)	Boys		Girls	
	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)
2	56	45	26	46
3	55	31	22	45
5	49	29	19	42
10	25	20	9	44

TABLE IX

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
BRAIN STEM INVOLVEMENT AND PROGNOSIS

Interval (yr.)	Brain Stem*		Brain Stem†	
	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)
3	44	36	27	37
5	39	36	25	32
7	33	30	22	14
10	18	39	12	17

*= Free.
†= Involved.

SURGERY AND TYPE OF OPERATION

Radical surgery alone cannot be expected to control medulloblastoma; without irradiation all patients with this tumor will die, usually within 6 months of operation. This was recognized by Cushing[17] who also stressed that the immediate surgical risk was greater than for any other intracranial tumor. His operative and case mortalities were 25 and 32 per cent, respectively. Even today, in the best hands, the mortality for radical surgery in children suffering from this tumor is not less than 20 per cent. To avoid the immediate loss of life due to operation, Cutler *et al.*[19] suggested that irradiation might be used without preliminary decompression. Peirce *et al.*[40] also recommended radiotherapy as the sole treatment, but advised preliminary closed aspiration biopsy to establish the diagnosis. Needle biopsy, however, is not without risk, since 3

TABLE X

ROYAL MARSDEN HOSPITAL
CHILDREN WITH MEDULLOBLASTOMA
REFERRED FOR RADIOTHERAPY
SURVIVAL BY TYPE OF OPERATION

Interval (yr.)	"Complete" Excision		Partial Excision	
	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)
3	22	45	46	33
5	20	40	39	33
10	9	44	18	22

of 24 cases reported by Berger and Elvidge[4] died as a result of this procedure.

Elsberg and Gotten[23] showed that a conservative surgical approach (*i.e.*, decompression with removal of enough tumor for histology followed by radiotherapy) gave an average survival among the operation survivors comparable to that of a similar group of cases treated by radical surgery and irradiation; the operative mortality in the latter group, however, was 36 per cent, compared with only 13 per cent for the conservative surgical procedure. Most neurosurgeons today will attempt to remove as much of the tumor as possible without increasing unduly the operative mortality and risk of serious neurologic disability. Such a procedure will establish the diagnosis, create a decompression and reopen the cerebrospinal fluid pathway, which is the most certain way of preserving vision. In addition, by removing the bulk of tumor, including necrotic and anoxic elements, one hopes to assist in the task of destroying residual growth by irradiation.

In the present series a partial excision of the tumor was carried out in 50 children, and an apparently complete removal was effected in 23. Six children were submitted to biopsy only, and 3 were treated solely by irradiation, histologic verification in the latter cases being obtained subsequently at postmortem examination. The survival rate appears to be rather better following so-called complete excision of the tumor, but presumably this procedure is more likely to be accomplished in the more favorable cases (Table x).

RADIOTHERAPY TECHNIQUE

As stated previously, since 1959 a single irradiation technique has been used to include the whole intracranial cavity and spinal theca. A comparison of the results obtained before and after 1959 is shown in Table XI, with perhaps some improvement during the latter period.

The vast majority of fatal cases of medulloblastoma have persistent or recurrent disease at the primary site, and so a limited area of the cerebral hemispheres, which is not included in the treated volume, is unlikely to be responsible for an appreciable decline in survival, providing that the entire ventricular system and spinal theca are irradiated. In some cases, however, therapeutic failure can undoubtedly be ascribed to incomplete treatment of the central nervous system.

DOSE OF IRRADIATION

Arnold *et al.*[1] considered that tumors in the region of the brain-stem are incurable by irradiation because the necessary dose is likely to exceed the normal tolerance of this part of the brain. From our experience with

TABLE XI

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
SURVIVAL OF CASES 1959–1964

Interval (yr.)	1950–1958		1959–1964*	
	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)
2	50	38	32	53
3	50	30	27	44
5	50	30	18	39

* Cases treated by a more uniform technique. Whole central nervous system irradiation. Maximum dose (posterior fossa) 4,000–5,000 r.

TABLE XII

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
SURVIVAL BY RADIATION DOSE

Dose*	2 Year Results		3 Year Results		5 Year Results	
	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)	Cases	Alive (Per Cent)
<3,500 r	4	25	4	25	4	25
3,500–4,000 r	7	43	7	29	6	33
4,000–4,500 r	25	64	25	48	22	41
4,500–5,000 r	14	36	13	38	12	33
>5,000 r	22	45	18	33	18	33

* Maximum to posterior fossa.

older children and with adults, the brainstem appears to tolerate a maximum dose of 5,000 rads in 6–7 weeks from telecobalt or supervoltage roentgen-ray equipment. In the present series a maximum tumor dose of less than 4,000 r with 250 kv. roentgen rays appears to be inadequate for the treatment of medulloblastoma in children, whereas a dose of 5,000 r or more *per se* might be excessive (Table XII).

CAN CHILDREN WITH MEDULLOBLASTOMA BE CURED?

The concept of a "period of risk" for recurrence of embryonal tumors is based on the assumption that the growth rate of individual tumors is constant and dependent upon age; the younger the child, the more rapid the tumor growth. If at the end of the period of risk, defined as the age at treatment plus 9 months for gestation, there is no clinical evidence of recurrence, then the prognosis is considered to be excellent.[14] This idea was first formulated for Wilms' tumor, and although exceptions have been reported, most cases appear to fit the rule.

Since medulloblastoma appears to be an embryonal tumor, we applied the concept of "age at treatment plus 9 months" as a possible test of cure in the present series (Fig. 7). The oblique line in this figure represents the end of the "period of risk." No deaths have taken place to the right of the line, except 1 due to intercurrent disease. So far, all recurrences in our series of 82 children with medulloblastoma have occurred within the period of risk as defined above. Once a child with medulloblastoma passes this critical period without signs of recurrence, cure seems likely.

RECURRENCE AND RETREATMENT

Although cerebrospinal metastases are often present in fatal cases of medulloblastoma, the chief cause of failure, in our experience, has been recurrence of the original primary tumor. Of 14 patients in whom an autopsy was performed, 13 had tumor in the posterior fossa; the remaining case died of meningitis shortly after treatment with no sign of residual neoplasm. Occasionally, distant metastases occur in medulloblastoma.[5,26,38,48] Two girls in the present series, both aged 8 years when treated, are known to have subsequently developed skeletal deposits; osteosclerotic changes were present in both cases, and in 1 the nature of the bone lesions was confirmed at postmortem examination.

Retreatment of children with distressing symptoms (*e.g.*, dysphagia, root pain) due to tumor recurrence following the initial

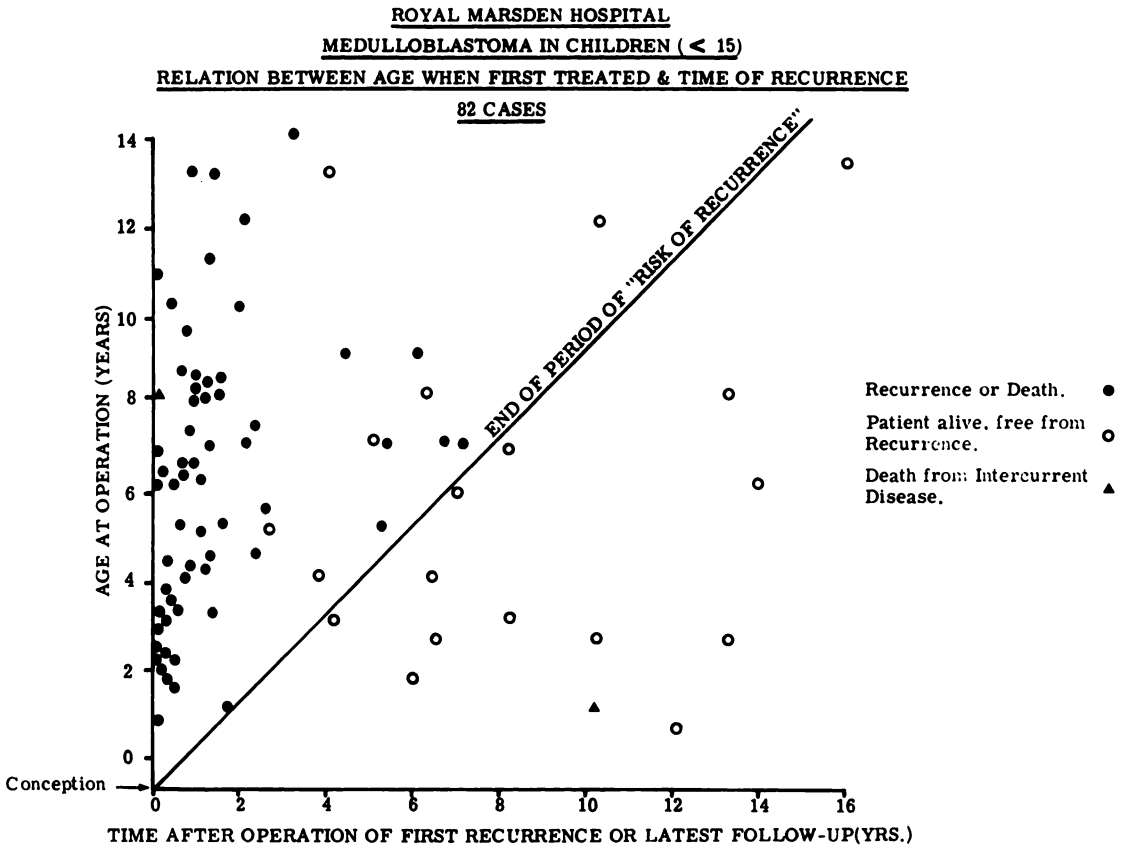

FIG. 7. All known recurrences of medulloblastoma have occurred to the left of the oblique line, *i.e.*, within the "period of risk" defined as age at treatment plus 9 months for gestation. Some patients, still well, have yet to pass the line.

radical course of radiotherapy is justified and often worthwhile. Irradiation in such cases should be limited to the affected areas and the dose restricted to that which brings relief (generally 1,500–2,000 r). An attempt at more radical treatment should be made for patients developing a recurrence in a previously untreated or low dose area. In the present series 16 courses of retreatment were given to 13 patients. Symptomatic relief was obtained on 9 occasions; 3 patients returned to active life for periods of from 13 months to over 3 years.

Remission in recurrent cases has also been reported following systemic chemotherapy with vincristine.[32] The subject of tumor recurrence in medulloblastoma and its treatment by irradiation and chemotherapy will be dealt with in greater detail in a separate communication.

QUALITY OF LIFE AND POSSIBLE LATE COMPLICATIONS IN MEDULLOBLASTOMA SURVIVORS

Lampe[29,31] has stressed that although some children with medulloblastoma appear to be cured, this may be at the price of serious brain damage due to irradiation. This complication was regarded as being present in 5, or perhaps 6, of 10 cases in his series surviving 5–15 years following a dose of 2,500 r in 7–10 days. Seven other patients in Lampe's series were treated by a more protracted technique, 5,000–6,000 r in 55 to 65 days, and of these, 4 were alive and well 3 to 6 years later, but 2 were said to be slow in learning.

The risk of radiotherapy for children with brain tumors may be considered from 2 aspects. First, gross brain damage or necrosis may occur, which is nearly always fa-

tal, and second, it is conceivable that more subtle neuropathologic changes may develop, producing an impaired intellect or disturbed emotions. One must also consider the consequences of irradiating extraneurologic structures such as the cranial bones, spine, marrow, pituitary, eye, and thyroid.

CENTRAL NERVOUS SYSTEM

(*a*) *Gross Damage* (*Necrosis*). In cases of medulloblastoma the brain-stem and upper cervical cord, which are considered to be among the most radiosensitive parts of the central nervous system, lie within the region receiving the maximum dose of irradiation. From a review of the general literature, especially the material reported by Boden[6,7] and by Lindgren,[33] it appears that a brain dose exceeding 5,500 r in approximately 4 weeks is dangerous. Individual idiosyncrasy, however, may occur, and at least 4 cases have been reported in which necrosis of the cervical cord, brain-stem or hypothalamus has followed doses of 4,500 r in 4–6 weeks—a dose normally well tolerated by these regions.[1,15,36]

A surgeon, when faced with a lesion threatening life, is prepared to accept an appreciable operative mortality, and for medulloblastoma this is at least 20 per cent. In the same way, the radiotherapist must be ready to face the risk of radiation complications when attempting curative treatment for a lethal disease, providing, of course, that the risk is not so great that the loss exceeds any gain. For cerebral gliomas in general we consider that a dose of 5,000 rads to a large volume from megavoltage equipment protracted over 6–7 weeks, in all but perhaps the youngest children, offers the greatest chance of cure while carrying the lowest risk of complications.

(*b*) *Functional Sequelae.* Although thousands of roentgens are required to produce recognizable histologic changes in the mature central nervous system, the brain, physiologically speaking, appears to be sensitive to doses of only a few roentgens, as evidenced by electroencephalographic changes, and the response of conditioned animals. We were reasonably confident that our dose-time schedule for medulloblastoma, 4,500–5,000 r to the posterior fossa in 6–7 weeks, carried only a small risk of necrosis. We were less certain about the possibility of more subtle neuropathologic sequelae occurring, especially in very young children, which might lead to serious functional changes in those who were to become long-term survivors.

Furthermore, the central nervous system of the developing mammal is particularly sensitive to irradiation, and from experiments in rodents the amount of damage inflicted is directly related to the dose, and inversely related to the age of the individual at the time of exposure. This applies to intra-uterine life, but there is a "carry-over" into at least the early postnatal period. Unfortunately, the experimental investigations have been confined to the immediate postnatal period, and we know of no comparable studies in rather older animals. Clemente *et al.*[13] showed that abnormal neurologic signs and neuropathologic changes in rats occurred more frequently and were more severe following head doses of 125–500 r when delivered within 3–4 days of birth, compared with irradiation after this time. Fifteen day old rats required a dose at least 4 times as great to produce the same changes as in 1–2 day old animals. The spinal cord is also far more sensitive to irradiation in the neonatal period, compared with 2–3 weeks after birth.[24]

In early childhood is there a stage when the brain is hypersensitive to irradiation, and if so, when does normal tolerance develop? No new nerve cells seem to appear after birth; mitoses of neurones are not evident after the seventh fetal month.[44] Although full maturation of the central nervous system, as judged by the degree of myelinization, may not be reached until puberty or even much later, this process is complete in most regions of the brain and cord by the end of the second year of postnatal life, generally by the first.[56] If there is a stage of unique radiosensitivity during

TABLE XIII

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDHOOD
5 YEAR SURVIVAL IN CASES AGED ≤3 YEARS

Age	Cases	5 Year Survival
Under 1 year	2	1
1–2 Years	4	1
2–3 Years	7	4
3 Years	7	1
Total	20	7 (35%)

postnatal development of the child's brain, then, judging from animal experiments, this is likely to be confined to the first year or two of life.

Information regarding neurologic sequelae following brain irradiation in very young children is difficult to obtain because of the almost impossible task of differentiating clinically between damage resulting from treatment, and that from the original tumor and its associated hydrocephalus. In the present series, of 6 children irradiated under 2 years of age, there were 2 long-term survivors, and both were demented, blind and epileptic. On the other hand, 4 out of 7 children treated at age 2 to 3 survived 5 years (Table XIII): 3 appeared normal both physically and mentally, while the fourth was ataxic and said to be slow at school, but otherwise well.

From the available data regarding human brain development, the radiosensitivity of the central nervous system in young experimental animals and the clinical experience in the present series, we now have arbitrarily chosen the age of 3 years (when the brain has reached 75 per cent of the adult weight and myelinization is well advanced) below which to prescribe a reduced maximum dose of 4,000–4,500 r in 6–7 weeks. Older children appear to tolerate brain irradiation well, and for them the full adult dose of 5,000 r in 7 weeks is given. In reaching this decision we have tried to balance the possible risks of treatment against the known high local recurrence rate and rapidly fatal course of so many medulloblastomas.

In spite of the potential dangers associated with irradiation of the young central nervous system, Bouchard and Peirce[9] were able to report that 86 per cent of 30 children with various brain tumors surviving 5—20 years after radical irradiation were leading an active life.

FUNCTIONAL RESULTS IN ROYAL MARSDEN SERIES

We have classified the survivors in the present series according to 4 categories of functional result:

I. *No disability, active life.* Patients in this group have no abnormal neurologic signs other than nystagmus. Children who are said to be slow at learning, but who, on general examination, are bright and appear intelligent, are included in this category.

II. *Mild disability, active life.* Here there may be ocular paresis, limited intention tremor and mild ataxia.

III. *Partial disability.* Patients may be severely ataxic or have seriously reduced vision, but all are capable of self-care. They may have definite impairment of intellect, but are capable of being taught a trade.

IV. *Total disability.* These cases are incapable of self-care.

Groups I and II, taken together, probably correspond to the category of "active life" proposed by Bouchard and Peirce.[9] Of the 22 children surviving 5–17 years in the present series, 18 (82 per cent) have led an active life, 15 without disability, and 3 with mild disability (Tables XIV and XV). Two patients were partly disabled, and 2 in category IV were demented and incapable of self-care. These last 2 children, who were still alive at 10 years, were treated at the age of 11 months and 15 months, respectively. Although it is

possible that severe neurologic disability including dementia and blindness may result from irradiating a young developing brain, such tragic sequelae are more likely to be due to cerebral damage produced by the original tumor and its associated hydrocephalus; in some cases surgical trauma and complications may also play a part. Enlargement of the head and gross neurologic disability were, in fact, already present in both of our demented cases at the time of the original admission for radiotherapy.

In children with severe disability such as decerebrate rigidity it may be humane to withhold treatment for fear of curing a demented and paralyzed child. On the other hand, limited palliative treatment is indicated to relieve distressing symptoms, even in hopeless cases if the child is alert and orientated. Should there be any doubt concerning the justification of treatment, a trial of irradiation may be undertaken, reviewing the situation at frequent intervals and only abandoning therapy in the absence of clear signs of improvement.

We have recently re-examined 12 of the 19 cases in this series who are still alive 3 to 17 years after treatment; 5 of the 7 remaining cases lived abroad. Reports on the patients who were unable to attend were obtained from parents or local doctors. Six of the 12 children of school age were making satisfactory progress, but one was blind (Table XVI). School progress in 2 was not known. Three were said to be slow at learning, had increased emotional reactions and were attending special schools. Problems of this type may be related more to missed schooling, parental anxiety and difficulties in the home rather than to brain damage *per se*; a history of husband-wife conflict, possibly aggravated by the child's illness, was found in 2 cases.

Seven cases are now adults (Table XVI) and 6 of them are in good health and capable of earning their own living (3 secretaries; 1 electrician; 1 telephonist; 1 instrument engineer). One woman, treated 17 years ago at the age of 13, has been a personal secretary to a solicitor and

TABLE XIV

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA IN CHILDREN
CLINICAL POST-TREATMENT GROUPS

Interval (yr.)	Cases Alive	I	II	III	IV
5	22	15	3	2	2
7	13	8	1	2	2
10	9	5	1	1	2

TABLE XV

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA: QUALITY OF LIFE IN 22 CHILDREN WHO SURVIVED 5–17 YEARS AFTER TREATMENT

Group	Group	Cases	
		No.	Per Cent
Active Life	I+II	18	82
Partial Disability	III	2	9
Total Disability	IV	2	9
Total		22	100

TABLE XVI

ROYAL MARSDEN HOSPITAL
MEDULLOBLASTOMA: CONDITION OF 19 PATIENTS STILL ALIVE 3–17 YEARS AFTER TREATMENT

Age	Cases	Clinical Condition
Still of School Age	12	1 Demented 3 Special schools. Slow learning or behavior problem 1 Good progress at school for blind 5 Well. Normal schooling—good progress 2 Well. School progress unknown
Now Adults	7	1 Well, but backward 6 Well, (3 secretaries; electrician; telephonist; instrument engineer)

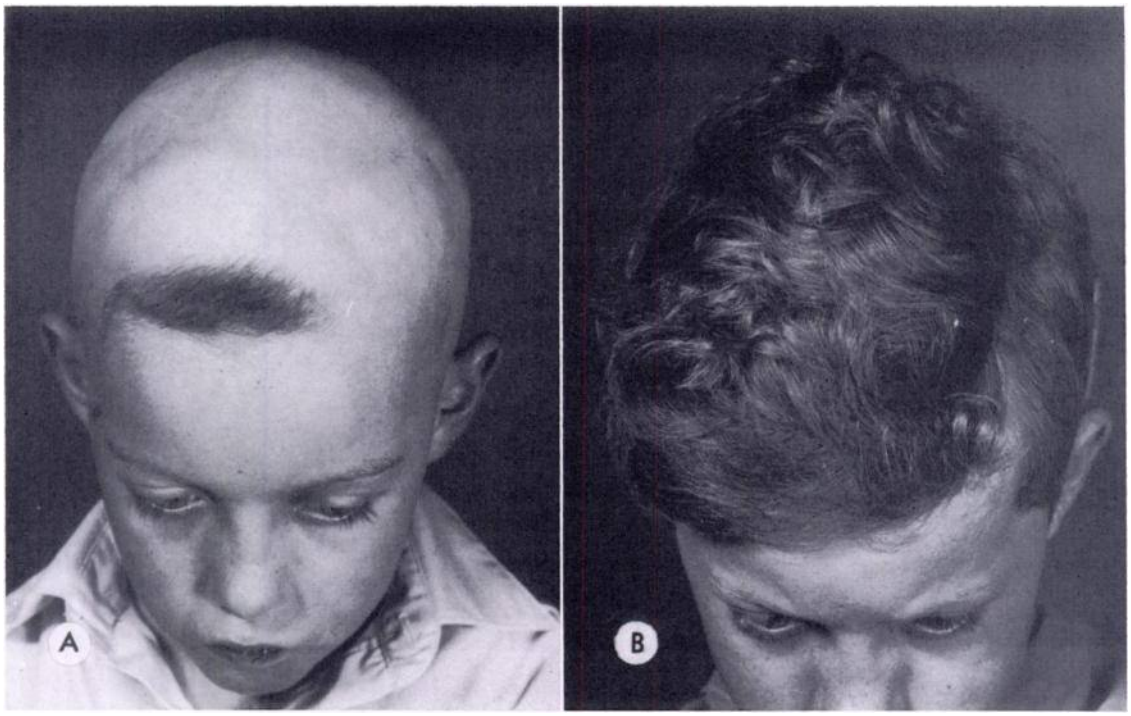

FIG. 8. (*A*) G. C., age 7. Total epilation, apart from small frontal tuft, following whole brain irradiation. (*B*) Full re-growth of wavy hair 8 months after treatment.

is now married with a normal child aged 2 years. The remaining case, a boy of 17, was treated at the age of 7 and is physically well, but mentally retarded: from the history and nature of the disability we believe this to be congenital and not acquired.

EXTRANEUROLOGIC TISSUES

(*a*) *Scalp and Skull.* Hair generally regrows well (Fig. 8, *A* and *B*), although some thinness and a bald patch or two may persist, especially in the occipital region at the site of the maximum dose of irradiation. A wig may be a great comfort to a sensitive girl or boy, but in most cases thin patches are well covered by hair from the surrounding regions of the scalp.

Berg *et al.*[3] have recently described 16 cases of osteonecrosis and 2 sarcomas of the cranium following irradiation for cerebral tumors. They reported that at least 7 of 35 cases of medulloblastoma (aged 3–18), and 6 of 55 cases of astrocytoma (aged 10–53) showed roentgenographic changes consistent with radiation necrosis. This condition appears to be symptomless and eventually becomes static or even regresses. In 1 of the 12 cases we have recently recalled for examination, 3–17 years after

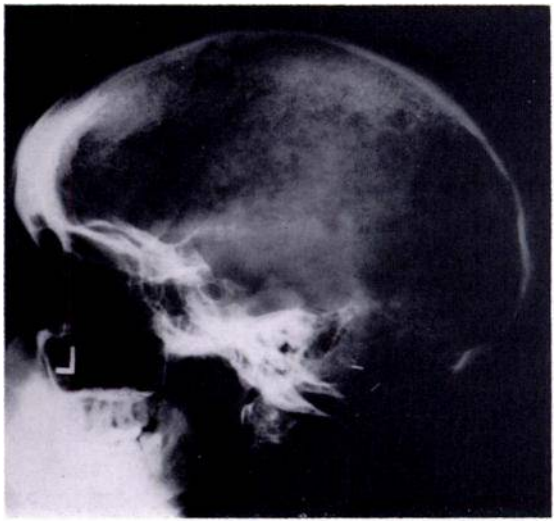

FIG. 9. L. W., roentgenogram of skull 15 years after treatment showing symptomless patchy osteoporosis probably secondary to irradiation.

treatment, the skull showed patchy osteoporosis of the parietal bones, the appearances being similar to those reported by Berg *et al.*[3] (Fig. 9). This female patient was 6 years old when treated, and is free from symptoms 15 years later.

(*b*) *Spine.* Neuhauser *et al.*[35] have reported that doses above 2,000 r of conventional roentgen irradiation (calculated at the center of the vertebral bodies) to the growing spine in children less than 2 years of age cause obvious roentgenologic changes. Rubin *et al.*[47] refer to 3 children aged 13 months to 5 years of age with medulloblastoma who each received a spinal cord dose of 3,000–3,200 r in 4 weeks with 280 kv. roentgen rays, and 1 other case, aged 4 years, who had 4,000 r in 4 weeks with 2 mev. equipment. In none of these cases were bone changes marked 2 to 7 years later.

In the present series the spine was clinically straight, and there were no obvious roentgenologic changes in any of the 12 cases recently re-examined 3–17 years after radiotherapy; their ages at the time of treatment had ranged between 2 and 13 years with 9 children less than 8 years. In some patients there may be reduction of stature but this is not marked. In our experience there appears to be little risk of producing serious disorders of bone growth following spinal irradiation (3,000 r skin dose) for medulloblastoma.

(*c*) *Eyes.* Britten *et al.*[11] have calculated that serious lens changes in adults (from radon seed implants) do not occur with doses of less than 2,000 r, but invariably follow 4,000 r or more. Qvist and Zachau-Christiansen[42] found that the minimum dose to produce cataract in children (from radium moulds) was 1,380 r; the maximum noncataract dose for infants was 990 r, and for children of school age, 1,140 r. On the other hand, Merriam and Focht[34] found that the lowest dose to the lens from fractionated roentgen therapy which produced cataract in children aged between 1 and 5 years was 650 r, and there was a 50 per cent incidence of opacities in lenses receiving between 530 and 1,050 r. Above 1,150 r, cataract occurred in all cases irrespective of age. Fortunately, the majority of cataracts occurring below a dose of 1,000 r seem to be stationary. The lenses of children under 1 year of age appear to be somewhat more sensitive to radiation than those of older children.[34]

Phantom and direct measurements have shown that the eye receives approximately 700 r from the 250 kv. technique used in our cases, which delivers a maximum tumor dose of 4,500–5,000 r to the posterior fossa in approximately 6 weeks. (With a more recent 6 mev. technique for older children we have been able to reduce the eye dose to 350 r.) No lens opacities were found in our limited material of 12 children recently examined by an ophthalmologist (Mr. J. M. Mallett) 3 to 17 years after treatment. In 27 children surviving at least 3 years, optic atrophy occurred in 5 cases, leading to impaired visual acuity in 2 and blindness in 3. This complication was undoubtedly secondary to raised intracranial pressure produced by the primary tumor.

(*d*) *Auditory Apparatus.* At this Hospital, Dias[21] has recently shown that following radical irradiation of the head and neck area there is generally no appreciable reduction in hearing as an early or late effect. In some cases slight impairment occurs, and this seems related to eustachian tube dysfunction, due either to the local effects of neighbouring tumor or to edema from radiation reaction. In the treatment of medulloblastoma, the auditory apparatus is included in the treated volume because of the necessity to extend the lateral skull fields inferiorly in order to cover the brainstem fully. Hearing was normal in 11 of our 12 cases re-examined 3 to 17 years after treatment; a long-standing and probably unrelated unilateral labyrinthine disturbance was present in the remaining case.

(*e*) *Blood.* Some degree of leukopenia is the rule, but it is uncommon for treatment to be suspended for more than a few

days on account of a falling blood cell count. Occasionally, as the result of a serious reduction in count, the course of treatment may excessively prolonged and, rarely, may have to be abandoned altogether, short of the prescribed dose. Even in such cases, full recovery of the marrow generally occurs during the ensuing months. The blood cell count (hemoglobin, total and differential white blood cells and platelets) in the 12 recently re-examined cases surviving 3 to 17 years after treatment was normal.

(*f*) *Gonads.* The dose received by the ovaries from spinal irradiation with 250 kv. roentgen rays in little girls, based on phantom measurements, is approximately 120 r. No disturbance of menstrual function was observed in our cases; one of the girls subsequently married and has a normal child now aged 2 years. In boys the scrotal region receives between 40 and 75 r (direct measurement during treatment).

(*g*) *Sexual Development.* There was no evidence of endocrine dysfunction resulting from pituitary irradiation. In those patients who have reached adult life sexual development appears to be normal, while those who are still children appear to be developing satisfactorily.

(*h*) *Malignancy.*

(1) *Leukemia.* We know of no examples of leukemia and of aplastic anemia occurring in the present series, nor in those reported in the literature. This is not surprising, since radiation-induced leukemia in, for example, patients with ankylosing spondylitis is very low – an incidence of 4 per 1,000 cases being reported over a follow-up period averaging 13 years.[12]

(2) *Thyroid Carcinoma.* There is an increased risk of thyroid carcinoma when this gland has been irradiated in childhood or infancy, such as during the treatment of thymic enlargement. A substantial increase in the expected number of thyroid tumors occurs following doses of only 100 to 400 rads.[27] Raventos and Duszynski[45] reported 2 cases of thyroid carcinoma occurring 7 and 11 years after treatment for medulloblastoma in a boy aged $4\frac{1}{2}$ and a girl aged $7\frac{1}{2}$ years, respectively.

The dose to the thyroid of a child from a direct cervicodorsal spinal field during irradiation for medulloblastoma with 250 kv. roentgen rays is approximately 1,500 r. There were no known cases of thyroid tumor in our medulloblastoma series, but 1 of our patients, a boy aged 13 years, who received cerebrospinal irradiation for a fourth ventricle ependymoblastoma has developed a well-differentiated papillary thyroid carcinoma 6 years after radiotherapy. The estimated dose received by the thyroid from the spinal field was approximately 1,700 r. The tumor has been treated by hemithyroidectomy, and the patient is alive and well, 8 years after treatment for the brain tumor and 2 years after thyroid surgery. Fortunately, radiation-induced thyroid cancer generally responds well to surgical treatment.[27]

(3) *Bone Sarcoma.* This tumor following radiotherapy is extremely rare and is nearly always associated with gross radiation changes in the bone and overlying tissues—a feature not associated with the doses generally employed in the treatment of medulloblastoma.

(4) *Intracranial Tumors.* Radiation-induced intracranial tumors are extremely rare; they are usually fibrosarcomas and develop after a latent period of 5 to 20 years. Goldberg *et al.*[25] reported 4 instances of malignancy arising 10 to 30 years after irradiation in 75 cases of acromegaly. Waltz and Brownell[54] have recently reviewed the literature and refer to a case of medulloblastoma in whom a sarcoma of the tentorium developed 5 years after irradiation (with perhaps 3,500 r).

CONCLUSION

It is still a wide belief that medulloblastoma in childhood is inevitably fatal, and exceptions to this rule have been ascribed to errors in diagnosis,[57] or even to spontaneous regression.[10] All the 82 cases

in the present series have been histologically verified, and from the inevitably fatal outcome of inadequately treated cases in the past one can discount spontaneous regression as a factor responsible for long survival in this disease. The 5 and 10 year survival rates for patients completing the course of postoperative irradiation was 39 and 31 per cent, respectively.

Serious late changes in the central nervous system and extraneurologic tissues, consequent on cerebrospinal axis irradiation, appear to be rare with the dose-time factors recommended here; 18 of 22 cases surviving 5–17 years have led active lives. Slowness in learning and behavior problems, however, occur in some cases, and in occasional long-term survivors the neurologic disability is severe. When profound changes occur they are more likely to be the result of brain damage produced by the original tumor and associated hydrocephalus than by radiotherapy.

While the serious prognosis associated with medulloblastoma is fully justified, it appears that a totally pessimistic attitude is unwarranted. Parents can be given some hope for their stricken child who, if he survives his age at treatment plus 9 months, is likely to be cured.

SUMMARY

A study has been made of 82 histologically verified cases of medulloblastoma under 15 years of age referred for irradiation to the Royal Marsden Hospital between 1950 and 1964. The age range was 11 months to 14 years. The ratio of boys to girls was 2.2:1.

The tempo of the disease is faster in children than in adults and the younger the patient the more rapidly will unsuccessful cases die. Survival rates are greater for girls than for boys. In some cases with brain-stem involvement radiotherapy can cure or control locally advanced disease for an appreciable time. There is no correlation between outcome and histologic grade of tumor. The survival rate is greater for patients in whom a "complete" surgical excision of the tumor was performed, compared with lesser procedures.

Of 68 unselected cases followed for 5 years, 22 (32 per cent) have survived, and of 34 cases, 9 (26 per cent) are alive at 10 years.

The treatment advised for medulloblastoma is surgical exploration with removal of as much of the tumor as possible without increasing unduly the operative risk. This must be followed by irradiation of the entire cerebrospinal axis. At present, a maximum dose to the cerebellum and brain-stem of 4,000–4,500 r in 6–7 weeks is recommended for children under 3 years, and 4,500–5,000 r in 6–7 weeks for older children. The "prophylactic" dose to the remainder of the brain falls from 4,000 r in the middle region to 3,000 r at the frontal poles. The spinal cord receives 2,000–2,500 r. The cases reported here have been treated with 250 kv. roentgen rays. Megavoltage equipment (6 mev.) is now being used for older children.

Although widespread intrathecal tumor is generally present in fatal cases, the chief cause of therapeutic failure in medulloblastoma is persistence or recurrence of tumor at the primary site.

The survival rate increases with higher radiation doses to the posterior fossa, but there may be an optimum level above which results deteriorate; with orthovoltage roentgen rays this level may be approximately 4,500 r.

All recurrences in this series obeyed Collins' law for embryonal tumors and produced symptoms within a period of time corresponding to the patient's age at treatment plus 9 months for gestation. Once a child with medulloblastoma passes this critical period safely, cure seems likely. Limited retreatment of tumor recurrence by irradiation in previously radically irradiated cases is justified and often brings worthwhile relief of distressing symptoms.

In spite of the many potential late complications in the central nervous system

and extraneurologic tissues associated with cerebrospinal irradiation in young children with medulloblastoma, 18 of 22 patients (82 per cent) surviving 5 years had no serious disability and were leading active lives. Two children were partly disabled, and 2 others, treated at age 11 months and 15 months, respectively, were demented. Serious neurologic sequelae are more likely to be due to the original primary tumor and its associated hydrocephalus than to radiotherapy.

While the grave prognosis associated with medulloblastoma is fully justified, it appears that some hope can be given to parents of children with this disease, since practically 40 per cent of our cases completing treatment have survived 5 years, and 30 per cent, 10 years.

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