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I. INTRODUCTION

This study was begun at the suggestion of Dr. Arthur Elvidge while the author was a Fellow in the Tumour Registry and Follow-Up Clinic. It was thought that by analyzing carefully the material gathered over a period of thirty years, and comprising the medulloblastomas and cerebellar sarcomas seen at the Montreal Neurological Institute during that time, pertinent information could be obtained concerning a) the difference in survival time in medulloblastomas and cerebellar sarcomas and b) types of treatment leading to prolongation of useful life in patients suffering from this disease. It had appeared to some of us, even at the onset of this study, that tumours classified as cerebellar sarcomas tended to occur in an older age group and that the prognosis was better in this type of tumour. Furthermore, we had the unusual opportunity of studying the subsequent course of patients treated at the Institute by two different methods, i.e. the classical or established one consisting of radical surgical removal of the tumour with subsequent radiotherapy and Dr. William Cone's method of twist drill biopsy and immediate irradiation. The late Dr. Cone felt very strongly about the inadvisability of doing a craniectomy and attempting the gross removal of the tumour since, he thought, this would only increase the chances of morbidity and seeding of the neoplasm. He had

begun using his method of twist drill biopsy and confirmation of the tumour type by stained smears, with immediate radiotherapy, some time following World War II, and consistently continued using this method until the time of his death in 1959. He was deeply interested in this problem and many hours, over a period of several years, were spent with him, Dr. Elvidge, Dr. J. Bouchard and other workers at the Institute discussing the cases analysed in this study.

In order to be able to evaluate treatment results, no cases diagnosed and treated after December 31st, 1958 are included in the present work.

No claim is being made for a clear-cut answer to the problem in the light of the present study. It is hoped, however, that it will stimulate continued interest and that eventually one will be able to draw definite conclusions concerning the best methods of treatment of this tragic disease.

II. REVIEW OF THE LITERATURE

I INCIDENCE

a) MEDULLOBLASTOMAS VERSUS OTHER INTRACRANIAL TUMOURS

Cushing (1932) reported 68 cases of cerebellar medulloblastoma among 2023 intracranial tumoura, or an incidence of a little over .5%. They make up, according to the same series, about 8% of the gliomatous tumours. In an earlier report (1930) Cushing had found 61 cerebellar medulloblastomas in 721 gliomas which would correspond to 8.4%. The cerebellar astrocytomas amounted to 9.4% of the total. Lereboullet (1932) found 51 medulloblastomas versus 29 cerebellar astrocytomas in his series but this author apparently also included tumours of the 4th ventricle in this series. Zulch (1940) reported 40 medulloblastomas versus 33 cerebellar astrocytomas. In a more recent series (1956) Zulch reported 159 patients with medulloblastomas in a total of 4000. Ringertz and Tola (1950) reported the incidence of medulloblastomas as 7.6% in a total of 1571 gliomas. Cuneo and Rand (1952) mention 32 medulloblastomas or 26.51% in a total of 83 brain tumoura in children. Kernohan and Sayre (1952) in a study of 427 cases of brain tumours in children, found that 65.8% were located in the posterior cranial fossa below the cerebellar tentorium. Of these, the distribution according to type included astrocytomas, 30.3%; medulloblastomas,

24.9%; and ependymomas, 12.5%. Henschen (1955) in his series had 66 medulloblastomas and 84 cerebellar astrocytomas. Christensen (1956) reported 93 intratentorial medulloblastomas in a total of 1928 gliomas or a percentage of 4.8%, treated at the neurosurgical clinics of the University Hospitals in Copenhagen until December 31st 1954. Pool, Ransohoff and Correll (1957), from the New York Neurological Institute, reported the incidence of medulloblastomas to be 8% in the total of gliomatous tumours.

The statistics given above, appear to establish the medulloblastomas as the third most common type of tumour in the posterior fossa after the acoustic neurinomas and cerebellar astrocytomas.

b) NEONATAL

Several cases have been reported in the literature of medulloblastomas in children shortly after birth. Seiler (1948) reported such an occurrence in a seven month old infant. Zulch (1956) reported one case in a baby three months old and ventriculographic demonstration of the tumour. Others to report on tumours in the neonatal period were Arnstein, Boldrey and Naffziger (1951) and Zondek (1954) whose patient was eight and a half months old.

It is evident from the above mentioned, that

the tumour was evidently present in the prenatal period in some of these infants.

c) AGE

Cushing (1930) reported 61 cases of medulloblastoma, in 21% of which, or 13, the patients were over the age of 16. Ten patients were between the ages of 16 and 30, and three were in the age group over 30. His oldest patient was 38. Cushing pointed out that the medulloblastomas in adults are usually associated with a longer survival period than pertains to the cerebellar medulloblastomas of childhood and suggested therefore the term neuroblastoma to designate them. Bailey, Buchanan and Bucy (1939) reported the peak incidence in cases of medulloblastomas to be around the age of five. Dyke and Davidoff (1942) reported a series of 16 cases of verified medulloblastomas in which the oldest patient was twenty four years old. They were impressed by the fact that three of their sixteen patients were over twenty years of age.

Similarly Spitz, Shenkin and Grant (1947) in a paper entitled Cerebellar Medulloblastoma in Adults, reported on 30 patients, 14 of whom were more than 30 years old. The oldest patient was 55 years old. Craig, Keith and Kernohan (1949) pointed out that medulloblastomas formed 20.1% of the tumours in childhood. Ringertz and Tola (1950) gave the average age of the patient

suffering from medulloblastoma as 13.8 years, the average age for medulloblastomas situated laterally was 17 years. The total number of cases was 111. Ingraham, Bailey and Barker (1948) in discussing 56 of their patients who had medulloblastoma stated that 42 were under ten years of age, and of these, 24 between five and ten years. The oldest patient was 65 years old. Furthermore, patients with tumours in the pons and cerebellar pontine angle averaged 60.1 years in age while patients with tumours in the midline and cerebellar hemispheres were on the average 7.5 years old.

Cuneo and Rand (1952) stated that 12 of their patients were less than six, and 6 patients were less than two, and ten patients were between 6 and 13 years of age. Pool, Ransohoff and Correll (1957) reported an age peak between 0 to 14 years.

d) SEX DISTRIBUTION

Persons of the male sex seem to be more often afflicted with this disease than those of the female sex. Bailey and Cushing (1925) gave the incidence of males to females as 2 to 1, but Cushing (1930) increased this proportion of 2 to 1 to 3 to 1 males versus females. Brody and German (1933) had 9 males and 6 females in their series. Elsberg and Gotten

(1933) had 14 males and 9 females. Elvidge, Penfield and Cone (1935) reported on a series of 19 male and 9 female patients with medulloblastomas an incidence of slightly over two to one. Cutler, Sosman and Vaughan (1936) had 14 male and 6 females with medulloblastomas. Bailey, Buchanan and Bucy (1939) reported an incidence of about 3 to 1 males versus females. Swan (1944) gave an incidence of 3 males to 1 female, 6 males to 2 females. Spitz, Shenkin and Grant (1947) were the first to report an incidence which was quite different from the one mentioned above. They had 12 male and 18 female patients afflicted with medulloblastomas, that is an inverse proportion of males to females. Their patients were generally of an older age group too. Cuneo and Rand (1952) had 13 boys and 9 girls with medulloblastomas. Christensen (1956) reported 56 males and 37 females. Henschen (1955) reported 39 males and 22 females in his series. Paterson and Farr (1953) reported an approximate incidence of 2 males to 1 female from a total number of 27 patients.

e) MEDULLOBLASTOMAS IN TWINS

There have been several mentions in the literature on medulloblastomas occurring in twins, the first mention being by Leavitt (1928). The children were apparently identical twins. Wilson and Wolfsohn (1929) reported medulloblastomas in identical twins and so did

Cushing (1930). A rather recent case has been reported by Griepentrog and Pauly (1953). Apparently there were intra and extra cranial manifestations of medulloblastoma metastases in identical uniovular twins.

f) COMPARATIVE NEUROPATHOLOGY

The occurrence of medulloblastomas in the animal kingdom has been reported on several occasions. Cordy (1953) states that up to 1953 medulloblastomas had been described in dogs on only two occasions. He adds another case, well documented, on a medulloblastoma occurring in a steer. McGrath (1956) quotes two further cases of medulloblastomas in dogs. Frauchiger and Frankhauser (1957) in their very detailed monograms on the comparative neuropathology of the human and the animal review the above mentioned cases and add another case of a cerebellar tumour in the cat which the two latter authors described as a medulloblastoma but which was diagnosed by Zulch who saw the specimen, as a peri-adventitial sarcoma, or a diffuse sarcomatosis.

II LOCATION

The origin of medulloblastomas is most frequently the roof of the 4th ventricle. This was pointed out by Bailey and Cushing (1925) and later, Ostertag (1936). Raaf and Kernohan (1944) showed the origin of these tumours to be more specifically the cell rest located at the base of the nodulus. Ostertag

(1941) demonstrated abnormal cell accumulations on the surface of the cerebellum, which, in his opinion, formed the origin of the medulloblastomas. Raaf and Kernohan (1944) found abnormal cell accumulations in the posterior medullary velum in 23 out of 104 human foetuses examined. They also made autopsy studies of medulloblastomas situated in the 4th ventricle. In 16 it could be demonstrated that the tumour actually arose there, and in 8, the tumour had its origin in the posterior medullary velum. Ringertz and Tola (1950), while agreeing that medulloblastomas probably arise from remnants of an embryonal proliferation centered near the fastigium or/and the remnants of the external granular layer of the cerebellum, pointed out that in some of their cases, the location was definitely anterior, a location not mentioned in the literature. These tumours may arise from the anterior medullary velum, which suggests that the embryonal cell proliferation may also originate there. Ringertz and Tola had 89 cases in which the location of the tumour was mid cerebellar-posterior, 6 cases in the mid cerebellar-anterior location and 16 cases in a lateral location. The medulloblastomas are not confined to the midline area of the cerebellum but can invade the cerebellar hemisphere and the cerebello-pontine angle. Cushing (1930) thought that these laterally placed tumours were more common among older patients, in whom the

chances of a longer post operative period of freedom from symptoms is somewhat greater. Spitz, Shenkin and Grant (1947) apparently concurred with this opinion in their review of cerebellar medulloblastomas in adults. No relation between the location and the course of the disease was seen by Ingraham, Bailey and Barker (1948) who, however, agreed that the location in the pons and cerebellar pontine angle was more common in the older group. Ringertz and Tola (1950) quoted some of their cases as being laterally located in the cerebello-pontine angle. The origin of such tumours according to Ringertz and Tola, is in possibly proliferating residues of the lateral medullary velum, the existence of which has been suggested by Woltman, Kernohan and Adson (1949). Other authors have mentioned the location of medulloblastomas in the cerebello-pontine angle. Among those were Akamatu (1938) and Meredith (1955).

A sizeable literature is available on the subject of location of medulloblastomas in the vermis, midline and 4th ventricle. A few of the authors are mentioned below; Bogaert and Martin (1928), Alajouanine, de Martel and Guillaume (1930), Cushing (1930), Guillain, Bertrand and Périsson (1930), Roussy, Oberling and Raileanu (1931) who amohg 15 cases reported 10 tumours located in or underneath the vermis, Rothschild (1931), Busscher and Dewulf (1933), Schwarz (1933), Guillain, Lereboullet and

Rudaux (1934), Urechia (1934), Borges Fortes and Costa Roderiguez (1938), Craig and Kernohan (1938), Spatafora (1940), Couto (1941), Spitz, Shenkin and Grant (1947), Ingraham, Bailey and Barker (1948), Ringertz and Tola (1950), Kernohan and Sayre (1952), Christensen (1956) and many others.

Among those reporting medulloblastomas primarily located in the cerebellar hemispheres were Bertrand and Girot (1929), Cushing (1930), Spitz, Shenkin and Grant (1947), Kernohan and Sayre (1952), and Christensen (1956).

The problem of cerebral medulloblastoma is a debatable one. Various authors maintain that such an entity exists. For example, in their original description of medulloblastomas, Bailey and Cushing found that these tumours were predominantly cerebellar but at the same time they described a number of cerebral medulloblastomas. In a later review of these cases they arrived at the conclusion that most, if not all of the latter were not medulloblastomas. Subsequent investigators also strongly doubted the existence of cerebral medulloblastomas. Ringertz and Tola (1950) also deny the existence of a cerebral medulloblastoma.

III METASTASES

Zulch (1956) quotes the incidence of metastases along the spine, or rather the spinal cord and nerve roots, etc., according to various authors as being

between 20 - 47.6%. Zulch also quotes three cases of medulloblastomas metastasizing to other parts of the body outside the central nervous system.

Seeding along the spinal cord and nerve roots was described by many authors among whom the following may be quoted; Roussy, Oberling and Raileanu (1931) and in the same year Cairns and Russell (1931) who pointed out that metastases spread centifugally with the CSF. After implantation on the ventricular walls or in the subarachnoid space, infiltration of the brain tissue proceeds along the vessels. The malignancy and rate of growth of the tumour tissue is of significance to the development and spreading of the metastases. Halpern (1942) reported on a case of spinal metastases with migration of cells in medulloblastoma. Abbott and Kernohan (1943) reported on six cases of spinal metastases in medulloblastomas. Poltmeteer and Kernohan (1947) in a review of 32 cases of medulloblastomas pointed out that 20 of those (47.6%) metastasized. The average age of their patients was rather high at 15.7 years. These authors pointed out that in the spinal metastases, proliferation of capillaries was commonly observed. Ingraham, Bailey and Barker (1948) found distal spinal or cerebral metastases in 10 of their 56 cases, and local extentions in 9 cases. Kalm (1948) pointed out that seeding along the spinal cord leads to absent ankle jerks and sciatica.

Tutnill (1949) reported a case of medulloblastoma with spinal cord symptoms as a first manifestation. Cuneo and Rand (1952) reported 4 patients in a total of 22 with medulloblastomas, that is 18.1%, who showed implantation to the spinal cord. These patients were respectively 2½, 6, 9, and 10 years of age. Signs of spinal cord implantation appeared 8, 9, 11 months postoperatively. Survivals were 8½ months, 11 months and 26 months after the appearance of spinal cord involvement. One of their cases showed a pressure erosion of the vertebral bodies of T3, T4, T5, T6. Elefant, Jeklerova and Lesny (1955) reported a case of compression of the spinal cord due to malignant medulloblastoma in a child and Perisic (1955) reported a case of a pinealoma with medulloblastoma of the Cauda Equina. Le Beau and Rosier (1956) reported a case of metastases to the spinal cord with an eight year interval of cure following radiotherapy and renewed cure after repeat irradiation.

Other authors describing metastases in cases of medulloblastoma were Pendergrass and Wilbur (1928) who reported on two cases of widespread metastases. Pendergrass, Hodes and Godfrey (1942) advocated irradiation of the spinal axis 4 - 6 weeks after suboccipital decompression since it was their opinion that previously implanted tumour cells are more X-Ray

sensitive than are "freely floating tumour cells" in the CSF. Alyea (1933) reported a medulloblastoma involving the kidney. This was probably a neuroblastoma. Busscher and Dewulf (1933) reported a medulloblastoma of the 4th ventricle with metastases to the tuber cinereum without an infundibular syndrome. Wohlwill (1930) reported on a medulloblastoma metastasizing to a supra clavicular lymph node. Dupin (1934) quotes a case of a 2 and 1/2 year old female child with a "neurospongioma" (medulloblastoma) who presented with metastases not only in the central nervous system but also in lymph nodes and in the liver. Winkelman and Eckel (1936) reported on a case of medulloblastoma completely filling all the other ventricles with enormous enlargement of the 4th ventricle. A clinical-pathological case reported in the New England Journal of Medicine (1939) - Cabot Case No 25481 - discussed a primary tumour of the pineal, a possible medulloblastoma. A report on the metastases of a medulloblastoma of the cerebellum into the frontal lobe came from Vodoginskaya (1940). Manlove (1946) reported on a medulloblastoma with spontaneous generalized infiltration of the pia-arachnoid. Barden and Lewey (1949) reviewed metastasizing cerebellar tumours and the difficulty in distinguishing between medulloblastoma and neuroblastoma and cited examples where the tumours had metastasized to other skeletal

structures. They pointed out the similarity in structure of medulloblastomas and neuroblastomas. Edith Paterson (1953) reported metastases of medulloblastomas to the lymph nodes. Rosenberg (1957) reported on intracerebral metastases of a medulloblastoma.

Reports of metastases of medulloblastomas to bone have appeared on several occasions in the literature. Schwartz (1933) mentioned a case of a medulloblastoma affecting the vermis cerebelli and later invasion and involvement of the spinal marrow. Similarly Nelson (1936) reported on seeding of medulloblastomas to the bone marrow. Sachs, Rubinstein and Arneson (1936) indicated that extra cranial metastases of medulloblastomas might have occurred to the sternum. Cornil, Paillas, Gastaut and Duplay (1946) reported on medulloblastomas metastasizing to bone and lymph nodes. Paterson and Farr (1953) reported three cases of metastases to the bones and lymph nodes, especially long bones and pelvis in a total of 27 patients with medulloblastomas. This is rather a high incidence. It is possible that some of the tumours alleged to be metastasizing to bone and lymph nodes are in reality cerebellar sarcomas and not medulloblastomas.

IV TUMOUR CELLS IN THE CSF

That certain types of brain tumour seed along the cerebrospinal fluid pathways was a known fact more than 50 years ago. Collier (1904), in his article on false localizing signs of intra cranial tumours, mentioned two of his cases in which it was quite obvious that the secondary deposits had been planted by the cerebrospinal fluid and which afforded important confirmatory evidence to the opinion that the main path of exit of the cerebrospinal fluid from the intradural spaces was along the spinal nerve roots. This tumour was described by Collier as a "fibro-sarcoma" and had apparently seeded from the 4th ventricle down into the filum terminale and root sheaths. Walt (1939) described a medulloblastoma in the infant with abnormal cells in the cerebrospinal fluid. Abbott and Kernohan (1943) stated that careful examination of the spinal fluid in most cases of glial tumours of the brain will disclose their component cells. Poltmeteer and Kernohan (1947) stated that desquamation of cells occurred in 47.6% of their tumour cases. Platt (1951) stated that pleocytosis is more common with cerebral tumours than with encephalitis. Burgman, Voznaia, Mitrofanova and Pershman (1955) reported on preoperative and post-operative cerebrospinal fluid in cerebellar medullo-blastomas and its clinical significance. Boyd (1957)

quoted one of her cases of medulloblastoma of the cerebellum simulating tuberculous meningitis and pointed out the presence of malignant cells in the CSF. These cells had the appearance of atypical lymphocytes. Forster (1930) demonstrated tumour cells in the CSF in cases of glial tumours and Crue (1958) reports several cases of medulloblastomas in which the diagnosis was made on spinal fluid sediment with subsequent operative verification. These cases were taken from the Yale Tumour Registry.

V SYMPTOMS AND SIGNS

It would appear impossible to review the very considerable literature on this subject in detail. However, an attempt will be made to list the most important contributions in the literature of the past 30 years or so. Detailed case histories of patients with medulloblastomas have been reported by Bailey, Buchanan and Bucy (1939), Bailey and Cushing (1925) and by Cushing in a later article on the subject in 1930.

Crue (1958) has suggested the following diagram as an outline of common signs and symptoms in cases of medulloblastoma:-

Due to generalized increased intracranial pressure

Symptoms	Findings
Vomiting	Papilloedema
Headache	6th nerve weakness
Decreased vision	Enlarged head with positive
Mother notes squint	Macewen's sign
Mother notes enlarging head	
Dizziness	
Drowsiness, stupour, coma	

Due to direct tumour pressure or destruction

Symptoms	Findings
Vomiting	Truncal ataxia
Staggering gait	Nystagmus
Suboccipital discomfort	7th nerve weakness
	Hypotonia
	Adiadochokinesia

Lereboullet (1932) found vomiting in 60% of his cases. Crue (1958) pointed out that vomiting is not in any way pathognomonic for medulloblastoma. Probably over 80% of children with all types of brain tumours have vomiting as an early symptom. Babonneix (1931) postulated that the abdominal pain sometimes seen in medulloblastomas and tumours of the 4th ventricle and associated with retching may perhaps be due to involvement around the 4th ventricle. Incidentally, cases where the final cause of death was due to perforated "Cushings"

ulcer, have been reported in the literature. One such case was by Fisher, Watkins, Gardner and Klotz (1951) who reported on a bleeding duodenal ulcer associated with cerebellar tumour in childhood (medulloblastoma). Cuneo and Rand (1952) reported headaches in 81.8% and vomiting in 91% of their cases. This appears to be, like vomiting, the most constant finding in other series. Crue (1958) points out that the bifrontal type of headaches in medulloblastoma should be differentiated from the complaint of suboccipital discomfort which usually, though not always, is a later development. There is also cervical rigidity which has been interpreted in the past as probably due to herniation of the cerebellar tonsils through the foramen magnum. Crue points out however that there must be cases where the neck rigidity is due to either direct pressure on, or invasion of the brain stem. Wolff (1950) has shown that the pain mechanism in this area is probably mediated through traction and, or other involvement of, the local vascular structures. Dow and Moruzzi (1958) quote the incidence of headaches and vomiting as the earliest signs in the vast majority of cases. Spitz, Shenkin and Grant (1947) made the point that in adults 80% of the lesions that are of hemispheral location and 75% of those in the midline begin with headaches and vomiting and that in

children the percentage is even higher.

Dow and Moruzzi (1958) state that when cerebellar signs appear they are usually those of a midline lesion and as seen in the syndrome of the flocculonodular lobe, ie. gait disturbance, rotated posture of the head, spontaneous nystagmus and disturbance of station. If the tumour involves only the hemisphere, the neurological symptoms according to Dow and Moruzzi are those seen in the syndrome of the posterior lobe of the corpus cerebelli and disturbances in the regulation of movements of the homolateral extremities results. Other signs and symptoms under the syndrome of the posterior lobe of the corpus cerebelli are reflex and postural disturbances such as hypotonia, pendular knee jerk, static tremor, disturbances in station and past pointing and spontaneous deviation of the limbs. Other disturbances, particularly involuntary movements are asthenia, delay in starting and stopping muscular contractions, disturbances in the rate of voluntary movements, dysmetria, adiadochokinesis, speech disturbances, disturbances in writing, gait disturbances, tremor of voluntary movements and loss of associated movements.

Staggering gait is another common symptom in medulloblastoma as was pointed out by Cuneo and Rand (1952) who found it in 77.2% of their cases. Grey (1957)

in his studies on the localization of cerebellar tumours reported on the significance of staggering gait, ataxia, the Romberg test and adiadochokinesia. A considerable body of knowledge has been accumulated recently concerning cerebellar functions. For good and exhaustive reviews on this subject, Fulton's physiology of the nervous system (1949) chapter 25, and Dow and Moruzzi (1958), Physiology and Pathology of the Cerebellum, should be consulted.

Cuneo and Rand (1952) quote the incidence of nystagmus in their series of cases as being 63.6% and Crue (1958) gives a similar figure of about two thirds of the cases. That the main vestibular mechanism is usually spared as the medulloblastomas rarely invade the floor of the 4th ventricle has been pointed out by Barre, Stolz and Alfandary (1929) and Barre and Metzger (1931). True vertigo is rarely found except in more adult patients. Van Gehuchten (1930) reported on the abolition of reflexes in tumours of the 4th ventricle and hypotonia. Holman (1926) reported on difficult urination associated with intracranial tumours of the posterior fossa. Papilloedema is a very common sign in medulloblastomas. Cuneo and Rand (1952) quoted the incidence of papilloedema in their series as being 72.7%. Crue (1958) gives an incidence of approximately 90%. Double vision has been reported

by Grant (1929) and the incidence of this sign is quoted as being 36.3% by Cuneo and Rand (1952). In the terminal stages, medulloblastoma may give rise to signs resulting from severe direct pressure in the region of the brain stem. For example, the cerebellar fits described by Jackson (1906) consist of retraction of the head, obvious opisthotonus and extensive rigidity of the decerebrate type affecting the extremities. That this dramatic occurrence had attracted attention even before the modern era of medical science was pointed out by Fulton (1929) who reported on a case of cerebellar tumour with seizures of head retraction described by Wurffbain (1691). Bodian and Lawson (1953) also quote papilloedema as their most common symptom in a series of 36 cases of subtentorial medulloblastomas of which 27 came to craniotomy. Bennett (1946) in his report of 45 cases of medulloblastoma between the ages of 18 and 38 with an average age of 23.5 years also listed headache, staggering gait and papilloedema among the most common symptoms and signs.

The problem of length of preoperative symptoms in patients afflicted with medulloblastoma is of some interest. Most authors are agreed that the symptomatology should be reckoned in months rather than years, although exceptions to the rule are known. For example, Cutler, Sosman and Vaughan (1936) in

their series of 20 patients with medulloblastomas have two children, aged 19 and 16 years who have had symptoms four and five years respectively. Elvidge, Penfield and Cone (1937) give an average preoperative figure of 5.2 months in 22 cases of cerebellar medulloblastoma. Ingraham and Matson (1954) reported a series of 68 children with medulloblastoma under the age of 12 years. The average preoperative duration of symptoms was from 4 - 6 weeks with a range from ten days to 14 months. Interestingly enough, the time interval is not much different in adults. Spitz, Shenkin and Grant (1947) in a series of 30 patients over the age of 16 years out of a total of 97 cases of medulloblastomas, gave an average preoperative duration of symptoms as 3.8 months with a range from 1 to 9 months. Bennett (1946) in his analysis of 45 cases of medulloblastomas in adults aged 18 to 38 years gave the length of symptoms prior to correct diagnosis as less than 6 months in 64% of the cases.

VI DIFFERENTIAL DIAGNOSIS

Crue (1958) lists among differential diagnosis, bacterial infections, virus and micotic diseases, parasites, toxins, non-neoplastic obstructive hydrocephalus, trauma, vascular malformations, cerebellar degeneration, psychiatric problems, other neoplasms and stypical tumours. It is not proposed to go into a detailed discussion of the literature with

regard to differential diagnosis. However, in the series to be reported presently and which comprises only medulloblastomas and posterior fossa sarcomas seen at this Institute, the most important differential diagnostic considerations to be made were usually between trauma and medulloblastomas or abscesses or, again, other subtentorial or supratentorial tumours. It is interesting to note that supratentorial tumours sometimes masquerade as subtentorial lesions and vice versa. Guillain, Lereboullet and Rudaux (1934) reported on an acute infectious syndrome as the first manifestation of medulloblastoma of the 4th ventricle, and Van den Bergn (1953) discussed tumours of posterior fossa with supratentorial symptomatology.

VII PATHOLOGY OF TYPICAL MIDLINE CEREBELLAR MEDULLOBLASTOMA GROSS

Most of the large series discussed in the literature give an account of the gross appearance of the tumour at surgery as well as at autopsy. Cushing (1930) showed in some original sketches the appearance and location of these tumours at time of operation. Bailey, Buchanan and Bucy (1939) give a detailed description of the appearance of these tumours.

VIII MICROSCOPIC

Here again excellent descriptions are available as to the microscopic nature of medulloblastomas.

To quote a few, Elvidge, Penfield and Cone (1935), Cushing and Bailey in their earlier papers and Bailey in his 1948 editions of "Intracranial Tumours". Bailey (1935) warned against the misdiagnosis of sarcoma where the excess of connective tissue made such a misdiagnosis seem likely. Special staining methods, which were used in great numbers in the original description of these tumours by Bailey and Cushing (1925), reveal cells which are identified as various developmental stages of the immature spongioblast. Also in most instances much rarer cell types can be seen, having large spherical nuclei, and very little chromatin material. These are identified as neuroblasts in various stages of development by Bailey and Cushing (1925). Is is chiefly the occurrence of cells of both the spongioblastic series and the neuroblastic series in the tumour that resulted in Bailey naming it as he did and in his concept of its histogenesis from the undifferentiated cell of development first described by Schaper (1897). A description of the histology of medulloblastoma and the various cells found in such a tumour was given by Elvidge, Penfield and Cone (1935); this will be discussed more fully in a subsequent chapter.

IX CELL TYPE AND ORIGIN OF THE TUMOUR

a) HISTORICAL RECOGNITION

The first ones to coin the term of medulloblastoma were Bailey and Cushing (1925) who described a series of 29 tumours occurring in the posterior vermis of the cerebellum in children. It should be added that these authors first called this tumour spongioblastoma, only to find that Globus and Strauss (1925) had used this name for an entirely different type of glioma, which is now more commonly known as glioblastoma multiforme.

Olivier (1837) is thought to have been the first to describe a tumour which had the appearance of what is now commonly called medulloblastoma as far back as 1823. For quite a time after, these tumours were called sarcomas. Wright (1910) described a similar posterior fossa tumour with the term "neuroblastoma" and compared the pathology of the tumour to the developing medulla of the adrenal gland. Sarcoma is not the only name used in the days before the term of medulloblastoma was coined by Bailey and Cushing. Other terms and other names were used depending on whether the author believed the tumour originated from actodermal or mesodermal structures and again if from neuro-ectoderm, whether glioblastic or neuroclastic elements predominated. Bailey and Cushing believed that these tumours were neuroepithelial

in origin and thought that the underlying cell could differentiate into either glial or neuronal cells since they were able to demonstrate both spongioblasts and neuroblasts within some of the tumours. They concluded that these tumours were very embryonic and advanced the name of medulloblasts for the formative cells. Obviously the tumour therefore had to be called medulloblastoma. However this term was not accepted without much debate. Although most of the cells resembled those seen in the spongioblastic series, some authors classified the tumour in the neuronal series. For example, Roussy, Oberling and Railianu (1931) and Roussy and Oberling (1932), the so called members of the "French School", preferred the term "neurospongioma" rejecting the terms "neurogliocytoma", "neurocytoma," and "neuroblastoma" as there was no one stage to be demonstrated in the developing neuronal series in this tumour. Marburg (1931) also disagreed with the term of medulloblastoma. He used instead the term "sphaeroblastoma polymorphon". Marburg thought medulloblastomas to be sarcomas possibly coming from the endothelium. He regarded as proof the abundant presence of connective tissue and the tendency of these tumours to spread into mesodermal structures of the leptomeninges. However, in 1935, he changed his opinion. Ostertag (1941) thought that medulloblastomas were tumoura with multipotential

cells, from which elements of ganglion cells as well as cells of the glial series could develop. He therefore proposed as the most logical name the term neurospongioma, as Roussy did, or neurospongioblastoma. Ostertag had demonstrated abnormal cell accumulations on the surface of the cerebellum and they formed in his opinion the origin of the medulloblastomas. Stevenson (1931), and Stevenson and Echlin (1934) proposed the term "granuloblastoma", apparently believing that the tumour arose from a specific structure, the external granular layer of Obersteiner of the cerebellum. These authors had two cases of medulloblastoma localized to the cerebellar hemispheres in one of which, remnants of the external granular cell layer were seen on the surface of the cerebellum immediately beside the tumour. These authors also state that in 4 other medulloblastomas in their material the tumour cells resembled those of the external granular cell layer. Schaper (1894, 1895, 1897), Ostertag (1932) and Jacob (1927, 1928) thought Stevenson and Echlin's term of granuloblastoma unsatisfactory since these authors had already suggested that these cells of the external granular layer could form glial as well as neuronal cells. Furthermore, Bailey, Buchanan and Bucy, (1939) doubted that some of the tumours presented by Stevenson and Echlin were truly typical medulloblastomas.

The followers of the so called "Spanish School" were of the opinion that this tumour belonged primarily in the glial series and Hortega (1932) proposed the name "glioblastoma isomorphe". Hortega stated that many of the undifferentiated wandering cells which Schaper had originally described were oligodendroglial cells. In other works, Hortega (1940, 1941, 1945), described the medulloblastoma as belonging partly to the "isomorphe glioblastomas" thus emphasizing their glial nature, but partly he thought of them as neuroblastomas. Hortega found in one and the same tumour all degrees of development from the pre spongioblastic to the astrocytic form. Wohlwill (1930, 1936) pointed out that peculiar aggregations of undifferentiated cells can be found in the cerebellum primarily in the roof in the 4th ventricle. Wohlwill, as well as Elvidge, Penfield and Cone (1937) and Marinesco and Goldstein (1933) established that this tumour may contain both glial and neuroblastic cells. Wohlwill suggested the terms "unripe neurospongioblastoma", "unripe neuroglioblastoma" and "embryonaegranulocytoma". Marinesco and Goldstein (1933) described in a case which they studied in great detail, a large tumour in the midline of the cerebellum in a 5 year old boy, the presence of striated musculature. This case is important because the tumour contained besides myoblasts and striated muscle fibres, also a considerable amount of well developed neuroblasts as

well as uni- or multi-nucleated neurons. These neurons were present in such numbers that it could hardly be assumed that these cells constituted anything else but pre-existing elements. This tumour was also called a medullo-myoblastoma but it was also called a "dysembryoma". This is not an unlikely possibility.

Recent embryological work has tended to support the original bi-potential hypothesis. The term medulloblastoma is now generally accepted.

X CELL TYPE AND ORIGIN OF THE TUMOUR

a) "INDIFFERENT CELL"

The term "medulloblast" was defined by Bailey and Cushing as a bipotential indifferent cell which was capable of formation of both neurones and glial elements. This concept of a bipotential cell type was similar to the one put forward by Schaper (1894, 1895, 1897). Schaper in 1897 wrote an article in which he tried to demonstrate that the cells in the external granular layer of the cerebellum previously distinguished by Hess (1858), but now generally known as Obersteiner's layer, were such indifferent cells capable of producing both glial and neuronal elements. In recent times Raaf and Kernohan (1944a) have studied this external granular layer in the cerebellum in some detail. Histologically

these cells in no way differed from "medulloblasts".

Schaper described the "indifferent cell" as an apolar element occurring through most of the central nervous system and capable to differentiate into neural elements and glia. These "indifferent cells" were called by various names such as "Nissl's neuroglia cells without expansions", "Eisathn's indifferent cell", Rosenthal's proameboid cell", "Bonome's naked nucleus". All these were thought to be similar to Schaper's indifferent cell. However, Schaper's view was not accepted without much discussion. Although some authors such as Lugaro (1894), and Popoff (1895, 1896) confirmed Schaper's findings and especially Popoff who found such cells in the external granular layer of the cerebellum in Golgi preparations, this was denied by other authors such as His (1889) and Ramon y Cajal (1890, 1906, 1909-1911). His had stated that the cells that were the forerunners of the glial cells of the nervous system were all derived from the columnar epithelium lining the internal limiting membrane of the primitive central canal which His called primitive spongioblasts, and that all nerve cells were derived from the germinal cells which were differentiated from the time of the earliest formation of the medullary canal. As it is therefore seen there were two schools of thought. Cajal (1913) was able to demonstrate the presence of astrocytes by means of the gold chloride technique. Del Rio Hortega (1932) with

his silver carbonate method demonstrated oligodendroglia and microglia. Hortega found that many of the undifferentiated wandering cells which Schaper had originally described were oligodendroglial cells. Other authors were for a while unconvinced of the existence of an "indifferent cell" such as Bailey (1932). Penfield (1931, 1932) appeared not quite convinced of the existence of neuroblasts. The tumour cells in medulloblastomas appeared to him to have more the character of apolar spongioblasts. The investigations of Del Rio Hortega and others throw doubt upon the whole concept of the existence of the medulloblasts and Kershman (1938) showed that, while he found no demonstrative bipotential cells except the primitive neuroepithelium in the spinal cord and cerebral hemisphere, there was definitely such a cell in the cerebellum. Kershman had the advantage of being able to use more modern methods that were available to the older histologists of Schaper's period. Kershman thus confirmed the studies of Schaper, Lugaro and Popoff that indifferent cells were present in the external granular layer of the cerebellum. Kershman found that the neuroepithelium in the region of the posterior medullary velum gave rise in foetal development to a germinal bud. This soon grew out and covered the surface of the cerebellum to form the external granular layer. These cells then migrated

down into the substance of the cerebellum so that after about the age of one year the external granular layer disappeared, leaving only small collections of cells. These migrating cells could be traced through the Purkinje zone where they left behind an expansion in the molecular layer which formed the axone of the granular cell--definitely in the neuronal series. About the time of birth, however, these ingrowing cells began to stop nearer the surface and form basket cells--also of the neuronal series. But, more important, they also began at four months after the birth to be transformed into Golgi-Bergman and Fananas cells, both a type of astrocyte, definitely belonging to the glial series. Thus, both from their morphological appearance and their subsequent bipotential behavior, these cells of the external granular layer deserved the name "medulloblasts". Kershman also pointed out that it is surprising that in some medulloblastomas with neuroblastic tendency one should find nerve cells showing intracellular neurofibrils and Nissl substance. In normal granular cells the intracellular neurofibrils are difficult to demonstrate and Nissl substance does not occur. This raises the question of the basic embryonic capabilities of these medulloblasts. Raaf and Kernohan (1944) believed that Purkinje cells may also be formed by the cells of the external granular layer.

Kershman's findings appeared to conform to the clinical observation that most if not all medulloblastomas are also found in the cerebellum and Kershman quotes Bailey to the effect that they all arose in the cerebellum and that those which had been described by himself and others as occurring in the cerebral hemisphere were actually some other tumour similar in histological appearance.

b) CONCEPT OF CELL RESTS

The poiht being made that there is an undifferentiated bipolar cell in the external granular layer of the cerebellum, the next move would be to investigate the relationship of this cell with the medulloblastoma as a possible source of origin. After the first month of extra-uterine life, the germinal bud at the posterior tip of the posterior medullary velum hormally disappears, while the external granular layer usually is not found after the age of one and a half years. If one keeps in mind that the bulk of the rapidly growing medulloblastomas occur only in a later age, one must study whether there is any evidence that some of these undifferentiated cells may have remained to act as true cell rests for formation of the tumour.

The occurrence of abnormal cell collections in the region of the cerebellum has been noted by many authors. Scheinker (1939) described a medulloblastoma in a 39 year old male in whom the tumour appeared to

have its origin in the persisting external granular cells in the vermis (Obersteiner's cell layer). Meschede (1872) demonstrated the presence of peculiar conglommerations of undifferentiated cells in certain places in the cerebellum. He described three such cases. Pfleger (1880) found abnormal cellular nests in 400 cerebelli, not including some that were visible grossly and not checked histologically. Wohlwill (1921) was able to demonstrate that these abnormal clusters of cells located usually in the roof of the 4th ventricle would persist after birth. Wanke (1933) pointed out that these cell collections contained immature neuroblastic and glial elements. Ostertag (1936) and Winkelman and Eckel (1936) commented that the cells of these remnants of germinal epithelium might possibly be stimulated under suitable conditions and activated into neoplastic growths.

Raaf and Kernohan (1944) reviewed the literature and reported their investigations on the cerebelli of 161 embryos, foetuses and infants. Sections from 104 of the 161 cerebellums included the region of the posterior medullary velum. Of these, thirty-seven were young enough to show the germinal bud, which was not observed after the age of one month. Of the 104 showing the region of the posterior medullary velum, twenty-three had abnormal collections of cells in that area. Eleven of these cerebelli were from foetuses or infants of less

than a month, but the morphological appearance of these collections of cells was not that of the normal germinal bud. Of the remaining twelve cerebelli containing abnormal collections of cells, the ages ranged from one month to four and a half years. They also presented a male, age twenty-four, who had a similar anomaly. The microscopic appearance of these abnormal cells varied with age. The immature appearance was more pronounced in young persons. There was no suggestion of orderly arrangement, although occasionally rosettes and Purkinje cells were noted. The usual picture was similar to that seen in a medulloblastoma with pseudorosettes and mitotic figures.

Raaf and Kernohan then made a gross and microscopic study of the cerebelli in twenty-five cases in which the patient had died from medulloblastoma. In all twenty-five cases, the tumour was situated within the 4th ventricle. In nine of the twenty-five cases, the growth of the tumour was so extensive it could not be stated from what region the neoplasm had originated. In the remaining sixteen cases, it could be shown that the growth had come from somewhere in the roof of the 4th ventricle. In eight of the sixteen cases, the gross and microscopic examination suggested that the tumour had its origin in the posterior medullary velum and there was no evidence that in the remaining seventeen cases the growth might not have arisen in the same area. These authors concluded that,

since the site of the abnormal collections of cells and the point of origin of medulloblastomas were observed to be in the region formerly occupied by the germinal bud, medulloblastomas arise frequently, if not exclusively, from cell rests in this region. Kuhlenbeck (1950) reported similar heterotopias as seen by some of the other workers.

Brzustowicz and Kernohan (1952) continued this type of investigation in even greater detail although they were concerned mostly with gliomas in the region of the 4th ventricle; they presented some pertinent findings which are of interest to the students of medulloblastomas. The authors undertook a three-part study regarding the relationship of cell rests in the region of the 4th ventricle and the various gliomas that arise in this region. In the first part, 253 cerebellums were examined in an attempt to determine the relative frequency of all rests in different locations in this region. The ponticulus and cerebellar nodules were the most frequent sites of cell rests, the region of the posterior medullary velum having about one-tenth as many abnormal collections of cells. When this was correlated with age and sex, however, several interesting points were ascertained. The number of rests per 100 cases was twice as high in the premature infants and foetuses as it was in the viable full-term infant to adult group. But on the other hand, there did not appear

to be much decline in the number of rests in adults as compared with infants and children. In comparing males to females, there did not appear to be a statisticaly significant difference in any age group in the number of rests per 100 cases, although in the younger group, females exceeded the males slightly, with a reversal in the older age group.

In the second part of the study, they divided the cell rests histologically into mixed-rests, ependymal cell rests, rests of the external granular layer, and neuronal rests. However, in the third part of the presentation, they were unable to find any correlation between the frequency of rests or type of cell rest and a series of severty-nine cases of glioma of the fourth ventricle (43 ependymomas, 23 astrocytomas, 13 subependymal-plate gliomas).

Thus, while not conclusive, there is certainly evidence in support of the original concept that medulloblastomas arise from retained medulloblasts, similar to those of the external granular layer, acting as true cell rests.

Abbott and Kernohan (1943a) brought up the suggestion that medulloblastomas could possibly be graded histologically in view of their uniform malignancy. However, at a later date, Kernohan, Mabon, Svien and Adson (1949) and Svien, Mabon, Kernohan and Adson (1949b)

decided against the grading of these tumours in view of their histological uniformity.

Before concluding this chapter on cell type and origin of medulloblastomas, a brief chronological review of articles hitherto not discussed will be given below. This review evidently cannot make any claim to completeness.

Borst (1909) described certain tumours as glioma sarcomatodes, tumours which we would at present call medulloblastomas, without however pointing to their particular location in the cerebellum. Similarly Kaurmann (1911) discusses in his textbook certain cellular malignant gliomas without specifying, however, that they occur in the cerebellum. Langelaan (1919) thought the origin of the tumours to be the external granular layer. Zulch takes issue with the view put forward by Bailey and Cushing (1925) that "indifferent cells" are the forerunners of ganglion cells as well as the precursors of astrocytes. Zulch thinks that this theory could have been proven only when the above mentioned cells could have been demonstrated in meningeal seedings. However, the consensus of opinion seems to be that no higher forms are being differentiated in meningeal seedings. (See also the proceedings of the 2nd International Congress of Neuropathology, London, 1955). Zulch also doubts the occurrence of true

spongioblasts as Bailey described them. Zulch was never able to see similar elements. In the same year that Bailey and Cushing's first article was published, Masson and Dreyfuss (1925) described as a vermis tumour the neurogliocytom embryonale. Bailey and Cushing's views which were reiterated in 1929 did not find unanimous approval. Henschen (1955) thought that the name of medulloblastoma was ill-chosen and prefered for his part the one proposed by Ostertag, ie. Neurospongioblastoma. Yaskin (1929) described developmental anomalies in the embryonic cerebellum and pointed out their importance for the pathology. Pfleger (1933) called again attention to the "heterotopias". Singer and Seiler (1933) pointed out that medulloblastomaw were central nervous system tumours in which different degrees of maturity could be demonstrated. The stroma of these tumours according to Singer and Seiler was astrocytic glia. Honeyman (1937) critically reviewed the cellular pathology of two cases of cerebral medulloblastoma and found"that tumours morphologically identical with the infra-tentorial medulloblastomas occur also in the cerebrum." This forms part of the discussion on cerebral medullo-blawtomas which has been reviewed earlier. Doring (1939) described glial reactions in the Bergman layer. Zulch found that the cells in question were tumour cells which were progressing from the meninges along the perivascular

spaces and the Bergman fibres of the molecular layer and thus penetrating the cortex of the cerebellum. However Zulch points out that Doring thought differently about that. Hasenjager (1939) found a more pronounced vascular pattern in medulloblastomas similar to the one seen in glioblastomas. Zulch contradicts him. Zulch (1940) pointed out that he could not demonstrate true spongioblasts in medulloblastomas. The different forms of glia for example, astrocytes, which as a matter of fact often showed clasmatodendrosis, could be assumed according to Zulch, to be derived from the glia found in the cerebellum. According to Zulch, the medulloblastoma is a tumour consisting of non-fibre forming cells with very fine processes without further differentiation. Zulch also pointed out the difference between ependymal tumours and medulloblastomas in as much as ependymal tumours rarely metastasize and as a rule there is only ependymal seeding from other tumours such as medulloblastomas. Dam (1941) put forward the view that medulloblastomas are more of a biological-clinical entity than of a histological. Henschen (1955) agreed with this view. Saccone and Epstein (1948) tried to introduce a new concept or rather subdivision of medulloblastomas on the bases of detailed examination of two cases of concentricaly and expansively growing medulloblastomas in a twelve and eighteen year old.

They coined the term "granuloblastoma" because the tumours showed elements of the external granular layer. According to Saccone and Epstein, these tumours would be characterized by the formation of neuroblasts and spongioblasts. Smith (1949) demonstrated the origin of the medulloblastoma in the velum posterius of a seventeen menth old female child. This tumour according to Smith was of particular interest since it did not contain only typical medulloblastoma tissue but also ependymoma like structures. This formed adenomatous cell islands in the medullary velum, which apparently were the origin of the tumour. The author also stated that by assuming that these tumours may arise wherever there is a possibility of the presence of remnants of the external embryonal cell layer, we have an explanation of why medulloblastomas are not always localized in the midline but also developed in the cerebellar hemispheres. Ringertz (1950) described the cytoplasm as being hardly distinguishable with the ordinary staining methods. It is shown to possess a unipolar elongation. A delicate undulated process arising from the elongated poles can be demonstrated by the several silver staining methods. The medulloblasts resemble morphologically a poorly differentiated malignant cell, and these tumours are often rich in mitotic figures. Kernohan and Sayre (1952) pointed out that medulloblastomas can contain complete and incomplete pseudorosettes.

A new concept into tumour classification was introduced by Bodian (1953) and Bodian and Lawson (1953). These authors, evaluating their material at the Hospital for Sick Children in London, stated that in 51 medulloblastomas they found 36 infratentorial and 15 supratentorial tumours. Bodian and Lawson's criteria for the histological diagnosis differ from those of most other investigators. The authors state that cerebellar medulloblastomata, the supra-tentorial oligodendrogliomata and an intermediate group of hitherto unclassifiable tumours in both locations constitute a single disease entity. They arise from primitive glial precursors which are capable of a variable degree of differentiation towards either astrocytes or loigodendroglia, or both. Bodian and Lawson called this type of tumour "differentiating medulloblastoma". Bodian (1953) took issue with both the Cushing school and the Mayo clinic and stated that the neoplastic cell does not reproduce itself indefinitely at the stage of development, but is subject to the influence of one or two basic processes, differentiation and anaplasia which accounts for a considerable variability from tumour to tumour in one group, from area to area in one tumour, and at different times in the evolution of any one tumour. Bodian claims that the failure to appreciate these factors had led to the definition of each of the many cytological variants as

individual diseases and thus to the overgrown Cushing classification. He attacks as well the grading of malignancy used at the Mayo Clinic. Needless to say, Bodian and Lawson's argument have not received wide acclaim.

Henschen (1955) found glial elements and fine fibrils only in tumour border zones.

At the second International Congress of Neuro Pathology in London 1955 several interesting views were put forward as to the histogenises of medulloblastomas. O.T. Bailey (1955) thought that medulloblastomas containing rosettes and demonstrable parallel groups of neuroblastic fibres are wholly of neuroblast origin and do not arise from "indifferent cells" Christensen (1955, 1956) tried to subdivide medulloblastomas into three subgroups: 1) classical medulloblastomas; 70 cases (53 midline tumours and 17 hemisphere tumours). 2) granular cell layer type; 18 cases, of which 10 are localized to one cerebellar hemisphere and 8 to the midline. These tumours according to Christensen are characterized by smaller cells, round nuclei, but a tendency to polymorphous, polynuclear cells rather than the classical medulloblastomas. Histologically they remind one a little of oligodendrogliomas. They probably have their origin in a rest of the foetal superficial granular layer on in the normal granular cell layer in the cerebral cortex. 3) Epenymoblastoma-like

type: 5 cases. The tumour cells show a tendency to arrangement in true rosettes, the nuclei are more polymorphous, and the cells contain more cytoplasm than the classical medulloblastomas.

Prompted by Christensen's investigations and theories, Ringertz (1955) went over his material of medulloblastomas which consisted of 111 cases treated at Professor Olivecrona's clinic from 1926 to 1948. Ringertz disagreed with Christensen's classification and also denied finding the pale areas or seeing neuroblasts as described by Elvidge, Penfield and Cone (1935). Summarizing his experiences of medulloblastomas, he believes that this tumour is a pathogenetic biological entity though capable of structural variations, probably mirroring different grades of differentiation. Structurally the most differentiated medulloblastomas show a certain similarity to the least differentiated sympathetic neuroblastomas. Biologically the two kinds of tumour are different, above all with regard to metastases. The cells of sympathetic neuroblastoma are adapted to life in tissues outside the central nervous system and they metastasize abundantly in the bone marrow and other organs, while seedings of medulloblastoma cells only grow out in the tissues of the central nervous system and meninges.

In conclusion, the tissue culture and electromicroscopical work on medulloblastomas will be briefly

mentioned; tissue cultures of medulloblastomas were attempted by Russell and Bland (1933), Canti, Bland and Russell in 1937. Russell and Bland (1933) were able to culture one out of three cases of medulloblastomas. The growing cells were poor in cytoplasm and spindle shaped with one to two fine processes at one or both poles of their oval nuclei. At times these cells would appear pear-shaped or round when not differentiating. Neuroblast-like cells were not observed. In one tumour which they cultured from a histologically undifferentiated cerebellar tumour of a nine year old boy, they were eventually able to prove a medulloblastoma with spongioblastic differentiation. Zimmerman and associates have done a considerable amount of work on tumour transplantations in animals. Zimmerman (1955) pointed out in repeated experiments that medulloblastomas originate almost exclusively in the cerebellum when carcinogenic agents are placed in that area. His conclusion was that the predominance and availability to malignant change of certain glial cells in different parts of the brain evidently determined the predilection of certain gliomas in different sites.

Fernandez Moran (1956) has done electromicroscopical investigations of medulloblastomas. He found that the tumour cells showed many granules from 5 to 15 microns either isolated or in a characteristic mosaic-like arrangement.

XI OPERATIVE TREATMENT OF MEDULLOBLASTOMAS

Crue (1958) states that "In the early attempts at surgical removal of medulloblastomas before their life history was known, the gross appearance at operation led to optimistic impressions regarding a surgical cure. The inevitable recurrence must have come as a distinct surprise. After their classification, in 1925, the pathologic condition was better understood and it was found that while they looked grossly circumscribed, they were invariably microscopically invasive, malignant neoplasms with a distinct propensity for leptomeningeal implantation."

Several schools of thought developed in conjunction with the question of treatment of medulloblastomas. The so-called "radical approach" where total removal of the tumour was advocated. Bucy (1936) stated that he knew of no case of medulloblastoma which had been cured. The realization of the fact that medulloblastomas were extremely malignant and recurrent tumours led to a swing into the opposite direction. The more conservative approach put forward by Elsberg and Gotten (1933) was that after identifying the tumour and obtaining a biopsy, the main treatment should be left to the radiotherapist. The reasoning was to make a wide dissemination of the tumour less likely. Even a more conservative view was held by Cutter,

Sosman and Vaughan (1936) who, because of the high operative mortality, advocated the therapeutic trial of roentgen therapy. For discussion of the pro's and con's, see the chapter on radiotherapy. Pierce, Cone, Bouchard and Lewis (1949) have described a modified method of brain biopsy through a twist drill hole. This is discussed in the section on radiotherapy. Crue (1958) thinks that this method does not prevent the possibility of direct pressure following irradiation in the non surgically decompressed posterior fossa. Crue states "most neurosurgeons prefer to take the time and trouble, and only possibly an added risk of exploring the tumour directly, rather than attempting a blind biopsy in this hazardous area." In all fairness, however, it should be mentioned that Cutler, Sosman and Vaughan (1936) advocated a radical decompression with excision of the tentorium but without a biopsy unless the tumour is readily accessible. Ingraham and Matson (1954) do not try for a total removal, but get a biopsy in all cases. If the blockage of the cerebrospinal fluid circulation cannot be easily relieved, they recommend a Torkildsen's shunt procedure before giving X-Ray therapy. These authors use a midline incision and in the younger children, the prone, rather than the sitting position. Consensus

of opinion seems therefore that a sub occipital craniotomy and posterior fossa exploration with biopsy should be done before X-Ray therapy is begun.

a) SURGICAL MORTALITY

Cushing, up to July 1st 1931 had 68 cases of cerebellar medulloblastoma. Sixty four patients underwent 99 operations and there were 25 postoperative deaths that is a 39% mortality from surgery and a 25.2% operative mortality. Bailey, Buchanan and Bucy (1939) reported on removal in 79 of 100 cases of brain tumour in children. Only exploration and biopsy were done in cases of medulloblastoma. In 13 cases of medulloblastoma there were 2 postoperative deaths giving a 15.4% operative mortality. One child died from lack of blood transfusion, the other from postoperative infection. Elvidge, Penfield and Cone (1935) quoted an immediate postoperative mortality of 14.3% in a total of 28 cases of medulloblastoma. Sachs, Rubinstein and Arneson (1936) reported 52 operations in 35 cases of medulloblastoma. Their case mortality was 28.5% with an operative mortality of 19.2%. Davis (1942) had fifteen deaths in twenty-four patients or a case mortality of 62.5%.

Bennett (1946) reported on 45 cases of medulloblastoma in adults aged 18 to 38 years during World War II. The mortality rate in 27 patients on whom

operation or biopsy was done, was 10 patients dead within 24 hours. Grant (1956) reported on 112 medulloblastomas over the previous thirty years. There were 44 postoperative deaths for a 37% mortality rate.

XII PROGNOSIS

In view of the fact that the operative mortality in medulloblastomas is between one half and one fourth of all the cases subjected to surgical intervention, the follow up and prognosis evaluation therefore becomes only a matter of studying those who survived operation or those, who in later years survived operation long enough to begin and finish X-Ray therapy.

a) STATISTICS

Bailey and Cushing (1925) reported a case of a six year old boy who, at the time of the report, was alive four years after operation although he almost died following the irradiation period. Bailey and Cushihg (1926) reported the average survival rate following operation as being 15 months. The longest date according to this later article was seven years (two years following the operation X-Ray therapy was also given). One patient who survived for five years

and was operated on repeatedly, finally succumbed to spinal metastases. Cushing (1930) reported on sixty one cerebellar medulloblastomas in which the longest survival was five years. Of the entire sixty one cases, only three recent cases were alive. Elsberg and Gotten (1933) were in favour of biopsy only and X-Ray therapy in their cases of medulloblastoma. Their series comprised twenty three patients, in twelve cases conservative procedures being carried out, while in eleven there was operative intervention and radical removal. Their total operative mortality was 20.5% and the average survival in months was 17.5 for the group receiving conservative therapy while the group in which primary radical or radical surgery after conservative treatment was carried out, the average survival in months was 16.5. Van Wagenen (1934) in a series of 149 cases of brain tumours listed 17 cases of medulloblastoma, the average survival being 14.5 months. Elvidge, Penfield and Cone (1935) had twenty eight cases, of which four were alive, one at seven years, but in this case, Bailey, Buchanan and Bucy (1939) doubted the diagnosis. Cutler, Sosman and Vaughan (1936) had eighty-one cases made up of Cushing's sixty-one cases (1930), thirteen later cases of Cushing's, and seven cases of his own.

Of the eighty-one cases, only three survived five years or more. Fifty-four received X-Ray therapy, among which there appeared to be one death and two cases of coma following irradiation. Cutler's et al conclusions have been discussed in the chapter on radiation therapy. Cairns (1936) in a report on the ultimate results of operations for intracranial tumours had five patients die within two to nineteen months. These patients had suffered from medulloblastomas and the average survival following treatment was thirteen months. Pendergrass, Hodes and Godfrey (1942) discussed their results in the treatment of medulloblastomas. This has been amply reviewed in the section on radiotherapy. Bailey, Buchanan and Bucy (1939) reported thirty months as their longest survival of medulloblastoma. Ingraham and Bailey (1944) reported survival times of 31.5 months on the average in 13 patients who had received from 4,000 to 10,000 r. radiotherapy and a survival time of 54 months in 9 patients who had received between 10,000 and 30,000 r. One patient was still alive three years following treatment , three were alive five years after treatment, two were alive more than ten years and one was alive twenty-two years following treatment. Ingraham, Bailey and Barker (1948) reviewed their figures again and pointed out that only those patients with the long

survivals could have lived long enough to receive high doses of radiation over a long period. Since other areas than the posterior fossa were irradiated, they did not use tumour doses. Penfield and Reindel (1947) reported on a patient twenty-two years of age who had a histologically highly malignant type of medulloblastoma and in whom there was a survival of seventeen years. She had intensive postoperative X-Ray therapy and was symptom free for hine years. However, then a rapid downhill course occurred in spite of X-Ray therapy and the patient died within one year of increased intracranial pressure. Zulch doubts whether this case can really be classified as a typical medulloblastoma. He put forward the suggestion that it might be a case of meningeal sarcomatosis. Pennybacker, Northfield, Parson-Smith and Tutton (1950) listed one survivor apparently out of 57 patients, alive and well, seven years after treatment. This patient was thirty-five years of age when treated. Grant and Sayers' (1951) survival figures are discussed in the section on radiotherapy. Cuneo and Rand (1952) reported survivals from four to thirty months in thirteen patients. Zulch (1950) stated that improvement followed radical medulloblastoma removal which would last for six to eighteen months, sometimes even longer with intensive X-Ray therapy,

but relapse always occurred, often accompanied by diffuse metastases. The survival figures given by Spitz, Shenkin and Grant (1847) have been discussed elsewhere. Ringertz and Tola (1950) discussed 111 cases of medulloblastoma from Olivecrona's clinic from 1926 to 1948. The postoperative mortality was 34 per cent. The surgical mortality was lowest (21%) where radical removal was done, but these were the smallest tumours. They attempted 42 radical removals and had fifty nonradical operations. Only four patients out of 111 were alive in 1950. The longest survival was sixty-four months. They also concur with the widely held opinion that medulloblastomas in older individuals have a better prognosis than in younger. Of sixty-nine under fifteen years of age at operation, the average postoperative survival was thirteen months. Of thirty-eight over the age of fifteen, the average survival was 21.5 months. Tice and Irving (1950) listed the average survival as 21.3 months in a total of ten cases. None lived five years. Tola (1951) reported twenty-seven cases of medulloblastoma. Four were alive at fifteen, fourteen, seven and four months postoperatively. The longest survival was twenty-eight months. Bodian and Lawson, in 1953, had thirty-six cases of subtentorial medulloblastoma in children of whom thirty-two were dead and the other four were alive

less than one year after operation. Twenty-three had a partial removal of the tumour. There were twelve postoperative deaths within one month of operation. Of the remaining eleven, six had X-Ray therapy. The six receiving irradiation lived from two to twenty-four months with an average of eleven months. The other five did not receive irradiation and lived from one to five months for an average of 1.4 months. Paterson and Farr (1953) presented twenty-seven patients with cerebellar medulloblatoma from 1941 to 1950. Results of their form of treatment have been discussed in detail in the section on radio-therapy. Ingraham and Matson (1954) reported on sixty-eight cases of cerebellar medulloblastomas with no cures, all in children under the age of thirteen years. They pointed out that the reported long survivals were not in children. The authors had eighteen postoperative deaths (within one month). Forty-five patients received X-Ray therapy. Grant (1956) listed 112 medulloblastomas. Fifty-eight survived operation. Only four lived over five years, all of whom were over age fifteen at onset. These included the series already reported in 1947 by Spitz, Shenkin and Grant, where of ninety-seven cases of medulloblastoma, thirty were over age sixteen years. Lampe and MacIntyre's

results (1949, 1954) have been discussed in the section on radiotherapy. Christensen (1956) reported that thirty-six patients (39%) of all their reported cases i.e. subtentorial medulloblastomas, died in the immediate postoperative period. Eight were alive and well from fifteen months to nine years postoperatively, while of twenty-seven patients with hemisphere tumours, nine died postoperatively, four died within six months postoperatively, five were alive and well between sixteen and eighty-six months postoperatively. In midline tumours 26 patients died postoperatively and three survived three and a half to nine years postoperatively. Pool, Ransohoff and Correll (1957) reported four patients out of fifty-eight who had survived five years, none had survived fifteen years.

b) LONG SURVIVALS

Eisenhardt (1935) pointed out that not only the actual survival but the usefulness of prolonged life must be considered in long survival statistics. In Eisenhardt's series, out of seventy patients with medulloblastomas, one boy age sixteen years had survived for seven years and one month at the time of the report. This child died in 1942 and thus had a total survival of fourteen years. Ingraham and Bailey (1944) reported a patient who was treated

repeatedly surgically as well as by radiation therapy and who was well nineteen years after the appearance of her initial symptoms. Penfield and Feindel's case (1947) has been discussed elsewhere. Horrax (1954) listed one case out of twenty medulloblastomas that survived five years. Grant (1956) had four adults with medulloblastomas who had a long survival. Grant had a total of 112 cases. One case died after twelve years, three were alive after nine, twelve and seventeen years respectively. Dr. Ernest Sachs has a patient still alive twenty-four years after craniotomy with a diagnosis of medulloblastoma. Histological review of the slides showed that there was no reticulin in the sections.

The question why some medulloblastomas have such long survival times while the majority seem to lead to an early death has not as yet been settled on a statistical bases. It is possible that just as malignant changes may occur in benign lesions (de-differentiation) the reverse phenomenon may also occur, albeit quite rarely; probably in medulloblastomas as well as in other tumours such a thing as tumour host relationship may influence survival time.

XIII RELATIONSHIP OF MEDULLOBLASTOMA TO LEPTOMENINGEAL SARCOMA

Before an attempted classification of the primary intracranial sarcomas was made by Bailey in 1929, the older histopathologists called all brain tumours or rather most of them, sarcomas. Later, realizing that some of the neoplasms of the brain were neuro-ectadermal in origin, the germ glio-sarcoma was used. Virchow was the one who proposed the simpler term of glioma. The most frequent malignant glioma was called a spongioblastoma, which is now known as a glioblastoma multiforme. At that time as well as later it was considered possible to have primary intracranial sarcomas, as the meninges and blood vessels were obviously mesodermal. It was also considered to be within the realm of possibility to have primary sarcomas in the brain since lepto-meninges developed and grew in with the blood vessels. Bailey (1929) thought that primary intracranial sarcomas originated either from the leptomeninges or the surface of the brain, or from the perivascular extention of the leptomeninges which surrounded the penetrating blood vessels. He termed this perivascular extention of the meninges, the perithelium. According to Bailey there were four types of cerebral sarcoma to be recognized; perithelioma, perithelial or perivascular sarcoma, fibrosarcoma and alveolar sarcoma. Bailey described two cases which he classified as peritheliomas

and described several others in the world literature. The tumour according to Bailey was rather slowly growing and involved the leptomeningeal and perivascular spaces diffusely or locally. He then went on to describe two cases of perithelial or perivascular sarcoma and felt that the concentric rings of reticulin surrounding the blood vessels and separated by tumour cells were characteristic of intracranial sarcomas, either primary or metastatic and that the reticulin was formed by the neoplastic cells. In his third group Bailey mentioned two cases of Fibrosarcoma, the fourth and final group concerned alveolar sarcomas, the histopathological examination showing partly degenerated, but still visible cells, round or irregular shaped, arranged in alveolar structures separated by connective tissue septa.

Yuile (1938) reported a case of primary intracranial sarcoma which showed coarse reticular strands closely related to tumour cells surrounding the blood vessels. Yuile called this tumour a primary reticulin cell sarcoma of microglial origin. Bailey, Buchanan and Bucy (1939) reported five cases in their series of malignant tumours of the cerebellum in childhood calling them leptomeningeal sarcomas, perithelial sarcomas, alveolar sarcomas on the basis of the perivascular arrangement of cells and the distribution of reticulin.

Hsu (1940) recognized again four types of intracranial sarcoma; one, the sarcomatosis of the meninges. Two, alveolar sarcomas. Three, fibrosarcomas. Four, perithelial sarcomas.

Abbott and Kernohan (1943) simplified the classification in as much as they stated that the primary intracranial sarcomas could be divided into two main groups, notably the primary sarcomas and the perivascular or perithelial sarcomas. According to these authors the fibrosarcoma was to be considered as histologically identical with the malignant "stromal" type of meningioma. They would include under fibrosarcoma the cases previously reported as reticulin cell sarcoma, alveolar sarcoma, retrothelial sarcoma, reticuloendothelioma, and sarcome primitif. Abbott and Kernohan in the same article then proceeded to a subdivision of their seven cases of perivascular sarcoma, the subdivision being based upon diffuseness of invasion in the perivascular leptomeningeal spaces; perivascular or perithelial sarcoma (Group A), diffuse sarcomatosis (Group B, Type 1), diffuse perivascular sarcoma (Group B, Type 2), and true diffuse leptomeningeal sarcomatosis (Group C). Three of their tumours occurred in the cerebellum. Reticulin was found associated closely with the neoplastic cells and

the tumour cells were seen in close contact with, and apparently budding off, the adventitia of the cerebral vessels. Abbott and Kernohan observed that tumour cells appeared to be growing out of the walls of the smallest capillaries which they felt precluded the origin of the tumour from the pia mater since it had been shown by Schattenbrandt and Bailey (1928) that the pial sheath did not extend so far along the cerebral vessels. Abbott and Kernohan, concluded from the preceding evidence that perivascular sarcomas probably arise from connective tissue surrounding or located within the walls of cerebral vessels. Kinney and Adams (1943) reported two cases of primary intracranial sarcoma which they felt to be reticulin cell sarcomas. It was their contention that these two neoplasms were identical with five other cases in the literature variously diagnosed as reticulin endothelioma (Ferens, 1938), perithelial sarcoma or microglioblastoma. Kinney and Adams found that these tumours were all identical with reticulin cell sarcomas found elsewhere in the body. Furthermore, they put forward the theory that the reticulin was not produced by the neoplastic cells but was derived from fibroblasts which had been activated by the presence of neoplastic cells. Their conclusion therefore was that this form of intracranial

sarcoma was derived not from meningeal or perithelial histiocytes or the microglia, but from an earlier cell, the primitive reticulum cell. Incidentally, Bailey considered the tumour in their second case to be identical with the neoplasm reported by Hsu (1938) as an alveolar sarcoma.

Russell, Marshall and Smith (1948) reported seven cases of focal tumour-like proliferations in the brain, which they designated by the term microgliomatosis. They described three types of lesions; 1) Dense focal accumulation by a proliferation of microglial cells of the mature resting type. 2) The second tumour type was composed of one of two cell forms, an adult microglial cell or a cell with a large spheroidal nucleus which approached the ameboid form. 3) The third type of lesion contained cells which resembled ameboid microglia. These were thought to be anaplastic or dedifferentiated histiocytes. Reticulin fibrils in variable amounts were present in all tumours. Russell and co-workers felt that the tumours which they had described as microgliomas were the same as those reported by other workers, for example Benedek and Juba (1941) and similar to the reticulum cell sarcomas described by Yuile and Kinney and Adams. In Russell and co-workers' opinion, the tumour described by other investigators as peritheliomas, perivascular sarcomas, alveolar sarcomas and

perithelial sarcomas would all be identical with the microgliomas described by Russell et al.

The question of from whence the reticulin came has agitated the minds of many workers. One group of workers includes Bailey (1929), and Abbott and Kernohan (1943). The other group of investigators of whom Troland, Sahyoun and Mandeville (1950) and Kinney and Adams (1943) were the protagonists, suggested that the reticulin was of fibroblastic origin. Hanbery and Dugger in a detailed review article on the question of perithelial sarcomas of the brain (1954) agreed with the latter suggestion and thought they had some evidence to support the contention that the reticulin was fibroblastic in origin. These latter authors had observed reticulin to be present most constantly in relation to vessels either as concentric rings or diffusely spreading fibrils. Hanbery and Dugger studied in detail 13 cases of which four were situated in the cerebellum. Their conclusions were as follows: It is doubtful that the reticulum is produced by the neoplastic cells. The reticulin was usually present in relation to vessels in areas of leptomeningeal invasion or in regions containing collateral connective tissue stroma. They advocated the retention of the term perithelial sarcoma the group so designated to include those similar neoplasms which have been classified variously as

alveolar sarcoma, perivascular sarcoma, reticulin cell sarcoma, microglioblastoma and primary reticuloendothelioma.

XIV ELECTROENCEPHALOGRAPHIC FINDINGS IN POSTERIOR FOSSA TUMOURS

Following the introduction of electroencephalography as a diagnostic method in the 1930's, attempts were made to localize cerebellar tumours using this method. However, it was thought that changes seen in cerebellar tumours were too variable to be of any diagnostic significance in the electrogram. The first report to the contrary was by Smith, Walter and Laidlaw (1940) who identified a focus of slow activity in eight patients aged four to nine years. This focus was located in the mastoid area being related to the side of the lesion and disappeared after the surgical relief of the symptoms. The authors thought that those changes, or rather the disappearance of those changes, were due to the age of the patient and the fact that the tentorium was sufficiently mobile to allow direct pressure of the growing tumour to affect the occipital lobe. Holland (1921) reported similar changes in two patients. Rheinberger and Davidoff (1942) analysed the electroencephalographic findings in twenty three patients

with posterior fossa tumours, of whom twenty two were adults. They could not find any consistent pattern of abnormality although in a few cases focal abnormalities were present. Their conclusion was as follows: "We conclude that there is no pattern or distribution of electrical abnormalities specifically indicative of posterior fossa disturbance. We are also impressed with the possibility that the bilateral inequality of cortical changes arising in association with some posterior fossa lesions may be sufficiently suggestive of primary cortical abnormality, to be so interpreted by the unwary."

Cobb (1945) in reviewing 229 patients with tumours, the records of 21 of whom contained rhythmic slow waves, pointed out that these could be grouped in three categories according to the site of the lesion and the corresponding distribution of delta rhythm. When the rhythm had a unilateral focus it was found to correspond with fair accuracy to the site of the lesion, while if it was bilaterally synchronous, the tumour was either in the region of the epithalamus or upper midbrain, or in the posterior fossa. Reasons were advanced for thinking that the posterior fossa tumours were causing the associated delta rhythm by a distortion of the upper midbrain region, rather than directly, and that all the bilateral rhythms, therefore, form one group. Cuneo and Rand (1952) stated that it

was impossible to obtain a direct EEG tracing from the cerebellum; however, tumours exercise pressure on the tentorium and thus on the occipital lobes. Similar changes are seen in internal hydrocephalus that is, slow waves. Sub tentorial tumours frequently show a combination of six cycles per second and three cycles per second slow waves as well as a high degree of bilateral synchrony. This is best recorded, according to the authors, from temporal, mastoid and occipital leads. Bilateral phase reversals are occasionally encountered in the occipital lobes. Bilateral synchrony suggests a deep seated midline lesion. Cuneo and Rand said that it is not unusual to see a normal EEG in cerebellar tumours.

Bagchi, Lam and Kooi (1951) Bagchi, Lam, Kooi and Bassett (1952), Bagchi and Bassett (1952) and Bagchi (1955) pointed out that in the majority of cases the maximal EEG changes were in the opposite cerebral hemisphere in cases of cerebellar hemisphere lesions. Furthermore, the changes observed were not specific for posterior fossa tumours. The authors stated that one could state with a reasonable amount of certainty that a patient was suffering from a posterior fossa tumour only when it could be established beyond doubt that he did not have:- a) acute vascular and traumatic conditions, b) cerebral arteriosclerosis,

c) hypertension, d) "degeneration", e) generalized cortical atrophy, f) temporal lobe seizures, and g) idiopathic epilepsy. According to Bagchi and associates, all these above mentioned conditions could give rise to the same electrical abnormalities recorded in the cases of posterior fossa tumours which they studied.

Daly, Whelan, Bickford and McCarty (1953) found essentially similar abnormalities in EEG's of patients suffering from third ventricle tumours, obstructive hydrocephalus and posterior fossa tumours. The authors studied sixty six cases of posterior fossa tumours, twelve cases of tumours of the third ventricle, and nine cases of obstructive hydrocephalus. It was their impression that the principal abnormality consisted of rhythmic, bilaterally synchronous slow waves and, less often , of irregular arhythmic waves. The degree of abnormality was greater when the lesions were rapidly advancing and in younger age groups. They found no lateralization in cerebellar hemisphere tumours, and they could not confirm the earlier observations of occipital foci. It was their contention that the abnormality was due to an effect on the thalamic nuclei which in turn caused an effect on the cortical activity. Daly and associates thought that this was probably caused by a dilatation or hypertension

within the third ventricle. They concurred with the findings of previous investigators that similar changes in the cerebral activity may be seen in a variety of diffuse degenerative, toxic and inflammatory processes as well as in trauma and in epilepsy. However, given the patient with a suspected brain tumour, it is rare to find such EEG changes from a cortical lesion, and when found, such changes would be a point in favour of a deep seated lesion in the region of the third or fourth ventricles. Dow (1956) studied the findings in fifty-one patients with posterior fossa tumours and arrived at similar conclusions.

Van der Drift (1957) in an analysis of seventy posterior fossa tumours of which twenty-one were medulloblastomas, found that the abnormalities in the electroencephalogram were, on the whole, independent of the nature of the tumour. According to this author, this is probably due to the fact that these EEG abnormalities are of a diffuse character and are caused by increased intracranial pressure or by influence of the tumour on the brain stem. As the medulloblastomas, because of their more rapid growth and because of their medial localization, bring about an early interruption of the CSF circulation with consequently increased intracranial pressure, diffuse EEG abnormalities also occur at an earlier stage in these astrocytomas. Apart

from this, the EEG abnormalities are in principle the same in medulloblastomas as in astrocytomas.

Hess (1958) in a review of the electroencephalographic abnormalities found in 126 posterior fossa tumours of which 53 were situated in the cerebellum, stated that many EEG tracings were apparently normal; if abnormalities were found, then they were of a more generalized nature, predominantly temporally situated, and almost one half post central-occipitally situated. These abnormalities never consist of delta waves alone, on the contrary, they contain theta waves as well as also some beta activity. Projected delta waves are not often seen and are rarely found on several locations. However, in up to one half of the cases these waves appear rather symmetrical with a tendency toward faster rhythms. Delta foci are rare and mostly single. True epileptiform potentials are rarely seen, however atypical epileptic potentials are fairly common.

Other noteworthy studies on the subject of EEG abnormalities in posterior fossa tumours were published by Bickford and Baldes (1947), Bohm (1948), Martin and Martin (1950) and Negri (1957). Lairy-Bounes and Fischgold reported on a series of thirty-eight posterior fossa tumours in 1950, and Broglia and Postir on a review of 100 tumours of the posterior fossa and 40 tumours of the third ventricle with concomitant EEG changes (1956)

From the work cited in the preceding paragraphs it appears therefore that the EEG changes seen in cases of posterior fossa lesions are non specific and that they are most probably brought about by a dilatation or hypertension of the third ventricle due to blockage of the CSF pathways caudally. It certainly does not appear from these studies that the activity observed is related in any way to either the spontaneous or induced electrical activity of the cerebellum.

XV ROENTGENOGRAPHIC FINDINGS

a) SKULL FILMS

Reports of changes in plain skull films in cases of cerebellar tumours have appeared early in the roentgenographic literature. Helmholz (1931) found X-Ray evidence of increased intracranial pressure in 67% of children with intracranial tumours but did not report the percentage in cases of cerebellar tumours, nor what the criteria were which indicated elevated intracranial pressure. Bailey, Buchanan and Bucy (1939) found that 90% of children with intracerebellar tumours showed separation of the sutures and concluded: "With malignant tumours of the cerebellum, the sella turcica is usually unaltered; with benign tumours of the cerebellum, the sella turcica is often enlarged, and the clinoid processes eroded." McRae and Elliott (1958), in their review

of the radiological features of 50 cerebellar astrocytomas and 54 medulloblastomas occurring from birth to the end of the fifteenth year, made the following interesting points; a normal appearance of the cranial bones was seen in only six out of fifty patients with cerebellar astrocytomas. It was seen in nineteen out of fifty-four patients with medulloblastomas, approximately three times as often. Signs of acute increased intracranial pressure were seen twice as often in medulloblastomas (24 out of 54) as in astrocytomas (13 out of 50). Signs of subacute or chronic increased intracranial pressure were seen much more often in astrocytomas (31 out of 50) than in medulloblastomas (7 out of 50). It was surprising how seldom chronic pressure changes were seen in medulloblastoma. For example, in only one out of fifty-four medulloblastomas was the head enlarged. These results are probably due to the relatively rapid growth of most medulloblastomas and the relatively slow growth of most astrocytomas. McRae and Elliott then continued on to say that calcifications in medulloblastomas are rare, being present only in one of their fifty-four medulloblastomas as compared to eight of their astrocytomas. In the children with medulloblastomas, the pineal was calcified in three, and in one of these it was displaced upwards 3mm above the upper limits of normal. In children with cerebellar astrocytomas a calcified pineal was seen in four and in none was it displaced.

b) PNEUMOENCEPHALOGRAMS

McConnell and Childe (1937) have discussed the localization of brain tumours by pneumoencephalography while Gardner and Noski (1942) have pointed to the dangers of such a diagnostic method in cerebellar tumours. McRae and Elliott (1958) have reviewed the findings in fifteen patients who underwent a lumbar encephalogram out of 172 cases with air studies. They state that in none of the fifteen patients having lumbar encephalograms were the neurological symptoms and/or signs increased by the encephalogram. For lumbar encephalography, very little cerebrospinal fluid is allowed to escape and the pressure is kept as high, or higher than the original pressure. McRae and Elliott share the opinion of others that this tends to prevent downward displacement of the posterior fossa structures and tends to elevate any structures that have been depressed. It was, however, their impression that lumbar encephalography is of much less value than ventriculography in the diagnosis of cerebellar tumours except in cases where a ventriculogram shows closure of the aqueduct of Sylvius. In such cases, if the fourth ventricle fills from below, the diagnosis is non-neoplastic stenosis of the aqueduct of Sylvius. If, however, the 4th ventricle does not fill from below a posterior fossa tumour is almost surely present.

c) VENTRICULOGRAMS

Differentiation of posterior fossa lesions from those which arise in the region of the aqueduct and posterior part of the 3rd ventricle is not always easy. This has been pointed out by Paterson and Baker (1941). Walker and Hopple (1949) had two cerebellar tumours in a series of forty-five such lesions in which the diagnosis was missed because of the presence of air in the 4th ventricle on ventriculography. McRae and Elliott (1958) state that in their 157 patients who had ventriculograms, the 4th ventricle did not fill in 16 only, and it is the author's contention that 4th ventricle can be filled by ventriculography in posterior fossa tumours, even in cerebellar tumours, in nearly all cases. To accomplish this the authors use a special manoeuvre in cases where non filling of the 4th ventricle is seen in preliminary films. This maneouvre consists of lifting the patient's body from the X-Ray table and depressing the head for a few seconds with the vertex almost touching the floor. If there is still little or no gas in the 4th ventricle, the patient's head is jarred with striking the side of the occiput a short sharp blow with the heel of the right hand. This results in a sudden rotation of the skull and seems to jerk the tumour enough to let a small amount of gas pass

through the 4th ventricle. There was only one untoward effect (opening up of an unsupected temporal lobe cyst.)

The distinguishing features of cerebellar tumours in ventriculogram have been described in detail by Twining (1939), Johnson and List (1940), Lysholm (1935, 1939, 1946), Le Beau (1944) and others. Johnson and List (1940) pointed out that along with the anterior displacement of the 4th ventricle, there is a reduction in the angle formed by the aqueduct and the floor of the ventricle. Davidoff and Epstein (1955) have emphasized the value of laminography in visualizing the 4th ventricle. They think this is a very important factor since displacement in any direction may indicate the site of the tumour. These authors also outlined certain measurements which may be applied for the 4th ventricle and some surrounding bony landmarks.

McRae and Elliott (1958) found it difficult to decide when there was elevation of the aqueduct and of the posterior part of the floor of the 3rd ventricle. It was their experience that the relationship of these structures to the temporal horns as described by Johnson and List (1938) and to the angles described by Ruggiero and Castellano (1953), Sutton (1950) and Wilson and Lutz (1946), varied considerably. McRae and Elliott (1958) thought that Twining's line from the tuberculum sella to the internal occipital

protruberance was of some value.. They measured the angle between Twining's line and a second line from the tuberculum sella to the beginning of the floor of the aqueduct or to the nabenular commisure. They found it to be increased in 34 of 44 cases of astrocytoma in which it could be measured, and increased in 30 of 49 cases of medulloblastoma. This angle varied from 12 to 34 degrees in a small number of normal individuals in whom it was measured and McRae and Elliott considered any angle over 35 degrees to be an increased angle, implying elevation of the posterior part of the floor of the 3rd ventricle.

Bull (1953) reviewed the radiological findings in 33 cases of medulloblastomas. He stated that he found no reliable radiological method of differentiating the benign posterior fossa astrocytomas from the malignant medulloblastomas. Each type can grow in like situations and produce the same ventriculographic picture. This, apparently, is not McRae and Elliott's (1958) opinion. The latter authors found many irregular tumour masses projecting into the 4th ventricle in cerebellar astrocytoma and medulloblastoma but much more often in medulloblastoma. Apparently they disagree also with Lysholm (1939) who said that sometimes tumours within the 4th ventricle could be outlined by air and if the tumour surface is irregular

the most probable diagnosis is papilloma, if smooth, medulloblastoma or ependymoma. In McRae and Elliott's series, 21 out of 45 cases of cerebellar astrocytoma presented with a smooth intraventricular mass while in 51 cases of medulloblastoma 25 showed an irregular intraventricular mass. The authors conclude that an intraventricular mass with an irregular surface is much more common in medulloblastomas than in astrocytomas.

XVI RADIOTHERAPY OF MEDULLOBLASTOMAS

Attempts at radiation treatment of medulloblastomas were made as early as in the 1920's. Olivecrona and Lysholm (1926), Bailey, Sosman and Van Dessel (1928), published their experiences with radiation therapy of gliomas of the brain. In an article published in 1930, Bailey abandoned the hope that medulloblastomas could be cured by radical removal and advocated surgery and radiation therapy. It is interesting to note that Bailey had sustained the hope still in 1926 that medulloblastomas were curable by surgery alone. Tracey and Manderville (1931) reported a series of cases of cerebellar medulloblastomas in which prolongation of life was attributed to radiation therapy. Brody and German, in a report of 15 cases of medulloblastomas of

cerebellum (1933) illustrated the photomicrographic alterations which occur following radiation. According to the authors the principal change was the diffuse fibrous transformation. Brody and German stressed the point that marked proliferation of the connective tissue fibres occurs not only around the adventitia of blood vessels but actually forms the stroma of the tumour. Alpers and Pancoast (1933), Sachs, Rubinstein and Arneson (1936) published their experiences with the roentgen treatment of normal and gliomatous brain tissue. Cutler, Sosman and Vaughan (1936) in a report of 20 cases of medulloblastomas advocated a therapeutic trial of roentgen therapy, because of the high operative mortality. The authors thought that if there was a good response in a week to ten days, it would be advisable to proceed with the full course of treatment. This course of action has not been accepted by any majority of neurosurgeons and radiotherapists in view of the possibility of missing a benign but radio insensitive lesion such as, for example, a cystic astrocytoma in the cerebellum. As a matter of fact, Ingraham and Campbell (1941) reported just such a case and made the point that it may be very difficult to differentiate astrocytomas and medulloblastomas with disastrous results as far as vision is concerned. Dyke and Davidoff (1942), using the technique of Pendergrass

(see below) found an average survival time of 22.3 months for patients who have received adequate X-Ray therapy. The most intensive X-Ray therapy tended to give the longest survival time. The authors thought that there were individual variations in radiosensitivity in medulloblastomas. The primary tumours appeared more radiosensitive than the final seedings. Pendergrass, Hodes and Godfrey (1942) published a report on the radiation treatment of cerebellar medulloblastomas in 31 cases. It was the authors' contention that survival time appeared to be much longer following adequate postoperative irradiation of the entire cerebrospinal axis. The technique outlined is as follows: decompression, biopsy and histological verification of the tumour. X-Ray treatment is not given until four to six weeks later and is distributed on two cerebral, three cerebellar, and two to three spinal fields. By adequate treatment, a dose between 50 and 300 r. b.i.d. is directed onto each field, with a total dose of 2000 r. on each. The survival times given by the authors were two months without post-operative X-Ray therapy, with inadequate X-Ray treatment 9.3 months, and when the above mentioned so-called adequate treatment was given, the survival time was as long as 28 months on the average. On the basis of theoretical considerations, these authors think that

frequently implanted tumour cells are more X-Ray sensitive than are "freely floating tumour cells" in the cerebrospinal fluid. Consequently, they prefer an interval of 4 to 6 weeks before X-Ray therapy is instituted. The figures given by Pendergrass et al are somewhat better than the results of Bailey and Cushing (1925) who observed that without postoperative irradiation the average survival was seven months and that with irradiation the average was 19 months.

Frazier, Alpers, Pendergrass, and Chamberlin (1937) pointed out the advantages to be gained by a postoperative course of X-Ray therapy in medulloblastomas. In their histological study of these tumours they remarked upon the ability of some of the tumour cells to survive radiation therapy and to recur at the primary tumour site as well as in more distant places. Spitz, Shenkin and Grant in 1947, reported on their results with operative and irradiation treatment of medulloblastomas. An attempt was made in every instance to restore the circulation of the cerebrospinal fluid by unblocking the aqueduct and the 4th ventricle. This often required the removal of large amounts of tumour. All patients were given adequate radiation therapy following the unblocking, according to the methods outlined by the department of Radiology of the hospital of the University of Pennsylvania (see Pendergrass, Hodes and Godfrey, 1945).

The differences in survival rates following X-Ray therapy of medulloblastomas could of course by attributed to various factors one of which was pointed out by Craig and Kernohan (1938). These authors thought that the variations might be due not only to the type of radiation therapy used, but also the grade of malignancy of the tumour tissue itself. Portmann and Thompson in 1947 published a long survival of a patient with medulloblastoma and malignant goitre treated by roentgen therapy. Bucy (1947) appears sceptical about the chances of longterm survival in medulloblastomas, but conceded that the tumours were very radiosensitive but apt to recur..Ingraham, Bailey, and Barker in a review of 56 cases of medulloblastoma compared the size of the X-Ray dose with the survival time and found a parallelism to exist between these two. Thus, for example, with X-Ray doses of 2500 r. - 2850 r., an average survival time of 7.6 months is recorded; With a dose of 4500 r. - 9600 r. it is 31.6 months, and with 10,800 - 30,000 r. it is 54 months. The authors recommend X-Ray therapy for the spinal canal also. Immediately postoperatively, they give a total dose of 5000 r., and only repeat the treatment 6 months later if there are signs of recurrence.

Lampe and MacIntyre in 1949 presented their results with X-Ray therapy of medulloblastomas following operation.

Each patient was subjected to operation and, subsequently, to irradiation. Examination of tissue removed at operation established an unequivocal diagnosis of medulloblastoma for each of the 25 patients. The surgical procedures varied from biopsy (1 patient) to gross total removal; in most of the patients, the removal was as extensive as was considered feasible from a surgical standpoint.

The scheme of postoperative irradiation was designed (1) to irradiate the entire cerebrospinal axis in a segmental fashion, beginning with the primary site, (2) to deliver a moderately large dose of roentgen radiation to each segment and (3) to complete the treatment of each segment in a relatively short time. Treatment was begun as soon as the incision was well healed unless some postoperative complication made further delay advisable. The average interval between operation and irradiation was about ten days.

Two fields were used in irradiation of the posterior half of the skull; the inferior borders extended below the occipital bone onto the posterior surface of the neck. The anterior half of the skull was irradiated by a second pair of lateral fields. The distance, from the lower margins of the fields of the posterior half of the skull to the coccyx, was divided into three fields (7 to 12 cm. wide), so that the entire subarachnoid system of the spinal axis was

irradiated.

On the first day, 250 r. (measured in air) was delivered to one of the fields of the posterior half of the skull; on the second day and thereafter, 250 r. was administered to each of two fields. The fields in the posterior half of the skull were treated daily until a dose of 1,759 r. per field was attained. The next segment, the anterior half of the skull, was then treated in the same fashion with the same total dose. The third segment, which consisted of the upper two spinal fields, was treated next, at the same daily rate, with the same total dose. The lowest spinal field was treated by itself during the last seven days. In some patients, if the high daily dose had been fairly well tolerated, the dose to the fields of the posterior half of the skull was increased by irradiating one of these fields along with irradiation of the last spinal field, alternating treatment to the right and left side on successive days and raising the total dose to 2,000 r. or more to each field. The entire course of treatment required four and one half to five weeks. No additional irradiation was given, unless evidence of recurrence developed. The voltage was 200 kilovolts (Villard circuit), and half value layer of 0.9mm. of aluminum, was used at a distance of 50cm; the output was about 50 r. a minute as measured in air.

The results in 25 patients with medulloblastomas of the cerebellum treated by surgical removal followed with vigorous postoperative irradiation was outlined above and was as follows:- Eighteen patients were dead (17 at 38 months or less, and one at 68 months after treatment), seven (28%) were alive without evidence of neoplams, 33, 47, 50, 70, 72, 83 and 92 months after treatment. Six of the seven patients were in good clinical condition. In one patient the only surgical procedure performed was biopsy; the patient was living and well 47 months after treatment. Compared to these survival figures, Lampe and MacIntyre stated that no substantiated report could be found of a patient who was living and well more then three years after treatment where surgical removal was the sole therapy. They concluded on an optimistic note stating that the evidence suggested that medulloblastoma of the cerebellum may be a curable disease and that cure is possible only with irradiation. In an article published at a later date (Lampe and MacIntyre, 1954) the authors appeared less optimistic; when their seven cases discussed in 1949 had been followed for a longer time they noticed the development of definite manifestations of brain damage in three patients, and possibly in a fourth patient. In one patient this was not evident until seven and a half years after treatment, when convulsions first appeared. Only three

patients were living in 1954, and symptom free, but as the authors point out, even these may yet develope seizures from central gliosis. In view of these sequelae of a technique of giving high daily doses and delivering the total dose per segment in the short time of seven to ten days, they abandoned it in favour of a more protracted course of treatment, delivering to the tumour area over a period of 55 to 65 days a dose of the order of 5,000 - 6,000 r. Nevertheless, Lampe and MacIntyre still felt that the neoplasm was radio curable. They stated that none of the other workers had been able to prolong life so long in such a large percentage of cases, survival of the patient beyond three to four years being very rare. In 1958, Lampe again reviewed his experiences with radiotherapy of medulloblastomas. Of 26 patients treated from 1938 to 1946 inclusive, seven survived beyond five years. From 1947 to 1949 inclusive, nine more patients were treated with the radiation technique outlined in Lampe and MacIntyre's paper of 1949. Of these nine patients, three are survivros, one at 7 and 5/6 years and one at 9 and 1/6 years, both in good health. The third is living at nine years, and is known to be on Dilantin, indicating a convulsive disorder probably due to radiation damage. Of seven patients treated from 1950 to 1953 using a fractional technique protracted over 55 to 65 days, introducing

an estimated dose of 5,000 to 6,000 r. including posterior cranial fossa, two patients are alive at 6, and 6 and 1/3 years and two at 3 and 1/2, and 3 and 11/12 years. All four are in good health.

Turning now to other series, Engeset (1949) reported four patients in 1949, three dying less than three years after operation and irradiation and one patient 19 years of age at the time of treatment, living at 11 and 1/2 years, almost blind, this being her visual status prior to treatment.

Pierce, Cone, Bouchard and Lewis (1949) introduced a novel concept into the diagnosis and treatment of medulloblastomas. On the assumption that children suffering from this disease would do as well, or maybe even better if the trauma necessarily incident upon surgical intervention could be avoided, that the operative mortality would thus be eliminated, that with the histological diagnosis the medulloblastomas could be sorted out from other posterior fossa lesions, and thus permit the immediate institution of roentgen therapy, Dr. W.V. Cone in 1945 began to perform asperation biopsies on cerebellar lesions which clinically seemed to be medulloblastomas. In this fashion, postoperative mortality could be avoided, which is rather high in children afflicted with this disease, and who are markedly poor operative risks anyway. Furthermore, with such a biopsy, no time would be lost, in fact from four to ten days

gained in starting radiotherapy. On the other hand, the objection raised at Cutler, Sosman and Vaughan's approach (1936) who treated all posterior fossa lesions without biopsy with X-Ray treatment would not apply to the type of management advocated by Pierce, Cone Bouchard and Lewis, since a definite histologic diagnosis would be established before any sort of treatment was started. The approach used by these authors, briefly consisted of ventriculographic orientation followed by biopsy through twist drill holes in the sub occipital region. The ventriculography, incidentally, was performed also through twist drill holes placed 4 cm. from the midline and 1/3rd the distance from the inion to the glabella. The technique of the biopsy method is as follows: Under local anaesthesia, a twist drill hole using a No. 30 drill, is placed halfway between the inion and the mastoid process, just below the bulge in the occipital bone. Care is thus taken to avoid the lateral sinus. The biopsy material is then withdrawn by means of a No. 15 brain biopsy needle, inserted not to exceed a depth of 7 cms., directed into the estimated site of the tumour. Biopsy is done only if the intracranial pressure is high. This reduces possible complications from a ruptured vessel. The whole neurosurgical procedure, including shaving of the head, according to the authors, can be done in less than 30 minutes and including the time for radiographic

exposures and processing should not exceed an hour. In the case of medulloblastomas, the "brain worms" containing tumour, in the gross, are soft in consistency and have a semi translucent appearance. The tumour material is very evenly and smoothly compressed between two glass slides. The smears are then stained with eosin and methylene blue for quick study. Frozen sections can be made and studied if sufficient material is removed. Upon confirmation of diagnosis microscopically, radiation therapy can be begun within a few hours after admission.

Pierce, Cone, Bouchard and Lewis then continued on to give details about technique of irradiation therapy which have been evolved by Pierce and Bouchard several years prior to the publication of their present article. In brief, the chief objective is to deliver a tumour dose of not less than 4500 r. to the primary lesion in four weeks. To that effect, doses of 2200 - 2400 r. measured in air are usually given to each of the three major cranial fields, that is the occipital and upper half of the cervical spinal cord and the right and left temporo-parietal-occipital fields. Following completion of the cranial treatment, in the following two weeks a further 2000 r. measured in air with an estimated tumour dose of 1500 r. is administered to each segment of the spinal axis (long narrow fields, 20x cm.).

During the first four or five days of treatment, 100 r. only are given daily, to a single port, in order to avoid any undesirable intracranial radiation reaction and systemic upsets.

Subsequently the same dose is delivered to each of two ports a day, to be increased by the beginning of the second week to 150 r., in air, to each of two ports. When the time comes for irradiation of the thoracic and lumbar segments of the spinal axis, a daily dose of 200 r., in air, per field is suitable. Five children were treated in this fashion and did surprisingly well immediately following institution of the treatment. Within three to four days under roentgen therapy, these children were sufficiently improved to respond more normally. Ventricular tap may be required during the initial days of treatment but should not be necessary after the fifth day. The programme of the treatment should therefore be planned to deliver an adequate tumour dose, that is "the maximum tolerable dose" to the primary area and a considerable portion of such a dose as a prophylactic measure to every level of the spinal axis. This is in contrast to other methods of repeated and oftentimes incomplete irradiation in variable periods.

Freid and Davidoff (1951) reported on six patients with three alive at 1 and 2/3, 3 and 1/2 and 4 and 1/2 years following treatment. The last patient

was 24 years old at final treatment and was in good health at last follow up. Grant and Sayers (1951) in a series of 50 cases all of which received post-operative X-Ray therapy, had three survivals for more than three years. One, ten years of age at the time of operation, was alive eleven years later. One died of recurrence seven years after operation of recurrent neoplams. This patient was sixteen years old when operated upon. The third, aged 15 years when operated upon, died eleven years later, probably of recurrence.

Cuneo and Rand (1952) stated that the general consensus of opinion among neurosurgeons was at that time that decompression and removal of enough of the tumour to re-establish adequate cerebrospinal fluid circulation should be carried out before deep X-Ray therapy is started. The decompression provided additional space to compensate for any early swelling of the tumour which might result from irradiation. Of the authors' 22 patients, 13 received X-Ray therapy following operation. Their average survivals were between four to thirty months. One child was alive 6 years and 2 months postoperatively but had no X-Ray therapy until a final recurrence six years later.

Palmer and Murphy (1952) appeared rather sceptical about craniotomy in cases of medulloblastoma and advocated instead biopsy for verification of the diagnosis with subsequent radiation therapy because

medulloblastomas metastasize more readily in the sub arachnoid space following surgical intervention. The average survival time after diagnosis was made, and was 16 - 18 months.

The exception to the reported poor treatment results is found in several reports coming from the Radium Institute in Manchester, England. R. Paterson, classifying the medulloblastomas as so called radio-sensitive and metastasizing tumours, adopted a "whole CNS irradiation" technique. In this technique the intention is to irradiate the whole cerebrospinal system from the front of the head to the end of the membranes surrounding the Cauda Equina. Technically, this raises problems owing to the peculiar shape of the tissues to be irradiated. An attempt was made at first by the use of a series of contiguous fields with variation of the position of the fusion lines from day to day. However it was the author's impression that recurrence took place at these fusion lines and an effort was then made to irradiate the whole of the tissue in continuity. Although difficult, this was possible as the majority of the cases were children. Technically, this could be accomplished by applying a lead jacket with narrow spinal slits and irradiating the primary tumour site in the sub occipital region at the same time that the final part was treated. Using

this technique, Paterson, Tod and Russell were able to report in 1950 ten patients with medulloblastomas treated during 1940 - 1944 of whom five were known to be alive five years later; two of these were stated to be "disabled". The irradiation technique consisted of a three field arrangement in which one large field posteriorly covered the head and spine down to the second sacral vertebra, using a focus skin distance of 120-150 cm. Two anterior or oblique fields are used to raise the dose in the anterior part of the brain. The statement was made that the maximum dose to the cerebrospinal system should be 3500 r. in five weeks with the maximum skin dose kept under 5000 r. This technique was started in the middle of the reported period of 1940 - 1944. Edith Paterson (1953) also of the Manchester Radium Institute reported on 22 cases of medulloblastomas, in which she administered a minimum tumour dose of 3500 r. in five weeks or 3000 r. in three weeks. Her three year results are impressive, nine patients out of sixteen being alive after three years which is a percentage of 56%. (1932 - 1948). Her five year results are somewhat less good, but still much better than in other published series. The five year survivals (1932 - 1947) include five patients alive out of twelve which is a percentage of 42%. In another report, Edith Paterson and Farr (1953) state that between 1941 and 1950 twenty-seven patients were

treated in an undivided volume, meaning head and spine together. All were section-proved medulloblastomas. Twenty-two patients between 14 months and 13 years were treated as well as five adults between the ages of 25 and 38 years. The proportion of males to females was approximately 2 to 1. Paterson and Farr go on record saying that the full daily quota of roentgen treatment should not be given on the first two or three days of the therapy, the reasons being first of all a possible sudden post irradiation swelling of the tissues round the iter with subsequent aggravation of the symptoms of increased intracranial pressure. Secondly, secondary haemorrhage into the cerebellum may occur due to a too rapid loss of support of the blood vessels supplying the tumour. This occurred in one of their cases. They also think that sub occipital decompression is necessary because it averts the development of an acute hydrocephalus during the first one or two weeks of radiation therapy. During this period the head sutures in small children sometimes separate while in bigger children there is also definite evidence of raised intracranial pressure. Paterson and Farr give their results as follows: Surviving after three years following treatment, children and adults combined, eleven survived out of seventeen (65%). In a series of children only seven children were alive out of thirteen after three years following treatment (54%). There were seven patients in the five year

survival group, six children and one adult. At the time of the publication of the article, five patients were still alive, the longest survival being over ten years. Amongst failures, the authors found two deaths, one following a cerebellar haemorrhage and one following a CNS infection which occurred during X-Ray therapy. Twelve patients died from 6 to 61 months following X-Ray therapy, this being an average survival of 25 months. It is interesting to note that Paterson and Farr state they had three metastases to bone, lymph nodes and soft tissues, the bones involved being mostly the pelvis and long bones. This is a rather high percentage in a series of twenty-seven patients and brings up the question of whether these three metastasizing medulloblastomas may not in fact have been cerebellar sarcomas.

Similarly good survival times have been published by Richmond (1953), who irradiated cases operated at the National Hospital, Queen Square, and the Atkinson Morley Neurosurgical Unit, although he uses a different method of radiation therapy than the one outlined by the Manchester group. Richmond thinks that Paterson's method of treating the intracranial contents and the cerebrospinal axis as an integral unit at the same time is a good one but he prefers his own method which is to concentrate on the intracranial growth (usually in the infra tentorial position),

in the first instance and then follow with treatment to the spinal axis as a second stage procedure. There is, of course, the technical disadvantage of difficulty in obtaining dosage uniformity at the junctional region, but it is probable that this is more than offset by the following two considerations: a) Rapidly growing tumours such as medulloblastomas are best treated as fast as possible. b) The fact that irradiation of the spinal axis has to be stopped occasionaly on account of the low leucocyte count. It is therefore better to irradiate the main tumour site at first. The survival time as mentioned by Richmond is surprisingly good; in a total of 33 patients he had 50% survival at three years, 30% survival at four years, and 43% survival at five years. The fact that the percentage survival rate appears at a higher level at five years than at three years is explained, of course, by the fact that the figures represent interim results only. In his series of 33 patients with medulloblastomas there were twenty-five patients up to the age of sixteen. Richmond uses 4000 r. over a period of four weeks in patients over twelve years old, which is really the adult dose, and at one year he gives 50% of the adult dose. At intervening ages he calculates the dosage on a pro rata basis. Richmond does not subscribe to the contention that tumours of similar histological types should receive comparable

minimum dosages irrespective of the age of the patient. He has seen well differentiated grade 1 astrocytomas prove highly sensitive to irradiation. Furthermore, it is obvious that the tolerance to radiotherapy of both intra and extra-cranial tissues of a baby must be appreciably lower than those of a fully developed adult.

Christensen (1956) in a review of 93 patients with medulloblastomas, concludes that the best results are obtained by surgical removal plus postoperative irradiation to the posterior fossa and the cerebro-spinal axis.

Le Beau and Rosier (1956) published an interesting case of a cerebellar medulloblastoma with apparent cure following operation and radiotherapy. Eighteen months later, spinal metastases appeared and were again treated and cured by radiotherapy. There was a free interval of eight years following which secondary tumour deposits to the right frontal region were discovered. Following further therapy this was again arrested.

XVII POST IRRADIATION DAMAGE TO THE CENTRAL NERVOUS SYSTEM

A fairly substantial literature is available on the subject of post irradiation damage to the CNS. There have been reports of post irradiation necrosis and CNS damage following radiotherapy of medulloblastoma.

Fischer (1922) reported a patient with a vermis glioma who, after receiving one single X-Ray treatment became comatose and died. At autopsy, cerebellar tonsillar coning was found. Fischer attributed the herniation directly to the effect of the radiotherapy and concluded that posterior fossa tumours are a definite contra-indication to radiation therapy. This case was quoted in turn by Béclére (1926) and Richmond (1953). Lampe (1954, 1958) reported on twenty-six patients treated from 1938 to 1946 inclusive as outlined in his paper of 1949. Out of this group, seven survived beyond five years, six showed post irradiation damage such as progressive mental and physical deterioration, epileptic seizures and failing vision. He concluded that in this above mentioned first group four patients out of seven survivors showed definite brain damage. Following Lampe's change of irradiation technique there were less post irradiation sequelae but nevertheless he reports that two of his six year survivors were slow in learning at school. Paterson, Tod and Russell (1950) reported ten medulloblastomas treated, with five known to be alive at five years, of which two are stated to be disabled. Edith Paterson (1953) states that treatment is usually well tolerated, with few after effects. In one or two of the children an effect on the epithyses has been demonstrated as a decreased growth of the spine years after treatment.

The mental level of the children following irradiation is apparently the same as before commencement of treatment. There was one exception in Edith Paterson's series, a child who was admitted in convulsions and was completely disorientated during her entire stay in hospital and who is now sub normal. In this case, permanent damage had probably already occured. Sometimes these children are unstable emotionally for several months but this is not seen exclusively in medulloblastoma cases. This is a transient symptom. Paterson and Farr (1953) state that it had not been possible to ascertain whether sterility occurs after treatment in females. Suggestive evidence pointing to an effect on the gonads was a temporary amenorrhoea of two years duration in one patient aged thirty-eight. No effects would be expected on the male gonads.

Molter, Henry and Brinaye (1956) reported a case of lesions in a child irradiated for a medulloblastoma of the cerebellum.

XVIII EXPERIMENTAL INVESTIGATIONS OF RADIOTHERAPY IN MEDULLOBLASTOMAS

Fowler, Gammill and Martin (1954) reported on distribution studies of intrathecally injected radioactive colloidal gold in cats and therapeutic implications for the medulloblastoma and other tumours

with meningeal metastases. Ten adult cats were given 2 millicuries per kilogram of radioactive colloidal gold by cisternal puncture with no adverse clinical sequelae to date. The colloid became distributed throughout the subarachnoid system, as demonstrated by scintiscanning and autopsy observations. The colloid was almost completely removed from the cerebrospinal fluid within 3-4 hours after injection and was deposited predominantly in the pia-arachnoid as demonstrated by microscopic examination, radioautographs, and quantitative radioactivity determinations on measured areas of the meninges and underlying nervous tissue.

It would seem reasonable to consider the possibility of injecting the radioactive colloid into the ventricles and the lumbar subarachnoid space immediately following the radical excision of a medulloblastoma. If this were done in the first crucial minutes the small aggregates of tumour cells, their viability already compromised by separation from their blood supply, would be circulating in a radioactive milieu of spinal fluid containing millions of point sources of beta and gamma radiation. Also, as practically all of the colloidal gold is taken up by the leptomeninges within the first three hours after injection, tumour cells reaching any area of the meninges might be subjected to highly localized radiation

and the initiation of metastases prevented.

Following cisternal injection only insignificant amounts of the colloid gain entrance into the ventricular system and the concentration in the lumbar region is also poor. This difficulty could probably be overcome by administering the colloid via the ventricular and lumbar routes, thus providing high radiation levels in the lumbar sac and the floor of the third ventricle, both of which are frequent sites of metastases.

One advantage in this method of irradiation is that the entire cerebrospinal fluid system is simultaneously treated, so that no matter in what direction the tumour cells may circulate, they will be subject to close range irradiation. Also, since the radiation effect is largely confined to a zone about 2mm. in width on either side of the leptomeninges, the danger of bone marrow depression from the effects of roentgen therapy to the spine is largely obviated. Because this zone of irradiation is so limited, deep roentgen therapy to the primary site of the lesion as well as the administration of intrathecal colloidal gold should be considered if the tumour cannot be completely removed at operation.

The length of survival of the animals in this experiment does not permit adequate evaluation of the potential dangers of this method of therapy. One of

the most obvious of these is the effect on the blood vessels penetrating the pia-arachnoid to supply nervous tissue. The possibility of producing a reaction within the walls of these vessels and their subsequent occlusion would seem to be a serious consideration. Investigation of this possibility can only be carried out on long term survivors as the effects of radiation are known to be progressive even after the disappearance of significant amounts of radioactivity.

III. MATERIALS AND METHODS

From 1926 to December 31st, 1956, that is over a thirty year period, 109 medulloblastomas and 20 cerebellar sarcomas were submitted to the department of neuropathology of the Neurological Institute in Montreal and thus classified. This amounts to 4.05% of a total of 2443 intracranial tumours examined during the same period of time by the department of neuropathology of the Institute (Fig. 1).

Montreal Neurological Institute. 1928-1958

Medulloblastomas	109
Cerebellar sarcomas	20
Total	129

4.05% of 2443 intracranial tumours

Fig. 1.

It is recognized that the existence of a separate entity of cerebellar tumours histologically very similar to, if not identical with, medulloblastomas has been a controversial subject for some time and the question has not yet been satisfactorily settled. Hanbery and Dugger (1954) suggested that the term perithelial sarcoma (Bailey, 1929) be retained to include similar tumours variously classified as primary reticuloendothelioma (Ferens, 1938), microglioblastoma (Ruile, 1938, Benedek and Juba, 1941), reticulum cell sarcoma (Kinney and Adams, 1943), perivascular sarcomas (Abbott and

Kernohan, 1943) and alveolar sarcoma (Bailey, 1929). Recently, Smith, Lampe and Kahn (1961) after reviewing the literature and evaluating their own therapeutic results, felt that from a practical clinical viewpoint, cerebellar sarcomas were not distinguishable from medulloblastomas and that the distinction of these sarcomas from medulloblastomas, usually on the basis of the reticulin stain on histopathological examination, was still a debatable point.

The percentage of medulloblastomas in 1522 gliomas (Montreal Neurological Institute series, 1957) amounted to 6.7%, which is comparable to the percentages of other large series, such as Ringertz and Tola (1950) who counted 7.06% or 111 medulloblastomas in a total of 1571 gliomas, or Christensen's series of 4.8% or 93 medulloblastomas in a total of 1928 gliomas (1956) (Fig. 2).

In our series, follow-up was obtained in 128 of the 129 cases reviewed (medulloblastomas and cerebellar sarcomas) i.e. 99.2%, one patient returning to her native Norway after operation and thus not traceable.

In the medulloblastoma group, 4 cases were not treated and there were 22 post-operative deaths (i.e. patients who died within one month following operation) (Fig. 3).

Medulloblastoma - post-operative deaths

(death within one month post-op.)

Total No.	Post-op. deaths
109	22

Fig. 3

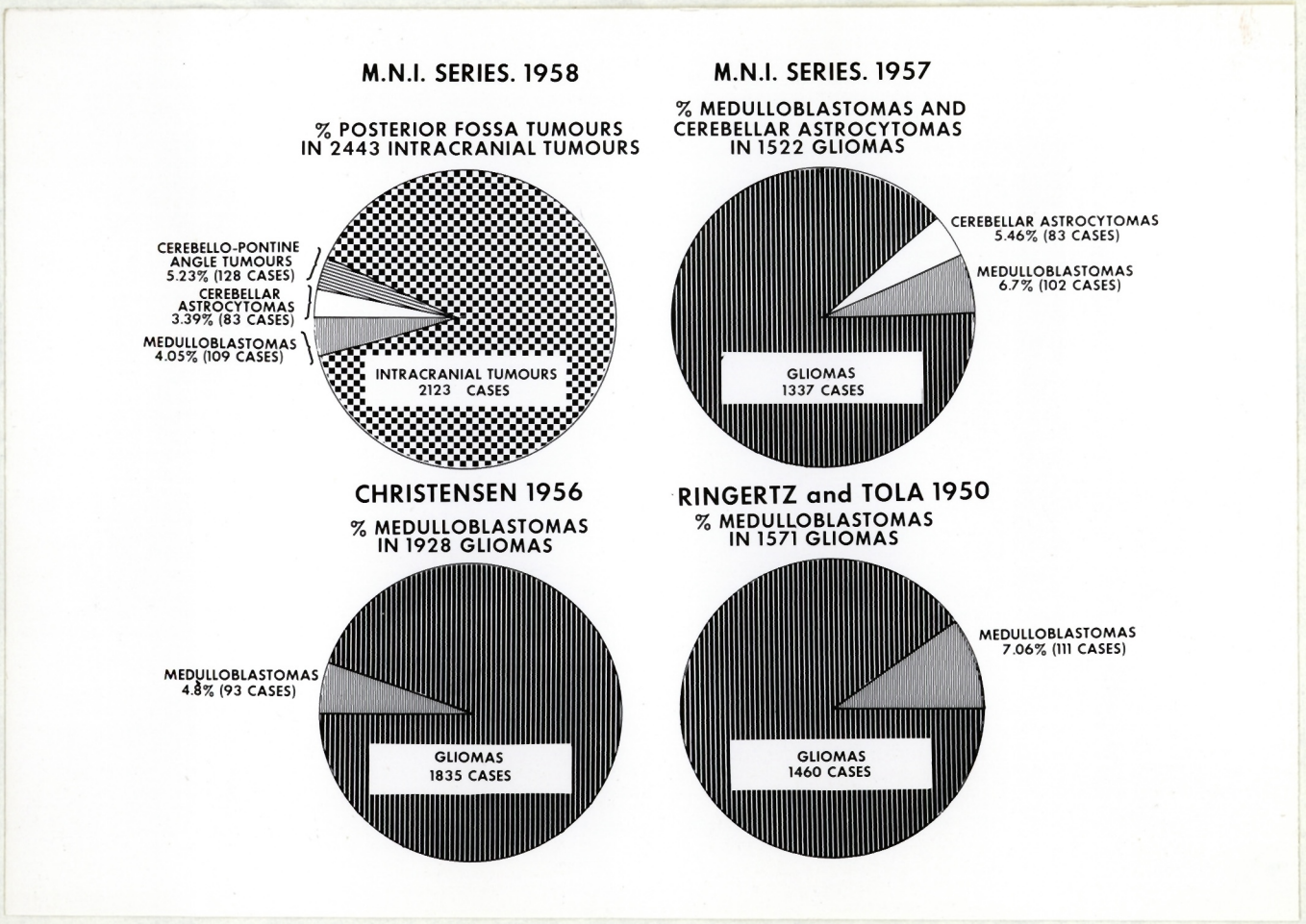

M.N.I. SERIES. 1958
% POSTERIOR FOSSA TUMOURS
IN 2443 INTRACRANIAL TUMOURS
CEREBELLO-PONTINE
ANGLE TUMOURS
5.23% (128 CASES)
CEREBELLAR
ASTROCYTOMAS
3.39% (83 CASES)
MEDULLOBLASTOMAS
4.05% (109 CASES)
INTRACRANIAL TUMOURS
2123 CASES
M.N.I. SERIES. 1957
% MEDULLOBLASTOMAS AND
CEREBELLAR ASTROCYTOMAS
IN 1522 GLIOMAS
CEREBELLAR ASTROCYTOMAS
5.46% (83 CASES)
MEDULLOBLASTOMAS
6.7% (102 CASES)
GLIOMAS
1337 CASES
CHRISTENSEN 1956
% MEDULLOBLASTOMAS
IN 1928 GLIOMAS
MEDULLOBLASTOMAS
4.8% (93 CASES)
GLIOMAS
1835 CASES
RINGERTZ and TOLA 1950
% MEDULLOBLASTOMAS
IN 1571 GLIOMAS
MEDULLOBLASTOMAS
7.06% (111 CASES)
GLIOMAS
1460 CASES

FIG. 2

Of these 22 post-operative deaths, twelve occurred following radical removal, 1 following partial removal and irradiation, 6 partial removal without radiotherapy, 2 were needle biopsies with radiotherapy, and one underwent needle biopsy followed by right ventriculo-peritoneal shunt (Fig. 4).

Medulloblastoma - post-operative deaths

Following radical removal	12
Following partial removal & irradiation	1
Following partial removal, no irradiation	6
Following twist drill biopsy & irradiation	2
Following twist drill biopsy & v-p shunt	1
Total	22

Fig. 4

Of the patients suffering from medulloblastoma and surviving longer than one month following the operative procedure, 7 had radical removal without radiotherapy, 47 had radical removal with radiotherapy, 7 had partial removal without radiotherapy, 11 had partial removal with radiotherapy, 10 had biopsy followed by radiotherapy, one of whom was a biopsy by craniotomy and the other nine, twist drill biopsies, and one patient was treated by ventriculo-peritoneal shunt. (Fig. 5).

Medulloblastomas. Types of treatment.

Radical removal without irradiation	7
Radical removal with irradiation	47
Partial removal without irradiation	7
Partial removal with irradiation	11
Needle biopsy with irradiation	10
Total	88

Fig. 5

Of the cerebellar sarcoma group, one was not treated, one died within the month following twist drill biopsy without radiotherapy, thus constituting a post-operative death. Ten had radical removal with radiotherapy, 2 had twist drill biopsy with radiotherapy, one had laminectomy and removal of secondary tumour deposit, without treatment of the primary lesion which was thought to be a third ventricle tumour on ventriculography, but at autopsy turned out to be a cerebellar sarcoma which had seeded through the shunt tube into the peritoneal cavity. (Fig. 6).

Cerebellar sarcoma. Types of treatment.

Not treated	1
Post-op death (T.D. biopsy without radiation)	1
Radical removal with radiotherapy	10
Partial removal without radiation	3
T.D. Biopsy with radiation	2
Laminectomy	1
Ventriculo-peritoneal shunt	1

Fig. 6

Age and Sex Incidence

In the medulloblastoma group, the highest incidence occurred in patients aged between five and seven, with a peak at six years of age. (Fig. 7).

In the incidence is computed on the basis of decades, the highest incidence was noted in the first decade with 65 cases, of whom 40 were male and 25 female. In the second decade there were 18 male and 7 female. In the third decade 7 male and 6 female, in the fourth decade 3 male and 2 female and one male patient was in the 51 - 60 age group. (Fig. 8).

AGE & SEX INCIDENCE
IN 109 CASES OF MEDULLOBLASTOMAS.
FEMALE
MALE
NO. OF CASES
AGES
0
1
2
3
4
5
6
7
8
9
10

FIG. 1

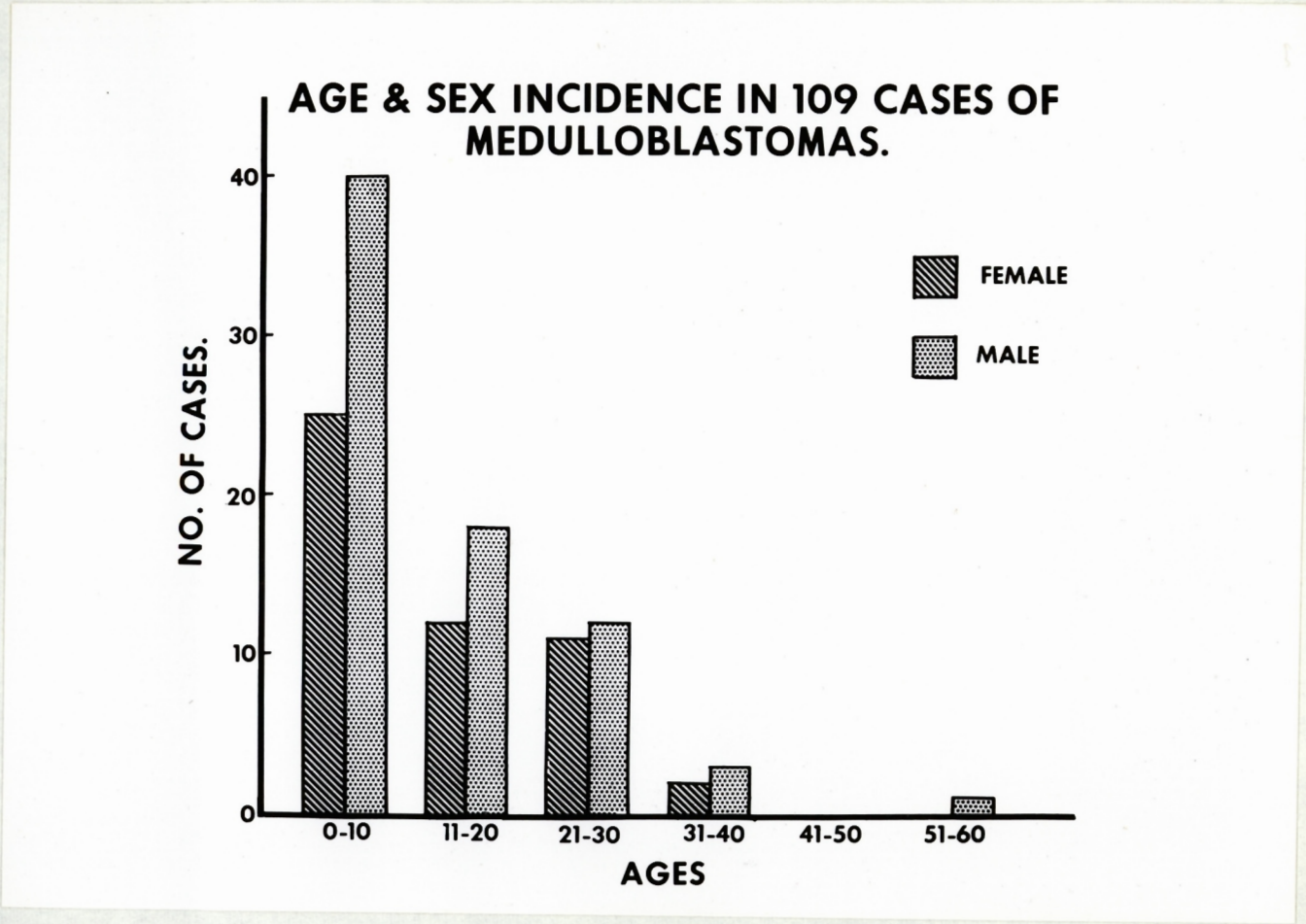

AGE & SEX INCIDENCE IN 109 CASES OF MEDULLOBLASTOMAS.
NO. OF CASES.
40
30
20
10
0
FEMALE
MALE
0-10
11-20
21-30
31-40
41-50
51-60
AGES

FIG. 8

In the sarcoma group the highest incidence was in the first and third decade. Contrary to the medulloblastoma figures, there were more female than male patients in the group. The youngest case of medulloblastoma was a three month old infant who was not operated upon, the tumour being found at autopsy. The oldest case was a man of 55 years. (Fig. 9).

Male incidence was 67.8% in the medulloblastoma group, 40% in the sarcoma group. (Fig. 10).

Sex Incidence

Medulloblastoma	67.8% males
Cerebellar sarcoma	40% males

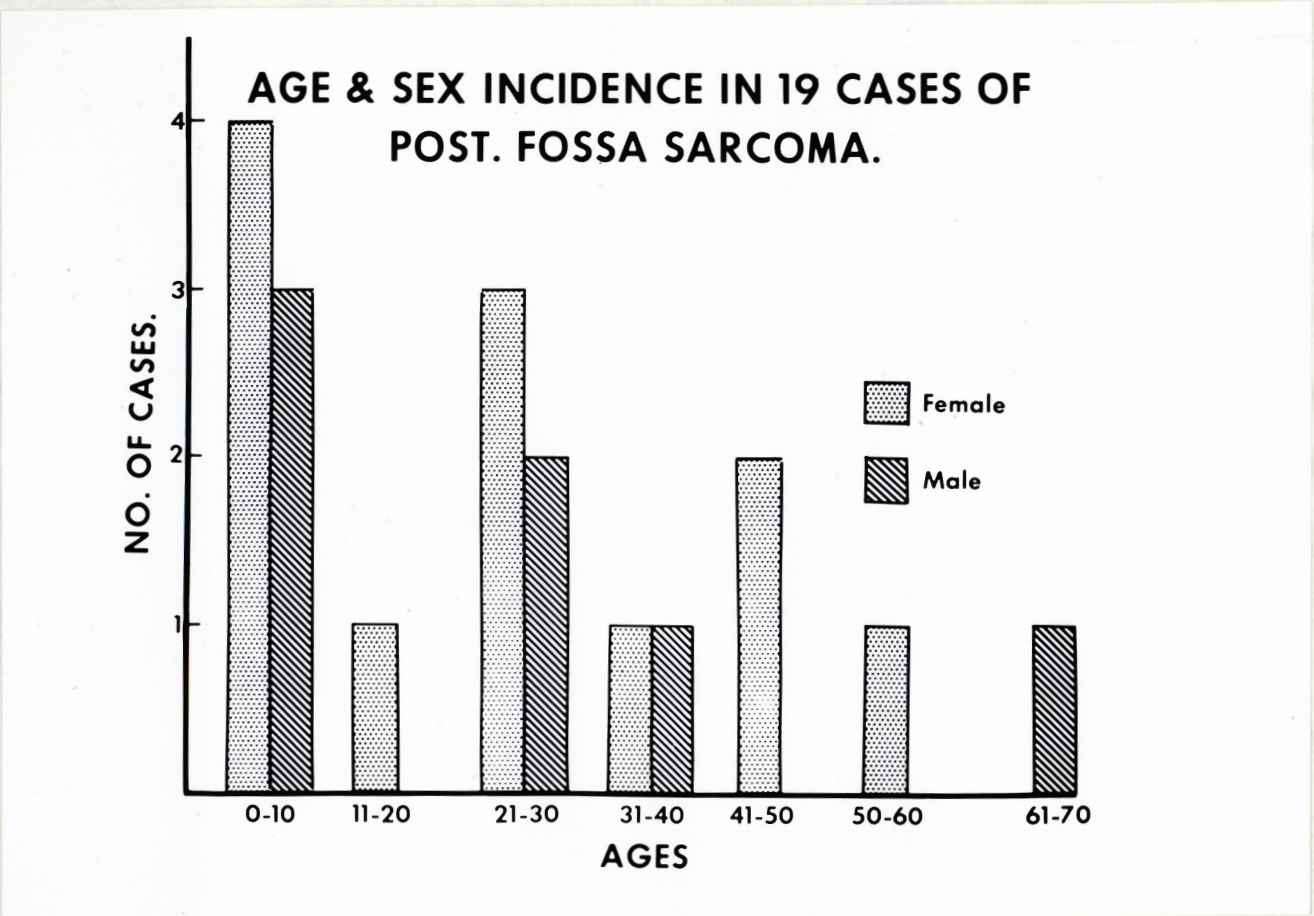
Fig. 10

Location of Tumours

Location of these tumours has been classified according to the findings at operation. Out of 109 medulloblastomata, 36 were confined mainly to the midline fourth ventricle and vermis, 23 to the hemisphere and the remaining 50 were combined. (Figs. 11 and 12).

In the sarcomata group of the total of twenty, 5 were found to be in the midline, fourth ventricle and vermis, 6 in the hemisphere and 9 were combined.

FIG. 9


AGE & SEX INCIDENCE IN 19 CASES OF POST. FOSSA SARCOMA.
NO. OF CASES.
4
3
2
1
Female
Male
0-10
11-20
21-30
31-40
41-50
50-60
61-70
AGES

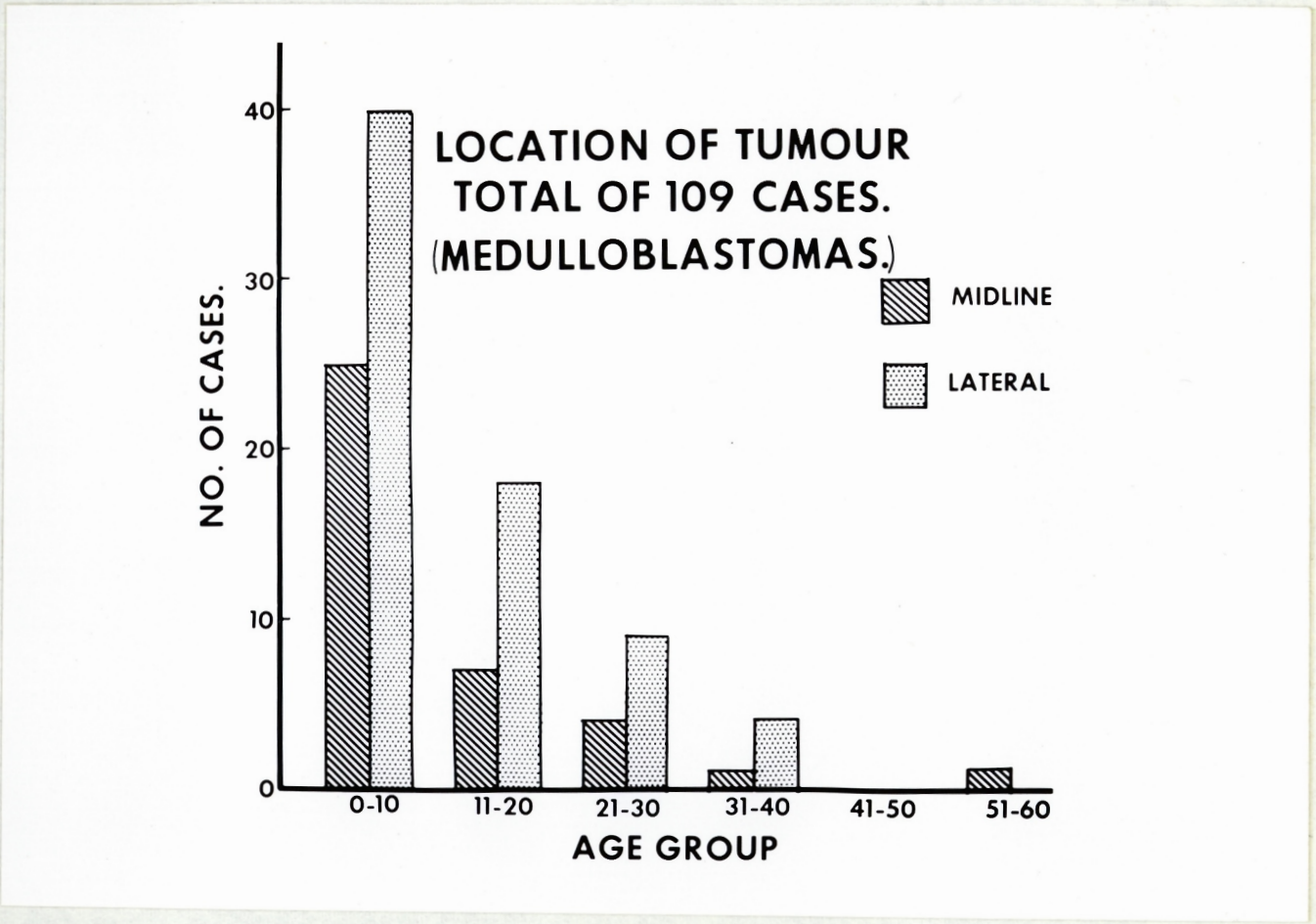

LOCATION OF TUMOUR
TOTAL OF 109 CASES.
(MEDULLOBLASTOMAS.)
MIDLINE
LATERAL
NO. OF CASES.
40
30
20
10
0
0-10
11-20
21-30
31-40
41-50
51-60
AGE GROUP

FIG. 11

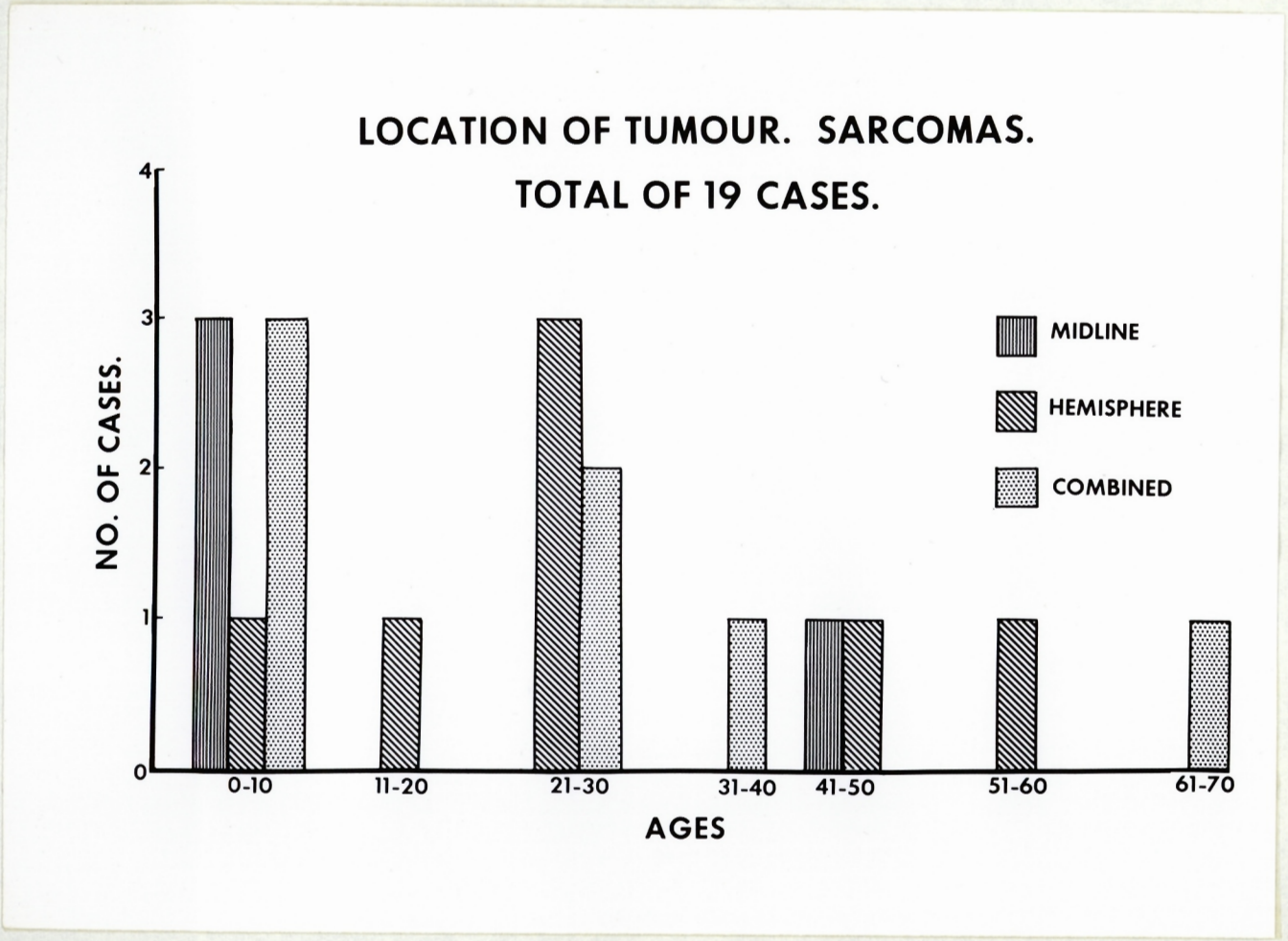

LOCATION OF TUMOUR. SARCOMAS.
TOTAL OF 19 CASES.
NO. OF CASES.
0
1
2
3
4
0-10
11-20
21-30
31-40
41-50
51-60
61-70
AGES
MIDLINE
HEMISPHERE
COMBINED

FIG. 12

Main Signs and Symptoms
Medulloblastomas and Cerebellar Sarcomas
(Figs. 13 and 14)

It may be seen from figures 13 and 14 that vomiting, headache and unsteady gait were the main symptoms in both the medulloblastoma and cerebellar sarcoma groups. As far as the objective findings were concerned, the three most important by far were increased intracranial pressure, cerebellar dysfunction and papilloedema. Diplopia, drowsiness and dizziness were of lesser importance in the symptomatology. It is interesting to note at this point that nine cases of medulloblastoma and three cases of cerebellar sarcoma were first investigated as a sequel to head injury. Turning now to the main signs presented by the patients, it was seen that nystagmus, 6th nerve palsy, facial weakness, nuchal rigidity and Macewen's sign were of lesser importance as a presenting symptom in the above order of decreasing frequency.

Radiological appearance: This has been discussed in detail in another paper from the Montreal Neurological Institute (D. L. McRae and Arthur Elliott, 1958) and will not be dealt with here. It is, however, interesting to note that on ventriculography two tumours were thought to be posterior 3rd ventricle lesions and therefore no other treatment but ventriculo-peritoneal shunt was performed. At autopsy both tumours were shown to have been primarily situated in the cerebellum and were medulloblastomas. In both cases there

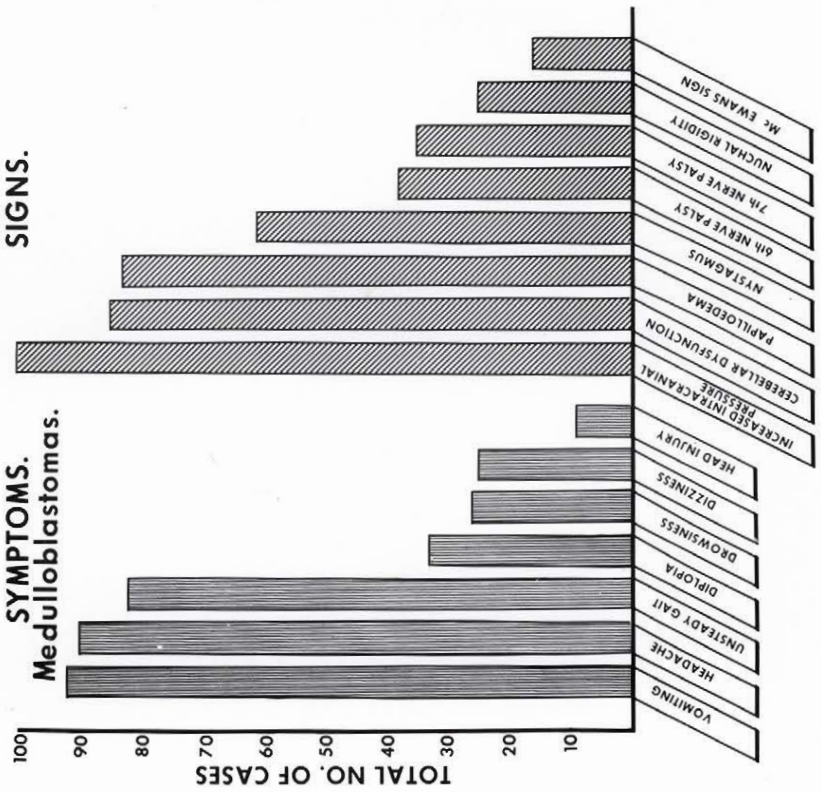

SYMPTOMS.
Medulloblastomas.
SIGNS.
VOMITING
HEADACHE
UNSTEADY GAIT
DIPLOPIA
DROWSINESS
DIZZINESS
HEAD INJURY
INCREASED INTRACRANIAL PRESSURE
CEREBELLAR DYSFUNCTION
PAPILLOEDEMA
NYSTAGMUS
6th NERVE PALSY
7th NERVE PALSY
NUCHAL RIGIDITY
Mc. EWANS SIGN
100
90
80
70
60
50
40
30
20
10
TOTAL NO. OF CASES

FIG. 13

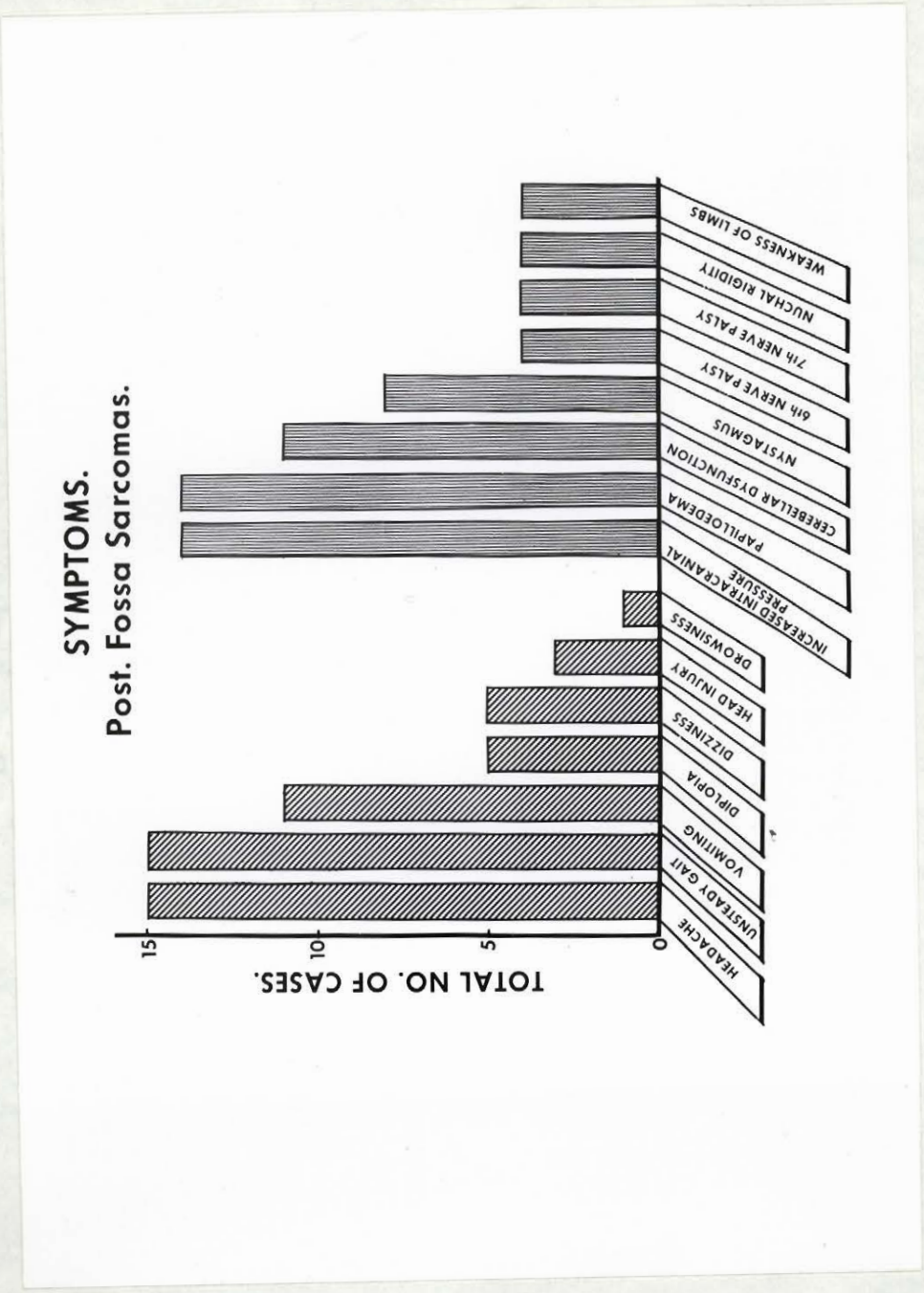

SYMPTOMS.
Post. Fossa Sarcomas.
TOTAL NO. OF CASES.
0
5
10
15
HEADACHE
UNSTEADY GAIT
VOMITING
DIPLOPIA
DIZZINESS
HEAD INJURY
DROWSINESS
INCREASED INTRACRANIAL PRESSURE
PAPILLOEDEMA
CEREBELLAR DYSFUNCTION
NYSTAGMUS
6th NERVE PALSY
7th NERVE PALSY
NUCHAL RIGIDITY
WEAKNESS OF LIMBS

FIG. 14

were secondary tumour implants in the peritoneal cavity via the shunt tubes.

Treatment: In reviewing the literature, one notes that various forms of therapy have been attempted. Spitz, Shenkin and Grant (1947) removed only enough tumour tissue to open up a pathway for the C.S.F. Bailey et al. (1939) advocated biopsy for diagnosis after craniectomy and wide decompression. Cushing (1930) did a thorough local removal by dissection and suction. Cutler, Bosman and Vaughan (1936) favoured radiation therapy of the suspected cerebellar tumours without histological diagnosis. Frazier and associates (1937) performed a biopsy only at the time of the initial decompression. Subtotal removal was attempted in other cases. At the Montreal Neurological Institute, the following methods of treatment were in use up to 1947: total (i.e. to the naked eye) and subtotal removal, with or without radiotherapy. In 1947, the late Dr. W. V. Cone began using twist drill biopsy of suspected cerebellar tumours; medulloblastomas and cerebellar sarcomas were not operated upon, but irradiated.

Following ventriculography and determination of location of the tumour, the biopsy is carried out in the surgical dressing room with the patient postured on the cerebellar headrest. A twist drill hole is made in the occipital bone, between the inion and the mastoid process, taking care to avoid the lateral sinus, the whole being performed under local anaesthesia. A no. 15 brain biopsy needle is inserted not more than 7 cm in the estimated site

of the lesion and the material for examination withdrawn. Biopsy is not attempted when intracranial pressure is low so as to avoid possible complications from ruptured blood vessels. Following confirmation of tumour, irradiation is begun.

IV. RESULTS

Results of therapy: Patients who died within one month following any sort of operative procedure, including twist drill biopsy, were arbitrarily designated as post-operative deaths.

In the medulloblastoma group of 56 cases who were operated upon and irradiated, the average survival was 3 years, 3 months and 3 weeks. The average survival in 10 cases treated by twist drill biopsy and irradiation was 3 years and 4 months. Fourteen cases were operated upon but received no radiotherapy and in this group the survival was markedly shorter, averaging 1 year and 3 weeks. (Fig. 15).

In the sarcoma group of 13 patients operated upon and irradiated, the average survival was 4 years, 9 months and 1 week. Two patients with cerebellar sarcomas in this series had twist drill biopsies and irradiation, their average survival being 3 years, 3 months and 2 weeks. (Fig. 15)

When the combined medulloblastoma and sarcoma group is considered, again excluding the post-operative deaths, the average survival in 69 cases operated upon and irradiated was found to be 3 years, 6 months and 2 weeks. Compared to this group, the 12 patients who underwent twist drill biopsy with irradiation showed a slightly shorter average survival time of 3 years and 4 months. (Fig. 15).

Survivals, Medulloblastoma & Sarcoma (combined)

Operation & irradiation	69 patients
Average survival	3 year 6 months 2 weeks
T.D. biopsy & irradiation	12 patients
Average survival	3 years 4 months
Medulloblastomas	
Operation & irradiation	56 patients
Average survival	3 years 3 months 3 weeks
T.D. biopsy & irradiation	10 patients
Average survival	3 years 4 months
Operation without irradiation	14 patients
Average survival	1 year 3 weeks
Sarcomas	
Operation & irradiation	13 patients
Average survival	4 years 9 months 1 week
T.D. biopsy & irradiation	2 patients
Average survival	3 years 3 months 2 weeks

Fig. 15

That twist drill biopsy with or without radiotherapy is not such an innocuous procedure can be seen from the example of the following three cases. The first was a three year old male child who received a total skin radiation of 300 r and died two days post-operatively. The other, an 8 year old boy, who received two x-ray treatments and died two days following twist drill biopsy. The third case, a cerebellar sarcoma, a female aged 33 years, died on the day twist drill biopsy was done, of cerebellar coning.

Five year survival: Of the total of 129 patients in the survey, 12 medulloblastomas and 7 sarcomas operated and irradiated, survived 5 years or more. Two (medulloblastomas) treated with Dr. Cone's method of biopsy followed by irradiation lived respectively 12 and 7 years, and are, to the best of our knowledge, still living and in good health, with no evidence of recurrence (Fig. 16).

Five year survivals

	Medulloblastoma	Sarcoma
Operation and irradiation	12	7
T.D. biopsy & irradiation	2	-

Fig. 16

Of the other 10 cases - all treated with irradiation - 7 treated by radical removal of the tumour survived an average of 10 years, 4 being alive at the time of the report with no signs of recurrence, the other three treated by partial removal of the tumour died after surviving 5, 10 and 24 years respectively (Fig. 17).

Long term survivals

Medulloblastomas (10) pts.) Operation and irradiation

7 patients	10 years average survival
4 patients	Still alive and well
3 patients	Died 5, 10, and 24 years after initial treatment.

Fig. 17

Out of 20 cases of sarcomata in a period of 13 years, from 1945 to 1958, all but one of which were treated by some form of operative procedure, 8 patients remain alive at the time of this report (June 1961) (Fig. 18). In one case there has been no recent follow-up, and this patient is presumed living. The only patient not treated surgically died two and a half months after admission from the effects of a lung abscess. This was a male patient of 64 years, in whom autopsy showed evidence of perithelial sarcoma.

Long term survival. Sarcoma.

Survival in years	No. of patients
5 - 6	2 (one living)
6 - 7	2 (one living)
9 - 10	1 (living)
12 - 13	1 (living)

Fig. 18

Statistical evaluation of therapeutic results.

The following pairs of "samples" have been compared by the means of the "t" test.

Medulloblastoma	"P" Value
Radical removal with radiotherapy vs. Radical removal without radiotherapy	between 0.1 & 0.2
Partial removal with radiotherapy vs. Partial removal without radiotherapy	between 0.1 & 0.2
Radical removal with radiotherapy vs. Partial removal with radiotherapy	between 0.1 & 0.2
T.D. biopsy with radiotherapy vs. Radical removal with radiotherapy	between 0.6 & 0.7
Cerebellar sarcoma	
Radical removal with radiotherapy vs. Partial removal with radiotherapy	0.2
Radical removal with radiotherapy vs. T.D. biopsy with radiotherapy	between 0.1 & 0.2
Medulloblastoma - all treatments vs. Sarcoma - all treatments	between 0.1 & 0.2

Our value of "t" for the above samples therefore lies between P. 0.1 and P. 0.2. In other words, between 10% and 20% of such samples would show by chance alone a difference as great as, or greater than, those obtained. Or, at the 10% level, there is no significant difference

between the results obtained, i.e. the difference can be explained by chance.

In conclusion, although the average survival time is longer in the sarcoma group, as compared to the medulloblastoma group, this difference is not statistically significant. Larger numbers of samples, i.e. cases will have to be studied and followed, before a statistically significant trend might become evident.

V. SUMMARY AND CONCLUSIONS

A total of 109 medulloblastomas and 20 cerebellar sarcomas were investigated during this 30 year period at the Montreal Neurological Institute. The cases of medulloblastomas are divided into groups according to age, number and sex of patients in each decade, location of tumour and predominance and duration of symptoms. The average survival is calculated, and the possible benefits of different treatments discussed including subtotal or total removal of the tumour without irradiation, operation plus irradiation, and Dr. Cone's method of twist drill needle biopsy and irradiation. The merits of each procedure are discussed and an attempt is made to determine whether these differences are statistically significant.

In reviewing the results it appears that there is very little difference in survival between the two groups, i.e. those medulloblastomas treated by twist drill biopsy and x-ray, and those treated by radical removal and radiation. The same may be said about those classified as sarcomas. In addition, longevity in the so-called medulloblastoma and sarcoma group is very similar in the categories of treatment just mentioned.

BIBLIOGRAPHY

1. Abbott, K. H., and Kernohan, J. W. Primary Sarcomas of the Brain, Review of the Literature and report of 12 cases. Arch. Neurol. 50:42-66, 1943.

2. Abbott, K. H., and Kernohan, J. W. Medulloblastomas; concerning the problems of spinal metastasis and malignancy: A report of 6 cases and discussion of problems involved. Bull. Los Angeles Neurol. Soc. 8:1-10, 1943.

3. Akamatu Ein Full von Medulloblastom in der rechten: Kleinhirnbrückenwingelgegend. Gann (jap) 32:144, 1938.

4. Alajouanine, de Martel and Guillaume Deux médullo-blastomes du 4e ventricule (ablation, guérison opératoire). Les troubles pseudo-digestifs initiaux des tumeurs de la fosse postérieure. Rev. Neurol. 2:94-100, July, 1930.

5. Alpers, B. J., and Pancoast, H. K. The Effect of Irradiation of Normal and Neoplastic Brain Tissue. A. J. Cancer 17:7-24, Jan., 1933.

Bibliography

6. Alyea, E. P. Medulloblastoma involving kidney.
South. Med. J. 26:753-763, Sept., 1933.

7. Arnstein, L. H., Boldrey, E., and Neffziger, H. C.
A case report & survey of brain tumours
during the neonatal period.
J. Neurosurg. 8:315-319, 1951.

8. Babonneix, L. Diagnostic des tumeurs cérébrales
chez l'enfant.
J. Méd. Paris, 51:1007-8, 1931.
Médecine 12:622-626, 1931. Semaine
Hôp. Paris, 7:273-284, 1931.

9. Bagchi, B. K. Electroencephalographic localization
of intracranial tumours.
Correlative Neurosurgery, pub. Charles C.
Thomas, Springfield, Illinois, pp. 48-51,
(1955).

10. Bagchi, B. K., Lam, R. L., Kooi, K. A., and Bassett,
R. C. EEG findings in posterior fossa
tumours.
EEG Clin. Neurophysiol. 4:23-40, 1952.

11. Bagchi, B. K., Lam, R. L., and Kooi, K. A.
Examination of the validity of new empirical
criteria for the localization of posterior
fossa lesions.
EEG Clin. Neurophysiol., 3:383, 1951.

Bibliography

12. Bailey, O. T. The histogenesis of the medulloblastoma.
Excerpta med. Neurol. & Psychiat., 8:814, 1955.

13. Bailey, P. Further notes on cerebellar medulloblastomas: the effect of roentgen radiation.
Am. J. Path., 6:125-136, March, 1930.

14. Bailey, P. Intracranial tumours.
2nd edition, Springfield, Thomas, 1948, p. 475.

15. Bailey, P. Cellular types in Primary tumours of the Brain.
Cytology and Cellular Pathology of the Nervous System. New York, Hoeber, 1932.

16. Bailey, P. Intracranial tumours.
Springfield, Charles C. Thomas, 1933.

17. Bailey, P. Intracranial sarcomatous tumours of leptomeningeal origin.
Arch. Surg. 18:1359-1402, 1929.

18. Bailey, P., Buchanan, D., and Bucy, P. Intracranial tumours of infancy and childhood.
Chicago, 1939.
(Über die Behandlung intrakranieller Tumoren in Kindesalter.
Nervenarzt 12:1-9, 1939).

Bibliography

19. Bailey and Cushing Gewebsverschiedenheit der Hirngliome.
Jena 1929, Folke HENSCHEN: J. 707
Vol. 13: III.

20. Bailey, P., and Cushing, H. A Classification of the tumours of the Glioma group, on a histogenic basis with a correlated study of prognosis.
175 p. Philadelphia, J. B. Lippincott Co., 1926.

21. Bailey, P., and Cushing, H. Medulloblastoma cerebelli.
Arch. Neurol. & Psychiat., 14:192-225, Aug. 1925.

22. Bailey, P., Sosman, M. D., and Van Dessel, A. Roentgen Therapy of Gliomas of the Brain.
Am. J. Roentgenol. 19:203-264, March, 1928.

23. Barden, R. P., and Lewey, F. H. Metastasizing cerebellar tumours; difficulty in distinguishing between medulloblastoma and neuroblastoma.
J. Neurosurg., 6:439-449, Nov., 1949.

24. Barre, J. A., Stolz, and Alfandary Contribution à la Symptomatologie des tumeurs du IV ventricule. Tumeurs du IV ventricule à symptomatologie vestibulaire presque pure.
Rev. méd., 46:869-85, 1929.

25. Béclére, A.
J. Radiol. Electrol., 10:556, 1926.

26. Benedek, L., and Juba, A. Uber das Mikrogliom.
Deutsche Ztschr. Nervenh.,
152:159-169, 1941.

27. Bennett, W. A. Primary Intracranial neoplasms in military age groups - World War II.
Mil. Surgeon, 99:594-652, 1946.

28. Bertrand, L., and Girot, L. Tumeur du lobe droit du cervelet (médulloblastome).
Rev. neurol., 1:245-248, Fév. 1929.

29. Bickford, R. B., and Baldes, E. J. The EEG in tumours of the posterior fossa.
Proc. Soc. Clin. Res., 20:87-88, 1947.

30. Bodian, M. The pathology of intracranial tumours in children.
Journ. Fac. Radiol., 4:171-174, 1953.

31. Bodian, M., and Lawson, D. The intracranial neoplastic diseases of childhood; a description of their natural history based on a clinico-pathological study of 129 cases.
Brit. J. Surg. 40:368-392, 1953.

32. Bogaert, L. van, et Martin, P. Les tumeurs du 4ième ventricule etc.
Revue neur., 35:431-483, 1928.

33. Bohm, M. Valeur prognostique de L'EEG dans les tumeurs de la fosse postérieure. Rev. Neurol., 80:647, 1948.

34. Borges Fortes, A., and Costa Rodrigues, I. Medulloblastoma of 4th ventricle, with report of case. Hospital, Rio de Janeiro, 14:63-76, July, 1938.

35. Borst in Aschoff's Allg. path. Anatomie 1909.

36. Boyd, Gladys Medulloblastoma of the cerebellum simulating tuberculous meningitis. Canad. M.A.J., 77:871, Nov., 1957.

37. Brody, B. S., and German, W. J., Medulloblastoma of Cerebellum, report of 15 cases. Yale J. Biol. & Med., 6:19-29, Oct., 1933.

38. Broglia, S., and Postir, A. Aspetti elettroencephalografici di 100 tumori della fossa posteriora e 40 del terzo ventricolo. Riv. Neurol., 26:29-50, 1956.

39. Brzystowicz, R. J., and Kernohan, J. W. Cells rests in the region of the fourth ventricle. Arch. Neurol. & Psychiat., 67:585-611, 1952.

40. Bucy, P. C. Tumours of the Brain, in Trice's Practice of Medicine.
Hagerstown, Prior, 1936.

41. Bucy, P.C.
J. Pediat. 1947, 30:726.

42. Bull, James The radiological diagnosis of intracranial tumours in children.
J. Fac. Radiol., 4:149 no. 3, 1952-53.

43. Burgman, G. P., and Voznaia, A. S., Mitrofanova, N. P. and Pershman, R. E. Vpimomozgovaia zhidkost pri medulloblastomakh mozzhechka v do - i poslesperatsionnom periode i ee klinicheskaia otsenka. (Pre operative and post operative cerebro spinal fluid in cerebellar medulloblastomas and its clinical significance).
p. 25-32. Vopr (osy) neirokhir (urgii) (Moskva) 19 (5) Sept.-Oct., 1955.

44. de Busscher, J. and Dewulf, A. Médulloblastome du 4ième ventricule avec métastase tubérienne sans syndrome infundibulaire.
J. Belge de Neurol. et de Psychiat., 33:605-624, Sept., 1933.

45. Cabot, Case 25481. Primary tumour of pineal, ? medulloblastoma.
New England Med. J., 221:863-866, Nov., 30, 1939.

Bibliography

46. Cairns, H. and Russell, D. S. Intracranial and spinal metastases in gliomas of the brain.
Brain 1931, 54:377.

47. Canti, R. G., Bland, J. O. W., and Russell, D. S. Tissue culture of gliomata (1935).
Ac. Res. Nerv. & Ment. Dis., Proct., 16:1-24, 1937.

48. Cajal, Ramon, J. Contribucion al conocimiento de la neuroglia del cerebro humano.
Trab. lab. invest. biol. Univ. Madrid, 11:254, 1913.

49. Cajal, Ramon, J. Sur les fibres nerveuses de la couche granuleuse du cervelet et sur l'évolution des éléments cérébelleux.
Internat. Monatsehr. f. Anat. u. Physiol., 7:12-31, 1890.
Genesis de las fibras nerviosas del embryon y observaciones a la teoria catenaria.
Trav. du lab. u. recherches biol. de l'Univ. de Madrid, 4:227-294, 1906.
Histologie du système nerveux de l'homme et des vertébrés.
Ed. francaise; traduite de l'espagnol par Dr. L. Azonlay. 2 vols. Paris, A. Maloire, 1909-1911.

Bibliography

50. Christensen, E. Medulloblastomas.
Excerpta Med., Neurol., & Psychiat.,
8:815, 1955. Ref. fbl. Neuroch.
16:44, 1956.

51. Cobb, W. A. Rhythmic slow discharges in the
electroencephalogram.
J. Neurol., Neurosurg., Psychiat.
8:65, 1945.

52. Collier, J. The false localizing signs of intra-
cranial tumour.
Brain, 27:490, 1904.

53. Cordy, D. R. Medulloblastoma in a steer.
Cornell Vet., 43:189, 1953.

54. Cornill, Paillas, Gastaut et Duplay Neuroglio-
blastome (médulloblastome) du cervelet
chez un adulte, terminaison par généra-
lisation ganglionnaire et osseuse.
Revue Neurol., 78:85, 1946.

55. Couto, D. Medulloblastoma of fourth ventricle,
with report of case.
Cultura Med., 3:33-47, July, 1941.

56. Craig, J., Keith, H. M. & Kernohan, J. W. Tumours
of the brain occurring in childhood.
Acta. Psychiat. (Copenh.) 24:375-390, 1949.

57. Craig and Kernohan Tumours of the fourth ventricle.
J. Amer. Med. Assoc. III, 2370, 1938.

Bibliography

58. Crue, B. L. Medulloblastoma.
Publ. Charles Thomas, Springfield, Ill.
pp. 206, 1958. (American Lecture Series).

59. Cuneo, Henry, M. and Rand, Carl W. Brain Tumours of Childhood.
Publ. Charles C. Thomas, Springfield, Ill.

60. Cushing, H. Intracranial tumours: notes upon a series of two thousand verified cases with surgical mortality percentages pertaining thereto.
Springfield, Ill., Charles C. Thomas, 1932.

61. Cushing, H. Experiences with the Cerebellar Medulloblastomas.
Acta Path. et microbiol. Scand. 7:1-86, 1930.

62. Cutler, E. C., Sosman, M. C. and Vaughan, W. W. The place of radiation in treatment of medulloblastomas. Report of 20 cases.
Am. J. Roentgenol., 35:429-453, April, 1936.

63. Daly, D., Whelan, J. L., Bickford, R. G. & MacCarthy, C. S. The Electroencephalogram in cases of tumours of the posterior fossa and 3rd ventricle.
EEG & clin. Neurophysiol. 5:203-216, May, 1953.

64. Dam, van Cerebellaire gliomen.
Assen 1941.

65. Davidoff, L. M. and Epstein, B. S. The abnormal pneumoencephalogram.
Philadelphia: Lea & Febiger, 1955.

66. Davis, L. E. The principles of Neurologic Surgery.
Philadelphia, Lea, 1942.

67. Döring, G. Fur Histologie der Umgebung unreifer Hirngeschwülste.
Dtsch. Z. Nervenheilk., 149:201-221, 1939.

68. Dow, R. S. Electroencephalographic findings in cerebellar tumours. A review of current and old concepts.
EEG Clin. Neurophysiol., 8:165, 1956.

69. Dow, R. S., and Moruzzi, G. The Physiology and Pathology of the Cerebellum.
University of Minnesotta Press, Minneapolis, pp. 675 (1958)

70. Dupin Diagnostic des Tumeurs Cérébrales chez l'enfant.
Thèse de Bordeaux 1934/35.

71. Dyke, C. G., and Davidoff, L. M. Roentgen treatment of Diseases of the Nervous System.
London, Kingston, 1942.

72. Eisenhardt, L. Long post-operative survivals in cases of intracranial tumour.
A. Rev. Nerv. and Mart. Dis., Proc., 16:390-416, 1937.

Bibliography

73. Elefant, E., Jeklerova, J., and Lesny, I. Compression of Spinal Cord due to malignant medulloblastoma in child; case. Ann. Paediat., 184:253-261, April, 1955.

74. Elsberg, C. A., and Gotten, N. The results of conservative compared with radical operations in the cerebellar medulloblastomas: Analysis of 23 cases. Bull. Neurol. Inst. New York 3:33-52, June, 1933.

75. Elvidge, A., Penfield, W. and Cone, W. The Gliomas of the Central Nervous System. Proc. Assoc. Res. Nerv. & Ment. Dis., 16:107-101, 1935.

76. Engeset, A. On roentgen treatment of intracranial gliomas. Acta radiol., 32:210-228, 1949.

77. Ferens, E. Case of Primary Reticuloendothelioma of Central Nervous System. Neurol. polska, 21:387-402, 1938.

78. Fisher, E. R., Watkins, T. W., Gardner, W. J. and Klotz, J. G. Bleeding duodenal ulcer associated with cerebellar tumour in childhood (Medulloblastoma). Gastroenterology, 18:626-631, 1951.

79. Fischer, Oskar Beiträge zur Pathologie und Therapie der Rückenmarks tumoren. Zeitschift für die gesamte Neurologie und Psychiatrie, 76:81, 1922.

80. Forster Die diagnostische Bedeutung des Liquorzellbildes. Zentralbl. ges. Neurol. u. Psychiat., 55:787-788, 1930.

81. Fowler, F. D., Gammill, James C. and Martin, J. Distribution studies of intrathecally injected radioactive colloidal gold in cats: therapeutic implications for the medulloblastoma and other tumours with meningeal metastases. J. of Neuropath. and Exper. Neurology, 13:435, 1954.

82. Frauchiger, E. and Fankhauser, R. Vergleichende Neuropathologie des Menschen und der Tiere. Springer Verlag, Berlin, 1957, pp. 451.

83. Frazier, C. H., Alpers, B. J., Pendergrass, E. P. and Chamberlin, G. W. Effects of Irradiation on Gliomas. Am. J. Roentgenol., 38:203-236, July, 1937.

84. Freid, J. R., and Davidoff, L. M. Roentgen therapy of primary neoplasms of brain. Radiology, 57:25-36, 1951.

85. Fulton, J. F. Case of cerebellar tumour with seizures of head retraction described by Wurffbain in 1691.
J. Nerv. & Ment. Dis., 70:577-583, 1929.

86. Fulton, J. F. Physiology of the Nervous System.
3rd Ed. New York, Oxford, 1949.

87. Gardner, W. J., and Nosik, W. A. Experience with encephalography in cerebellar tumour.
Am. J. Roentgenol., 47:691-698, 1942.

88. Gehuchten, P. van L'abolition des réflexes tendineux dans les tumeurs du IV ventricule.
J. Belge Neurol. et Psychiat., 30:201-213, 1930.

89. Globus, J., and Strauss, I. Spongioblastoma multiforme, a primary malignant form of brain neoplasm: its clinical and anatomic features.
Arch. Neurol. & Psychiat., 14:139-191, 1925.

90. Grant, F. C. A study of the results of surgical treatment in 2,320 consecutive patients with brain tumour.
J. Neurosurg., 13:479-488, 1956.

91. Grant, F. C. A clinical study of midline tumours in children.
Surg. Clin. N. Amer., 9:1155-1168, 1929.

92. Grant, F. C., and Sayers, M. P. Notes on a series of brain tumours.
Tr. Am. Neurol. A., 102-106, 1951.

93. Grey, E. Studies on the localization of cerebellar tumours. 1. Significance of staggering gait, ataxia, the Romberg test and adiadochokinesis.
J. Nerv. & Ment. Dis., 42:670-679, 1915.

94. Griepentrog, F., and Pauly, H. Intra und extrakranielle, frühmanifeste Medulloblastome bei erbgleichen Zwillingen (intracranial & extracranial medulloblastoma with early manifestations in uniovular twins).
Zbl. Neurochi., 17(3):129-140, 1953.

95. Guillain, G., Bertrand, I., et Périsson, J. Médulloblastome du quatrième ventricule à évolution aigüe.
Revue neur., 37:62, 1930.

96. Guillain, G., Lereboullet, J., and Rudaux, P. Acute infectious syndrome as first manifestation of medulloblastoma of fourth ventricle: case.
Soc. méd. d'hôp. de Paris, 50:240-251, 1934.

97. Halpern, L. Remarkable case of spinal metastases (with migration of clip) in medulloblastoma.
J.A.M.A., 118:803, 1942 (March 7).

98. Hanbery, J. W., and Dugger, G. S. Perithelial Sarcoma of the Brain. A Clinico-pathological Study of Thirteen Cases. A.M.A. Arch. Neurol. and Psychiat. 71: 1954.

99. Hasenjäger, Th. Uber die Ependymitis blastomatosa bei ventrikelnahen Gliomen. Arch. F. Psychiatr. 110:605-632, 1939.

100. Helmholz, H. F. Malignant neoplasms in childhood. Proc. Staff Meet., Mayo Clinic, 6:721, 1931.

101. Henschen, Folke im Handbuch d. speziellen pathologischen. Anatomie und Histologie, Vol VIII Erkrankungen d. ZNS III Medulloblastome, p. 707, 1955.

102. Hess, Rudolph Electroencephalographische Studien bei Hirntumoren. Georg Thieme Verlag-Stuttgart, p. 106, 1958.

103. His, W. Die Neuroblasten und deren Entstehung im embryonaeen Mark. Arch. F. Anat. u. physiol., Anat. Abt., 249-300, 1889.

104. Holland, C. G. Changes caused by cerebellar neoplasms in electroencephalography. Virginia M. Monthly, 68:459-462, 1941.

105. Holman, E. Difficult urination associated with intracranial tumours of the posterior fossa.
Arch. Neurol. & Psychiat., 15:371-380, 1926.

106. Honeyman, W. M. Cerebral medulloblastoma.
Am. J. Path., 13:1003-1014, 1937.

107. Horrax, G. Benign forms of gliomas of the brain.
Lahey Clinic, Bull., 9:2-5, July, 1954.

108. Del-Rio, Hortega, P. Estructura y sistematizacion de los gliomas y paragliomas.
Arch. espan. d. oncol., 2:411-677, 1932.

109. Del-Rio, Hortega, P. Nomenclatura y classifacion de los tumores del sistema nerviosa.
Arch. Argentin. Neurol., 7:22-24, 1940/41.

110. Del-Rio, Hortega, P. Nomenclatura y classificacion de los tumores del sistema nervioso.
Buenos Aires, 1945.

111. Hsü, J. K. Primary intracranial sarcomas.
Arch. of Neurol. & Psychiat., 43:901-924, 1940.

112. Ingraham, F. D., and Bailey, O. T. Cerebellar medulloblastoma with verification nineteen years after the onset of symptoms.
J. Neurosurg., 1:252-257, 1944.

113. Ingraham, F. D., Bailey, O. T., and Barker, W. F. Medulloblastoma cerebelli: diagnosis, treatment and survivals, with report of 56 cases. New England J. Med., 238:171, 1948.

114. Ingraham, F. D., and Campbell, J. B. Dangers of radiation without biopsy in brain tumours in children: report of case. New England J. Med., 224:925-927, 1941.

115. Ingraham, F. D., and Matson, D. D. Neurosurgery of Infancy and Childhood. Springfield, Thomas, 1954.

116. Jackson, J. H. Case of tumour of the middle lobe of the cerebellum. Cerebellar paralysis rigidity (cerebellar attitude) occasional tetanus-like seizures (1871). Brain, 29:425-445, 1906.

117. Jacob, A. Nervengewebe, in Handbuch der mikroskopischen. Anatomie des Menschen. W. von Mollendorf, Ed. Berlin, Springer, Berlin 4, pt. 1, 155, 1928.

118. Jacob, A. Normale und pathologische Anatomie und Histologie des Grosshirns, vol. 1, Vienna, Deuticke, p. 71, 1927.

119. Johnson, V. C., and List, C. F. Ventriculographic localization of intracranial tumours; tumours of cerebellum and fourth ventricle.
Am. J. Roentgenol., 43:346-355, 1940.

120. Kalm, K. Über die Metastasierung von Geschwülsten in die Liquorräume.
Dtsch. Z. Nervenheilk., 159:397-407, 1948.

121. Kaufmann, Lehrbuch d. spez. pathol. Anatomie.
Berlin 1911.

122. Kernohan, J. W., Mabon, R. F., Svien, H. J. and Adson, A. W. A simplified classification of the gliomas.
Proc. Staff Meet., Mayo Clinic, 24:71-75, 1949.

123. Kernohan, J. W., and Sayre, G. P. Tumours of C.N.S.
Armed Forces Institute of Pathology, Washington, 1952.

124. Kershman, J. The medulloblast and the medulloblastomas.
Arch. Neurol. Psychiat., 40:937-967, 1938.

125. King Medulloblastoma with onset during the neonatal period. Report of a case.
J. of Neurosurg., 10:75, 1953.

126. Kunmey, T. D., and Adams, R. D. Reticulum cell sarcoma of the Brain. Arch. Neurol. & Psychiat., 50:552-564, 1943.

127. Kenlenbeck, H. Transitory superficial granular layer of cerebellar cortex. Its relationsnip to certain cerebellar neoplasms. J. Am. M. Women's A., 5:347-351, 1950.

128. Lairy-Bounes, G. C., and Fischgold, H. L'électroencéphalographie dans une série de trente-huit tumeurs de la fosse postérieure. Sem. Hôp., 54:2633-2635, 1950.

129. Lampe, Isadore Radiation tolerance of the Central Nervous System in Progressive Radiation Therapy. pp. 224-236, 1950.

130. Lampe, I., and MacIntyre, R. S. Experiences in the radiation therapy of medulloblastoma of the cerebellum. Am. J. Roentgenol., 71:659-668, 1954.

131. Lampe, I., and MacIntyre, R. S. Medulloblastoma of the Cerebellum. Arch. of Neurol., 62:322-329, 1949.

132. Langelaan, J. W. On the development of the external form of the human cerebellum.
Brain, 42:130, 1919.

133. Leavitt, F. H. Cerebellar tumours occurring in in identical twins.
Arch. Neurol. Psychiat., 19:617-623, 1928.

134. Le Beau, J. La hernie du cervelet au-dessus du tentorium. Diagnostic ventriculographique entre les tumeurs de la partie haute du cervelet et les tumeurs de la partie postérieure du troisième ventricule. Leur voie d'abord chirurgicale.
Union méd. du Canada, 73:243-252, 1944.

135. Le Beau, J., Rosier, M. Médulloblastome du cervelet.
Neurochirurgie (Paris), 2:206-208, April-June 1956.

136. Lereboullet, J. Les tumeurs du 4ième ventricule.
Paris 1932, pp. 431-440.

137. Lugaro, E. Ueber die Histogenese der Körner der Kleinhirnrinde.
Anat. Anz., 9:710-713, 1894.

138. Lysholm, E. Experiences in ventriculography of tumours below the tentorium.
Brit. J. Radiol., 19:437-452, 1946.

Bibliography

139. Lysholm, E. Ventriculography of the fourth ventricle.
Amer. J. Roentgenol., 41:18, 1939.

140. Lysholm, E. Das Ventrikulogram. III. Dritter und vierter Ventrikel.
Acta Radiol., 26: suppl. 124 pp. 1935.

141. Manlove, C. H. Medulloblastoma, with spontaneous generalized infiltration of pia-arachnoid.
Northwest Med., 45:339-343, May 1946.

142. Marburg, O. Weitere Beiträge zur Pathologie und Pathogenese der Medulloblastome.
Folia neuropath. estoniana 15-16:74-87, 1935/36.

143. Marburg, O. Zur Kenntnis der sogenannten Meduloblastome. Sphaeroblastoma polymorphon.
Dtsch. Z. Nervenhk., 117:289-308, 1931.

144. Marinesco, T. and Goldstein, M. Sur une forme anatomique, non encore décrite, de médulloblastome: médullo-myoblastome.
Ann. d'anat. path., Paris, 10:513-525, 1933.

145. Martin, M. P. and Martin, M. Signes électrographiques des tumeurs de la fosse postérieure.
Rev. Neurol., 82:540-546, 1950.

140. Masson, C. B. et R. Dreyfuss Neurogliocytome embryonnaire du vermis.
Rev. Neurol., 2:227, 1925.

147. McConnell, I. H. and Childe, A. E. Pneumographic localization of tumours of the brain.
I. Tumours of the lobes of the cerebellum.
Arch. Neurol. & Psychiat., 37:33-55, 1937.

148. McGrath, J. T. Neurologic examination of the dog with clinicopathologic observations.
Philadelphia, Lea and Febiger, 1956.

149. McRae, D. L. and Elliott, A. W. Radiological aspects of cerebellar astrocytomas and medulloblastomas.
Acta Radiologica, 50:52, 1958.

150. Meredith, John M. Malignant round-cell neoplasm of cerebellum simulating an angle tumour with petrous ridge erosion.
J. Neurosurg., 12:311-316, May, 1955.

151. Meschede Heterotopie grauer Hirnsubstanz im Markstamme der Hemisphären des kleinen Gehirns. Drei Beobachtungen.
Virchows Arch. path. Anat., 56, 82, 1872.

152. Molter, F., Henry, J. A. and Brihaye, J. A propos d'un cas de radiolésions survenues chez un enfant irradié pour un médulloblastome du cervelet.
J. Belge de Radiol., 38:3, 1955.

153. Negri, S. Considerationi sull electroencefalgramma dei tumori della fossa posteriora e del terzo ventricolo. Exc. Med. VIII, 10:115, 1957.

154. Nelson, A. A. Metastases of intracranial tumours (with case of medulloblastoma). Am. J. Cancer, 28:1-12, Sept., 1936.

155. Olivecrona, H. and Lysholm, E. Notes on the Roentgen Therapy of Gliomas of the Brain. Acta Radiol., 7:259-268, 1926.

156. Ollivier, C. P. Traité de la moelle épinière et de ses maladies. 2nd ed. Paris, Crevot, 1837, pp. 847, Obs. XVII.

157. Ostertag, B. Pathologie der raumfordernden Prozesse des Schädelbinnenraums. Stuttgart, 1941.

158. Ostertag, B. Einteilung und Charakteristik der Hirngewächse. Ihre natürliche Klassifizierung zum Verständnis von Sitz, Ausbreitung und Gewebsaufbau. Jena, Gustav Fischer 1936.

159. Ostertag, B. Die typischen Geschwulstbildungen des Kleinhirns und ihre Beziehungen zu den Fehlbildungen des übrigen Medullarohres. Klin. Wchnschr., 11:1651-56, 1932.

160. Palmer, H. D. and Murphy, E. S.
J.A.M.A. 1952, 149:220.

161. Paterson, Edith Treatment of cerebral tumours in children by irradiation.
Journ. Fac. Radiol., 4:175, 1953.

162. Paterson, E. and Farr, R. F. Cerebellar medulloblastoma: treatment by irradiation of the whole central nervous system.
Acta radiol., 39:323-336, April, 1953.

163. Paterson, R. Treatment of malignant disease by radium and x-rays.
Williams and Wilkins Co., Baltimore, 1948, 466-469.

164. Paterson, R., Tod, M., and Russell, M. Results of radium and x-ray therapy in malignant disease.
Williams and Wilkins Co., Baltimore, 1950, 125-127.

165. Peirce, C. V., Cone, W. V., Bouchard, J. and Lewis, R. C. Medulloblastoma: non-operative management with roentgen therapy after aspiration biopsy.
Radiology, 52:no. 5, 621-632, May, 1949.

166. Pendergrass, E. P., Hodes, P. and Godfrey, E. W. The radiation treatment of cerebellar medulloblastoma: Report of 31 cases.
Am. J. Roentgenology, 48:476-490, 1942.

Bibliography

167. Pendergrass, E. P. and Wilbur, D. L. Tumour of cerebellum with widespread metastases; two cases.
Arch. Neurol. & Psychiat. 19:437-445, March, 1928.

168. Penfield, W. Neuroglia, normal and pathological. Cytology and cellular pathology of the nervous system. Bd. 2. S. 421.
New York, 1932.

169. Penfield, W. The classification of gliomas and neuroglia cell types.
Arch. Neurol. & Psychiat. 26:745, 1931.

170. Penfield, W. and Feindel, W. Medulloblastoma of the cerebellum with survival for seventeen years.
Arch. Neurol. 57:481, 1947.

171. Pennybacker, J., Northfield, D. W. C., Parsons-Smith, G. P. and Tutton, G. K. Discussion on current trends in management of the gliomata.
Proc. Roy. Soc. Med. 43:329-338, 1950.

172. Perisic, M. Pinealom u kombinaciji sa medulloblastomom caudae equinae.
Srpski ark. iv, celok. lek.
83, Feb. 1955.

Bibliography

173. Peterson, H. O. and Baker, A. B. Difficulties in differentiating midbrain lesions from cerebellar lesions.
Am. J. Roentgenol. 46:37-51, 1941.

174. Pfleger, R. Die blastomatöse Form der diffusen Hirnsklerose. (Leucenphalopathia blastomatosa).
Jb. Psychiatr. 50:142-194, 1933.

175. Pfleger, L. Beobachtungen über Heterotopie grauer Substanz im Mark des Kleinhirns.
Zbl. med. Wiss. 26: 46-469, 1880.

176. Pfleger, L. Beobachtungen über Heterotopie grauer Substanz im Marke des Kleinhirns.
Centralbl.f.d. med. Wissensch. 18:468-470.

177. Platt, W. R. Exfoliative cell diagnosis of Central Nervous System lesions.
Arch. Neurol. & Psychiat. 66:119, 1951.

178. Poltmeteer, F. E. and Kernohan, J. W. Meningeal gliomatosis. Study of 42 cases.
Arch. of Neurol. 57:593-616, 1947.

179. Pool, L. J., Ransohoff, J. and Correll, J. W. The treatment of malignant brain tumours, primary and metastatic.
N. Y. St. J. Med. 57:3983-3988, Dec. 15, 1957.

Bibliography

180. Popoff, S. Zur Frage über die Histogenese der Kleinhirnrinde.
Biol. Zentralb. 15:745-752, 1895.
Weitere Beiträge über die Histogenese der Kleinhirnrinde.
Ibid, 16:462-466.

181. Portmann, U. V. and Thompson, R. H. Long survival of patient with medulloblastoma and malignant goitre treated by roentgen therapy; case.
Cleveland Clin. Quart. 14:44-46, Jan., 1947.

182. Raaf, J. E. and Kernohan, J. W. Relation of abnormal collections of cells in posterior medullary velum of cerebellum to origin of medulloblastoma.
Arch. Neurol. & Psychiat. 52:163-169, 1944.

183. Raaf, J. and Kernohan, J. A study of the external granular layer in the cerebellum.
Am. J. Anat. 75:151-172, 1944.

184. Rheinberger, M. B. and Davidoff, L. M. Posterior fossa tumours and electroencephalogram.
J. Mt. Sinai Hosp. 9:734-754, 1942.

185. Richmond, J. J. Radiotherapy of intracranial tumours in children.
J. Fac. Radiol. 4:180, 1953.

Bibliography

186. Ringertz, N. On the question of different histologic types of medulloblastoma.
Excerpta Med. Neurol. Psychiat. 8:820, 1955.

187. Ringertz, N. and Tola, J. H. Medulloblastoma.
J. Neuropath. & Experiment. Neurol.
9:354-372, 1950.

188. Rosenberg, A. W. Intracerebral metastasis of a medulloblastoma; report of case.
Bull. Los Angeles Neur. Soc., 22:1,
March, 1957.

189. Rothschild, K. Medulloblastoma cerebelli; case with autopsy. Midline cerebellar tumours in children and young adults.
Ann. Int. Med. 5:643-650, Nov., 1931.

190. Roussy, G. and Oberling, C. Histologic classification of tumours of the central nervous system.
Arch. Neurol. & Psychiat. 27:1281-1289, 1932.

191. Roussy, G., Oberling, C. and Raileanu, C. Les neurospongiomes.
Presse Méd. 977-981, 1931.

192. Ruggiero, G. and Castellano, F. Upward displacement of the posterior part of the third ventricle. A method for its evaluation.
Acta Radiol. 39:377, 1953.

Bibliography

193. Russell, D. S. and Bland, G. O. W. A study of gliomas by the method of tissue culture.
J. Path. & Bact. 36:273-283, 1933.

194. Russell, D. S., Marshall, A. H. E. and Smith, F. B. Microgliomatosis, a form of reticulosis affecting the brain.
Brain 71:1-15, 1948.

195. Saccone and Epstein Granuloblastoma, a primary neuroectodermal tumour of the cerebellum.
J. Neuropath. 7:287, 1948.

196. Sachs, E., Rubinstein, J. E. and Arneson, A. N. Results of roentgen treatment of a series of one hundred and nineteen gliomas.
Arch. Neurol. & Psychiat. 35:597-616, March 1936.

197. Schaltenbrand, G. and Bailey, P. Die perivaskuläre Piagliamembran des Gehirns.
J. Psychol. u. Neurol. 35:199-278, 1928.

198. Schaper, A. Die frühesten Differenzierungsvorgänge im Centralnervensystem.
Arch. Entw. mechn. 5:81-130, 1897.

199. Schaper, A. Einige kritische Bemerkungen zu Lugaro's Aufsatz: "Ueber die Histogenese der Körner der Kleinhirnrinde".
Anat. Anz. 10:422-426, 1895.

200. Schaper, A. Die morphologische und histologische Entwickelung des Kleinhirns der Teleostier.
Anat. Anz. 9:489-501.

201. Scheinker, I. Zur Frage der Pathogenese und Pathologie der Medulloblastome.
Monatsschr. Psychiat. u. Neurol.
101:103-113, 1939.

202. Schwartz, E. Sindrome tumorale ventriculo-vermiana e midollare da medulloblastoma.
Pediatria 41:1057-1070, Aug., 1933.

203. Seiler, W. C. Jr. Medulloblastoma in 7 month old infant.
J. Pediat. 32:317-319, 1948.

204. Singer, L. and Seiler, J. Untersuchungen über die Morphologie der Gliome.
Virchows Arch. 287, 823, 1933.
Klin. Wschr. 12, 20, 1933.

205. Smith, J. R., Walter, C. W. P., Laidlaw, R. W. and Casamajor, L. The electroencephalogram in cases of neoplasms of the posterior fossa.
Arch. Neurol. Psychiat., Chicago,
43:472-487, 1940.

206. Smith, R. A., Lampe, I. and Kahn, E. A. The prognosis of medulloblastoma in children.
J. Neurosurg. 18:91-97, 1961.

207. Spatafora, G. Medulloblastoma of fourth ventricle; clinical and anatomicopathologic study of case.
Gior. di med. mil. 88:509-521, July, 1940.

208. Spitz, E. B., Shenkin, H. A. and Grant, F. C. Cerebellar medulloblastoma in adults.
Arch. Neurol. & Psychiat. 57:417-422, 1947.

209. Stevenson, L. Tumours of the cerebellum.
Arch. Neurol. & Psychiat. 26:875-876, 1931.

210. Stevenson, L. and Echlin, F. Nature and origin of some tumours of the cerebellum.
Arch. Neurol. & Psychiat. 31:93-109, 1934.

211. Sutton, D. Radiologic assessment of the normal aqueduct and fourth ventricle.
Brit. J. Radiol. 23:208, 1950.

212. Svien, H. J., Mabon, R. F., Kernohan, J. H. and Adson, A. W. A simplified classification of the gliomas, based on the concept of anaplasia.
Clin. North America, 29:1169-1187, 1949.

213. Tice, G. M. and Irving, N. W. Roentgen Therapy supplementing surgery in the treatment of gliomas.
J. Neurosurg. 7:509-520, 1950.

214. Tola, J. S. The histopathological and biological characteristics of primary neoplasms of the cerebellum and the fourth ventricle, with some aspects of their clinical picture, diagnosis, and treatment on the basis of 71 verified cases.
Acta Chir. Scandinav. Suppl. 164:112, 1951.

215. Tracy, F. E. and Mandeville, F. B. Roentgen therapy of medulloblastoma cerebelli.
Radiology 17:259-264, August, 1931.

216. Troland, C. E., Sahyoun, P. F. and Mandeville, F. B. Primary tumours of the brain, so-called reticulum cell sarcoma. Report of five cases.
J. of Neuropath. 7:322-334, 1950.

217. Tuthill, S. W. Spinal cord symptoms and signs as first manifestations of a medulloblastoma.
Mil. Surgeon 104:264-270, April, 1949.

218. Twining, E. W. Radiology of the 3rd and 4th ventricles.
Brit. J. Radiol. U. S. 12:385-416, 569-596, 1939.

219. Urechia, C. I. Medulloblastoma of vermis.
Vol. jubilaire, Parhon, 531-534, 1934.

220. Van den Bergh, R. Tumours of posterior fossa with supratentorial symptomatology.
Acta neurol. et psychiat. Belg. 53:472-482, 1953.

221. van der Drift, J. H. A. The significance of electro-encephalography for the diagnosis and localisation of cerebral tumours. H. L. Stenfert Kroese N. V. Leiden, 135, 1957.

222. Vodoginskaya, S. V. Metastasis of medulloblastoma of cerebellum into frontal lobe; case. Nevropat. i. psikhiat. 1-2, 9:105-108, 1940.

223. Wagenen, W. P. van. Verified brain tumours. End results of 149 cases eight years after operation. J. Amer. Med. Assoc. 102:1454-1458, 1934.

224. Walker, A. E. and Kople, T. L. Brain tumours in children: General considerations. J. Pediatr. 35:671-687, 1949.

225. Walt, F. Medulloblastoma in infant with abnormal cells in cerebrospinal fluid. Arch. Dis. Childhood 14:84-86, March, 1939.

226. Wanke, R. Anatomy and surgical treatment of medulloblastoma. Arch. f klin. Chir. 177:528-564, 1933.

227. Wilson, H. M. and Lutz, W. G. Lesions of the Aqueduct of Sylvius. Radiology 46:13[illegible], 1946.

Bibliography

228. Wilson, S. A. K. and Wolfsohn Organic Nervous Diseases in Identical Twins.
Arch. Neurol. & Psychiat. 21:477, 1929.

229. Winkelman, N. W. and Eckel, J. L. Midline cerebellar tumours. A clinico-pathologic report of cases showing diffuse dissemination throughout the central nervous system.
Surg., Gynec. & Obst. 63:372-381, 1936.

230. Wohlwill, Fr. Zur pathologischen Anatomie der malignen medianen Kleinhirntumoren der Kinder.
Zschr. Neurol. 128:587-614, 1930.

231. Wohlwill, F. Morphologic study of radiosensitive tumours; embryonary tumours of nervous tissue (medulloblastomas).
Lisboa med. 13:489-519, August, 1936.

232. Wohlwill, F. Zur Frage der sogenannten encephalitis congenita (Virchow).
Ztschr. ges. Neurol. u. Psychiat.
68:384-415, 1921.

233. Wolff, H. G. Headache and other head pain.
New York. Oxford. 1950.

234. Wright, J. H. Neurocytoma or neuroblastoma, a kind of tumour not generally recognised.
J. of Exper. Med. 12:556-560, 1910.

Bibliography

235. Yaskin, Ueber Entwicklungsanomalien bei Kleinhirnembryonen als Grundlage patholo-gischer Bildungen.
Arb. neur. Inst. Wien, 31, 13, 1929.

236. Yuile, C. L. Case of primary reticulum cell sarcoma of the brain: Relation of microglia cells to histiocytes.
Arch. Path. 26: 1036-1044, 1938.

237. Zimmerman, H. M. The nature of gliomas as revealed by animal experimentation.
Am. J. Path. 31:1-29, 1955.

238. Zondek, T. Case of medulloblastoma in child aged eight and a half months.
Ann. Paediat. 183:218-223, 1954.

239. Zülch, K. Y. Das Medulloblastom.
Arch. Psychiatr. 112:343-367, 1940.

240. Zülch, K. J. Ein Medulloblastom mit glatten Muskelfasern.
Arch. f. Psychiat. 114, 349-352, 1941.

241. Zülch, K. J. Fortschr. Neurol. & Psychiat. 18:513, 1950.

242. Zülch, K. J. Biologie und Pathologie der Hirngeschwülste in "Handbuch der Neurochirurgie" edited by H. Olivecrona and W. Tönnis.
Springer, Berlin, 3.

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AND

CEREBELLAR SARCOMAS

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