Surgery of the Diencephalon

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Series Editors: Robert N. N. Holtzman, M.D., and Bennett M. Stein, M.D.

SURGERY OF THE DIENCEPHALON

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Surgery of the Diencephalon

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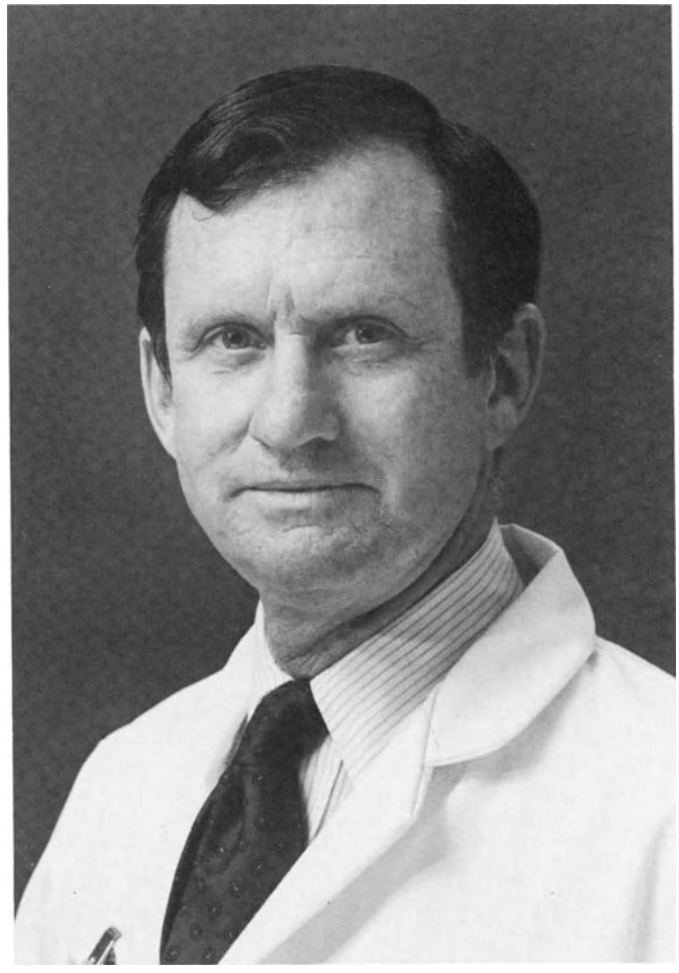
This volume is dedicated to

Bonita Stein, for her love and youthful vitality

—BMS

Nisson Ravitz, for his inspiration and courage,
and the memory of his small bag of gold coins
buried in the soil near his home
in Byelaya Tsyerkov

—RNNH



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Foreword

The problems of surgical intervention in and about the diencephalic region have stimulated the interest of neurosurgeons throughout the world. It was therefore not totally surprising when Professor A. N. Konovalov proposed this topic for discussion at the Fifth Annual Stonwin Medical Conference. Bringing the leading figures in this area to New York for a roundtable conference was an exciting challenge. Professor Russel H. Patterson, Jr., generously consented to be our guest of honor. The conference was held at the Winston Estate on July 13–14, 1987, and met our every expectation for a vigorous exchange of individual experiences and more importantly for a dialogue directed toward present and future expectations in the surgery of this region.

In addition, the discussions at that small dinner at the Harvard Club of New York led to the creation of an exchange program for neurosurgical residents, fellows, and faculty members of the N. N. Burdenko Neurosurgical Institute, Academy of Medical Science, and the Department of Neurosurgery of the New York Neurological Institute, which was planned for the spring and summer of 1988.

The Stonwin Conference and the exchange agreement and program fostered by the Harry Winston Medical Foundation, Inc., represent the fulfillment of goals conceived by Harry Winston and promulgated by his sons Ronald and Bruce.

Henry B. Roberts, Jr.
Publishing and Editorial
Consultant for the Stonwin
Medical Conference

Preface

The participants at the Fifth Annual Stonwin Medical Conference constituted an international group of specialists challenged by the limitations of present-day knowledge and the technical difficulties of dealing with the diencephalic region of the brain.

Their formal presentations and the subsequent discussions touched upon multiple facets of the diencephalon, including its anatomy and intrathalamic integrative processes, and its functions as a relay system and as an elaborator of hormones and neurotransmitters. The effects of a variety of pathological processes were discussed, and their respective appearances on the newest CT-scanning and MR-imaging devices were presented.

The surgical procedures currently available to alleviate pain, including electrode stimulation of the periaqueductal gray and the implantation of an externally fillable programmable pump, were discussed in detail along with the transcallosal, subfrontal, and pterional approaches for the removal of intraventricular, extraventricular, and parenchymal lesions. Considerable attention was given to ways to avoid the morbidity often encountered with intervention in the thalamic and hypothalamic regions.

The diversity of surgical approaches developed recently is indicative of the intense interest among neurosurgeons in overcoming some of the technical limitations previously encountered. The use of remote interventional techniques, such as ventriculoscopy, stereotaxy for electrode implantation and neuroaugmentation, and ND:Yag and CO_2 laser techniques, are currently evolving. These efforts represent a much-needed response to the deep-seated pathological processes that were heretofore considered inaccessible and irremediable.

Robert N. N. Holtzman
Bennett M. Stein

New York

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The Stonwin Medical Conference could not have taken place over the past five years without the help of numerous individuals who have generously given of their time. Their names are mentioned with great respect and appreciation.

Mr. Bruno Bartolini and Mrs. Margaret Bartolini, for their preparation of the estate each year to provide as comfortable an atmosphere as possible for our guests

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R.N.N.H.
B.M.S.

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Basic Science

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The Functional Organization of the Mammalian Dorsal Thalamus

Anatomy of the Primate Ventral Lateral Complex

Chisato Asanuma

INTRODUCTION

Sir Wilfrid Le Gros Clark, in his Arris and Gale lectures some 50 years ago, noted that "the thalamus is the anatomical equivalent of the very threshold of consciousness."[1] This dramatic statement very effectively draws attention to this centrally located, distinctive cell mass in the forebrain of all vertebrates within which all outside information (with few exceptions) first conspicuously pauses before being transmitted to its targets in the cerebral cortex or basal ganglia. At about the same time that Clark made that statement, a monograph on the thalamus was written by Walker.[2] More recently, Jones[3] has summarized our knowledge of the thalamus in a monograph several times the size of Walker's, and the difference in the amount of information contained in the two books gives one a good indication of the tremendous research activity on the thalamus that has taken place during the intervening 50 years or so. Yet, in spite of all that has transpired, precisely what the thalamus does and how it does it remain elusive; while (as will be seen in later chapters in this book) the effects of destruction of portions of the thalamus and/or associated neural structures in humans can be blandly straightforward (as in blindness), they can, in other situations, be extraordinarily enigmatic (as in the thalamic pain syndrome, recovery from certain types of severe chronic pain, and memory deficits).

Chisato Asanuma ▪ Laboratory of Neurophysiology, National Institute of Mental Health, NIH Animal Center, Poolesville, Maryland 20837.

In this chapter, some recent experimental studies of the thalamus will be briefly reviewed. Because of limitations of space, my intent here is to give only a flavor of some of the progress made in basic research during the past 10 years, particularly in the ventral lateral thalamic region of monkeys. For a more comprehensive treatment of our present state of knowledge of the thalamus, the reader is referred to the excellent review by Jones.[3]

BACKGROUND

The dorsal part of the diencephalon is that portion which is intimately related to the cerebral cortex. This general region has traditionally been divided into the dorsal thalamus, the ventral thalamus, and the epithalamus on both ontogenetic and phylogenetic grounds.[1,4,5] It is through the dorsal thalamus, which undergoes marked structural changes following cortical lesions, that all subcortically generated information (with the exception of some olfactory information and diffuse noradrenergic, serotonergic, and cholinergic inputs from the brainstem and basal forebrain) reaches the cerebral cortex.

The dorsal thalamus is divided into the anterior, ventral, lateral, and medial groups of nuclei by the internal medullary lamina. Each group contains several identifiable nuclear aggregates, all or most of which undergo severe retrograde atrophy after removal of appropriate areas of the cerebral cortex.[1,2,5–7] Within the internal medullary lamina lie several additional nuclear groupings, which show only a mild to moderate degree of retrograde changes following cortical ablations. These "intralaminar" nuclei show severe degenerative changes following lesions in the striatum.[8] While the nuclei of the dorsal thalamus have also been divided into "extrinsic" (relay) and "intrinsic" (associational) nuclei in the past,[7] recent experiments using modern anatomical tracing techniques have revealed that virtually all dorsal thalamic nuclei receive afferent input from at least one extrathalamic source, and project to some part of the cerebral cortex (see Jones[9] for review).

Experimental studies, both anatomical and physiological, carried out during the last 10 years have identified several organizational features that may be common to most thalamic nuclei. Several facets of the anatomy of the thalamus underlying these organizational features will be reviewed in this chapter. First, some important and fundamental features of the organization of thalamic relay nuclei will be described. To illustrate these, the discussion will focus on the ventral lateral nucleus of primates, in part because I will be able to draw from my own work on this nucleus, but also because it is of some clinical relevance. Several selected recent findings, addressing features shared by the entire dorsal thalamus, will be briefly reviewed at the end of the chapter.

THE VENTRAL LATERAL COMPLEX OF PRIMATES

The ventral lateral complex is the principal thalamic relay to the agranular cortex of the precentral gyrus.[2] It is through this thalamic region that the cerebellum and other

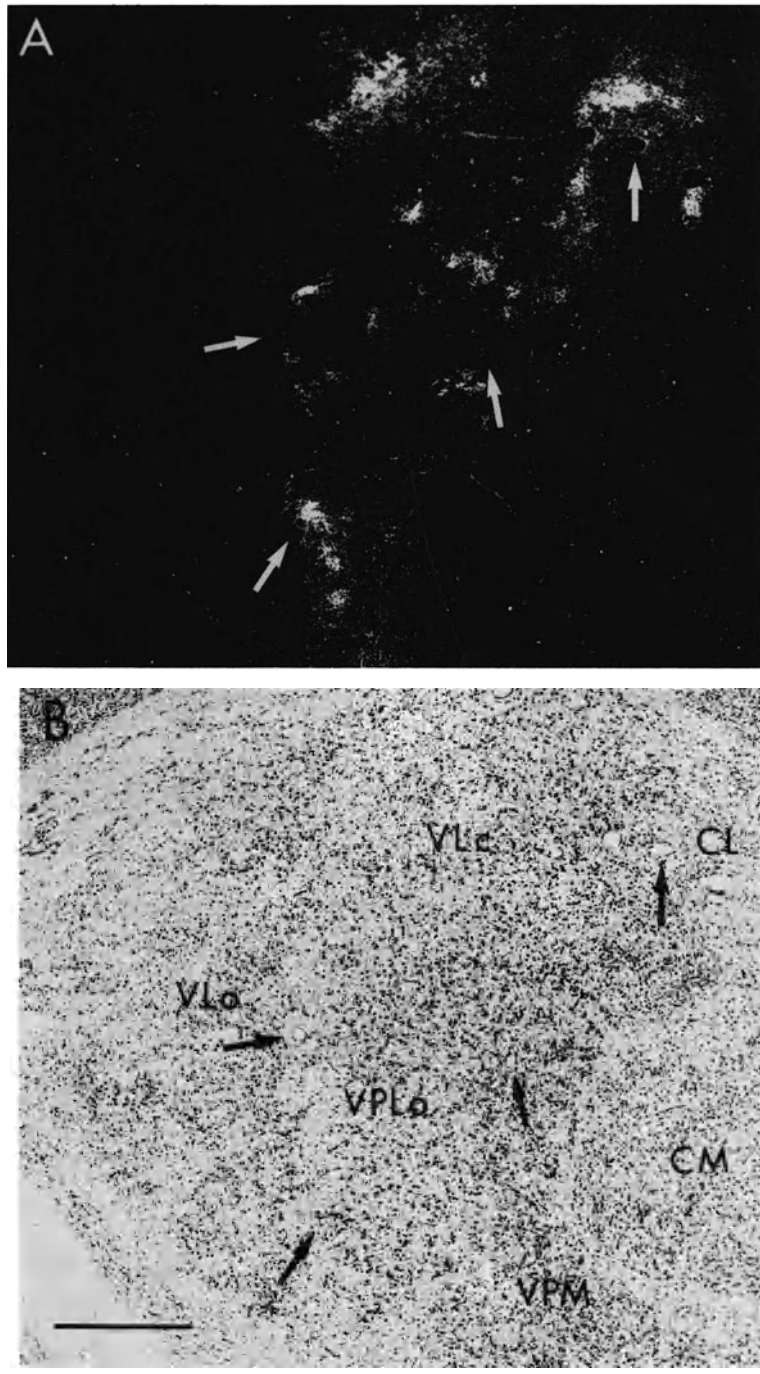
motor-related subcortical regions, such as the basal ganglia, are thought to exert a profound influence over movement performance controlled by the motor cortex.[10–12] Although this general concept has been accepted for many years, there has been little agreement about the exact distributions within this thalamic region of the various subcortical inputs and the projections of each upon the various motor-related fields within the precentral gyrus. What emerges from recent anatomical and physiological studies is that the ventral lateral complex is not a diffuse, homogeneous entity in which cerebellar, pallidal, and substantia nigral inputs converge, and through which they project to the motor cortex. Evidence obtained in experiments on primates as well as nonprimate species indicates that each of these thalamic afferent systems terminates in a separate component of the ventral lateral complex, and that these separate components in turn project independently upon distinct cortical targets.[13–19]

Another traditional view is that the cerebellothalamic fibers originate only in the dentate nucelus of the cerebellum, while the interposed nucleus projects principally to the red nucleus, and the fastigial nucleus projects to the brainstem vestibular nuclei and reticular formation.[10,20–25] More recent experimental evidence, however, indicates that all three deep cerebellar nuclei project upon the ventral lateral complex—the dentate and interposed nuclei contralaterally and the fastigial nucleus bilaterally.[13–15,26–31] Furthermore, the long-held belief that the red nucleus, to which the dentate and interposed nuclei project,[16,31,32] projects in turn upon the ventral lateral complex has also been disproved.[33,34]

General Organization

Within the ventral lateral complex of nonhuman primates there is a cytoarchitecturally unique cell-sparse zone, occupying the caudal portion of the complex,[13–15,28] that is probably homologous with portions of the nucleus ventralis intermedius in humans.[35] In macaque monkeys, this cell-sparse zone includes the following nuclei identified by Olszewski[36]: VPLo, VLc, VLps, X, and extensions of these around the cell clusters of VLo. Neurons with both large and small cell bodies are found evenly dispersed and at low density throughout this zone. In appropriately sectioned material, this zone can be readily distinguished, on the basis of Nissl staining characteristics, from adjacent thalamic nuclei (Fig. 1). The cell-sparse zone is the only part of the ventral lateral complex to receive ascending inputs from the deep nuclei of the cerebellum, and thus the cerebellorecipient region is more restricted than previously assumed. It occupies a region immediately rostral to the more clustered neurons of the ventrobasal complex (VPLc and VPM), which receives lemniscal input, and immediately caudal to the cell islands of the rostral ventral lateral nucleus (VLo), which receives projections from the globus pallidus.

The thalamic projections from the dentate and interposed nuclei are dense throughout the contralateral cell-sparse zone, and their terminal ramifications extend continuously throughout all subnuclear components[14] (Fig. 1). The thalamic projections of the fastigial nucleus are sparse, bilateral, and concentrated ventrally within the same thalamic zone,[14,26] and another, less dense input to this zone arises in the vestibular nuclei.[14,37]

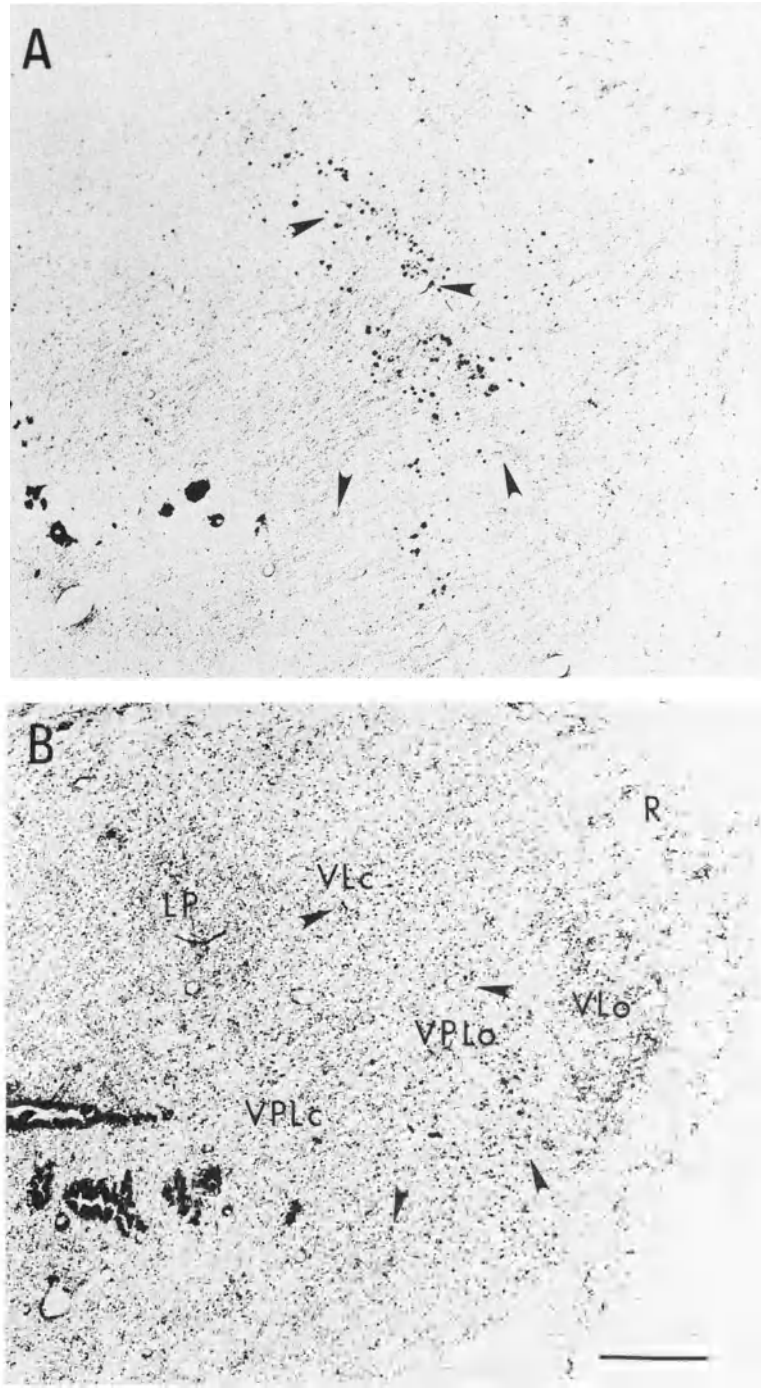

A
B
VLc
CL
VLo
VPLo
CM
VPM

The thalamic inputs from the principal somatic sensory pathway, the dorsal column–medial lemniscal system, in contrast, terminate more caudally within the adjacent, morphologically distinct, VPLc nucleus and do not extend into the cell-sparse cerebellar termination zone of the ventral lateral complex.[14,19] Although the dorsal column inputs do not terminate within the cell-sparse relay to the motor cortex, another somatosensory input, the spinothalamic terminations, extend into this region and interdigitate with the cerebellothalamic terminations.[14,19]

Other anatomical fiber-tracing studies indicate that the thalamic inputs from the basal ganglia do not overlap with the cerebellothalamic terminal territory. Inputs from the globus pallidus have been reported to terminate in the parvicellular portion of the ventroanterior nucleus (VApc) and in the VLo and VLm nuclei.[11,12,18,28,38–41] The latter two nuclei, VLo and VLm, while also subdivisions of the large primate ventral lateral complex, occupy regions rostral to and independent of the caudal, cell-sparse cerebellorecipient ventral lateral zone.[14,18] The thalamic inputs from the substantia nigra, in contrast, have been reported to terminate in the magnocellular portion of VA and the VLm nucleus.[38,42,43] Thus, nigrothalamic terminations have generally been reported to occupy thalamic regions that are independent of pallidothalamic terminations; however, there may be a small zone of overlap in the VLm nucleus. Direct comparisons of the thalamic projections from the substantia nigra with those from the globus pallidus are not yet available, and it is unclear whether the same portions of the VLm nucleus receive convergent inputs from these two afferent paths.

These distinct regions of the ventral lateral complex that differ in their major afferent input differ as well in the cortical regions to which they project. This cell-sparse zone of the ventral lateral complex is interconnected with the lateral agranular cortex of the frontal lobe, which includes the motor cortex and the premotor cortex. Following large retrograde tracer injections into cortical area 4, labeled thalamocortical relay cells are distributed throughout this cell-sparse thalamic zone (Fig. 2). Available information on the details of the cortical connectivity of this thalamic region indicates that the caudalmost portion of the cell-sparse zone, or the subnuclei VPLo and VLc, is selectively interconnected with the caudalmost primary motor cortex, or cortical area 4,[19,44] while the rostralmost premotor cortical field, which actually occupies a small portion of Brodmann's area 6, has been suggested to be more closely associated with the rostral, nucleus X component of the cell-sparse zone.[45] Although it is now clear that the cell-sparse, cerebellorecipient thalamic zone is exclusively interconnected with the lateral agranular cortex of the precentral gyrus (see Jones[3] for review), the precise relation of this thalamic zone to the primary motor cortex, to the premotor cortex, and to the intervening areas has not been worked out in adequate detail at this time.

Figure 1. Darkfield (A) and brightfield (B) photomicrographs of a parasagittal section through the thalamus of a cynomolgus monkey following an injection of tritiated amino acids into the interposed nucleus of the cerebellum, demonstrating the continuity of interpositothalamic terminations across the VPLo and VLc nuclei of the thalamic cell-sparse zone. Terminal clusters in CL are also evident. Arrows point to the same blood vessels in each panel. Bar, 1 mm. CL, central lateral nucleus; CM, centre médian nucleus; VLc, ventrolateral nucleus, pars caudalis; VLo, ventrolateral nucleus, pars oralis; VPLo, ventroposterolateral nucleus, pars oralis; VPM, ventroposteromedial nucleus. (Reproduced with permission from Asanuma et al.[14])


A
B
R
VLc
LP
VLo
VPLo
VPLc

The VPLc nucleus is one of the primary components of the ventrobasal complex, which relays somatic sensory information from the spinal cord to the primary somatic sensory cortex (e.g., see Jones et al.,[44] Jones and Friedman,[46] Mountcastle and Henneman,[47] Poggio and Mountcastle,[48] and Rose and Mountcastle[49]).

The cortical projections of the rostral portions of the ventral thalamic nuclei, receiving inputs from the basal ganglia, have not been examined in as much detail as have the projections of the caudal cell-sparse ventral lateral region to the primary motor cortex. The predominant cortical target of the VLo nucleus appears to be the supplementary motor cortex,[19,45,50] although whether or not VLo provides the only thalamic input to the supplementary motor cortex has been disputed.[50,51] The cortical projections of the other thalamic nuclei reported to receive inputs from the basal ganglia, while suggested to project to the dorsolateral prefrontal cortex and to portions of the premotor cortex,[52] remain to be convincingly detailed. Of course it is well established that the mediodorsal nucleus provides the primary thalamic input to the frontal granular cortex,[53,54] but the exact locus of the transition in the frontal lobe, between mediodorsal recipient regions and the cortical targets of the rostral ventral nuclei, also needs to be clarified.

Thus, anatomical studies indicate that the ventral lateral region is quite developed in primates, and that within this large thalamic expanse a caudal, cell-sparse zone, receiving cerebellothalamic terminations, can readily be differentiated from its adjoining nuclei located either rostrally or caudally (see Fig. 3). This zone receives afferent inputs from all three deep cerebellar nuclei as well as some afferent inputs from the vestibular nuclei and spinothalamic tract, and projects upon the lateral agranular cortex of the precentral gyrus. The caudally located VPLo and VLc nuclei of the cell-sparse zone project upon the primary motor cortex, and the rostral nucleus X projects upon the premotor cortex. Immediately caudal to the cell-sparse ventral lateral zone, the ventrobasal complex receives afferent inputs from the dorsal column nuclei and projects upon the first somatic sensory cortex. Rostral to the cell-sparse zone, another ventral lateral zone with islands of densely clustered neurons (VLo), receives pallidothalamic terminations and projects upon the supplementary motor cortex. Additional afferents from the globus pallidus project further rostrally, to the VApc and VLm nuclei, while afferents from the substantia nigra are restricted rostrally within the VAmc and VLm nuclei. The cortical projections of the rostralmost components of the ventral nuclei need to be investigated further.

Figure 2. Adjacent parasagittal sections through the thalamus of a cynomolgus monkey following an injection of horseradish peroxidase into the arm area of the motor cortex, demonstrating the continuity of thalamocortical projection neurons across the VPLo and VLc nuclei of the thalamic cell-sparse zone. (A) Uncounterstained section treated with tetramethylbenzidine; (B) adjacent Nissl-stained section. Arrows point to the same blood vessels in each panel. Bar, 1 mm; LP, lateroposterior nucleus; R, thalamic reticular nucleus; VLc, ventrolateral nucleus, pars caudalis; VLo, ventrolateral nucleus, pars oralis; VPLc, ventroposterolateral nucleus, pars caudalis; VPLo, ventroposterolateral nucleus, pars oralis. (Reproduced with permission from Asanuma et al.[14])

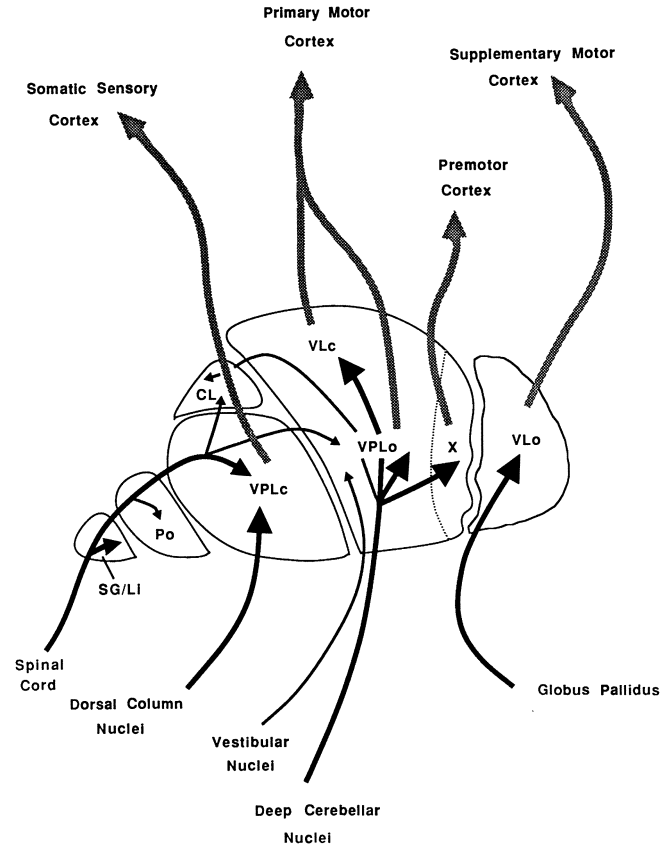


Figure 3. Schematic diagram, in the parasagittal plane, of the thalamic distributions of axons arising in the deep cerebellar nuclei, the dorsal column nuclei, the spinal cord, the vestibular nuclei, and the globus pallidus, and their cortical projections. CL, central lateral nucleus; Po, posterior nucleus; SG/Li, suprageniculatus/limitans nuclei; VLc, ventrolateral nucleus, pars caudalis; VLo, ventrolateral nucleus, pars oralis; VPLc, ventroposterolateral nucleus, pars caudalis; VPLo, ventroposterolateral nucleus, pars oralis; X, nucleus X. (Adapted from Asanuma et al.[14])

Detailed Organization

In addition to its readily differentiable cytoarchitectonic and general connectional features, several levels of organization intrinsic to the cell-sparse cerebellar relay to the motor cortex can be identified. These finer aspects provide several clues with regard to the types of information that could be transmitted by this thalamic nucleus and are, therefore, of interest in view of (1) the representation of motor functions in the deep nuclei of the cerebellum, and (2) the issue of whether the ascending motor-related signals are transmitted by the thalamus with precision, in a manner comparable to what has been reported for other, more intensively studied thalamic relay nuclei which

would be compatible with the focally specific, columnar organization that is known to exist in the primary motor cortex.[55]

The details of the representation of body parts within the deep nuclei of the cerebellum have proven elusive to a variety of electrophysiological approaches, undoubtedly due at least in part to the susceptibility of cerebellar neurons to anesthetics (see Thach[56] for discussion). While acute studies done in anesthetized animals have yielded conflicting results with regard to the body somatotopy within the deep nuclei,[58–62] single-unit recordings from conscious monkeys trained to perform tasks with different muscle groups have provided some preliminary evidence that, at least in the dentate and interposed nuclei, the activity of spatially separate groups of neurons is modulated during activity of different muscle groups, and that the distribution of these groups suggests that neurons representing leg muscles tend to be located more rostrally than those representing arm muscles.[63]

A general lamellar organization of the thalamic cell-sparse zone can be demonstrated anatomically on the basis of a topographic interconnection with the somatotopically organized motor cortex. Thus, retrogradely labeled thalamocortical relay cells, following restricted tracer injections into the motor cortex, are seen to occur within a curved lamella that is of restricted mediolateral thickness but extends through both the dorsoventral and anteroposterior dimensions of the cell-sparse zone. These individual lamellae are concentrically arranged in an onionlike configuration throughout the mediolateral extent of the cell-sparse zone, with anterior body parts represented in medially situated lamellae and posterior body parts within those situated laterally.[44,64]

The thalamic projections from each of the deep cerebellar nuclei terminate independently of one another upon similar concentrically organized lamellae within the cell-sparse zone.[15,59] The caudalmost portions of the dentate nucleus, the interpositus nucleus, and the fastigial nucleus project to the lateralmost lamellae, and rostral portions of each nucleus project medially. Thus, considering the known somatotopy of the motor map in area 4[65] and the topography of the thalamocortical projections to this region of cortex,[44] these anatomical connections suggest by extrapolation that within each of the three deep cerebellar nuclei different anteroposterior sectors are related to different body parts, and that indeed there is a complete and independent representation of body parts in each nucleus (Fig. 4).

Recent physiological experiments indicate that within the lateral precentral gyrus of monkeys, a premotor cortical field, separate from the primary motor cortex, occupies the postarcuate cortex (which also receives a cerebellar input by way of the thalamus). This rostrally located cortical field is now thought to be involved in motor preparation and the sensory guidance of movement (see Wise[66,67] for review). The details of the projections from the rostral part of the thalamic cell-sparse zone to this cortical field have not yet been thoroughly examined, so it is unclear whether the cerebellar projection to the premotor cortex is organized with the same degree of precision found in its projection to the primary motor cortex. The connectivity of this region of cortex, and for that matter of the entire frontal lobe, is presently attracting the research interest it merits, and hopefully the details of the thalamic relations of this region will soon be clarified.

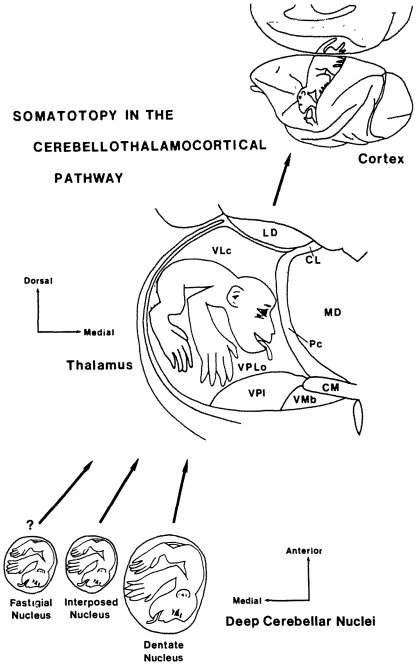


Figure 4. Schematic diagram of the somatotopic organization of each of the deep cerebellar nuclei, as predicted by their connectivities with the VPLo–VLc nuclei of the thalamic cell-sparse zone, and their well-established relationship with the primary motor cortex. The motor cortex figurine at top right is derived from Woolsey et al.[65] [It should be noted that recent studies indicate that an additional motor representation area—the premotor cortex, quite separate from the primary motor cortex—occupies the rostral postarcuate region of the precentral gyrus (e.g., see Wise[66] and Wise[67]); the details of the relationship of the premotor cortex with the rostral, nucleus X region of the cell-sparse zone has yet to be explored.] CL, central lateral nucleus; CM, centre médian nucleus; LD, laterodorsal nucleus; MD, mediodorsal nucleus; Pc, paracentral nucleus; VLc, ventrolateral nucleus, pars caudalis; VMb, basal ventromedial nucleus; VPI, ventroposterior, inferior nucleus; VPLo, ventroposterolateral nucleus, pars oralis. (Reproduced with permission from Asanuma et al.[15])

Recent anatomical studies have begun to reveal a finer level of organization within the curved lamellae of the thalamic cell-sparse zone, and the precision of this organization is comparable to that seen within the adjacent somatic sensory relay nucleus, the ventrobasal complex. Within the ventrobasal complex as well as the cell-sparse ventral lateral region, different body parts are systematically represented in a series of concentrically organized lamellae.[44,46,48,68–71] A subsidiary, detailed organization within these somatotopic lamellae of the ventrobasal complex was first noted by Poggio and Mountcastle,[48] who demonstrated that there are clusters of neurons within regions responsive to similar body parts the receptive fields of which have the same place and modality properties. Upon detailed examination, it was found that these clusters of place- and modality-specific nuerons in the ventrobasal complex are arranged as elongated rodlike aggregations of cells, extending rostrocaudally throughout the complex, that receive inputs from similarly oriented, rostrocaudally elongated aggregations of incoming medial lemniscal terminal arborizations.[44,46,71]

A similar subsidiary organization within the cell-sparse zone was first identified following retrograde tracer injections into the motor cortex, when it was demonstrated that intralamellar, rostrocaudally elongated rodlike aggregations of thalamocortical relay cells, quite similar in both size and orientation to those established to occupy the adjacent ventrobasal complex, were labeled within the cell-sparse zone of the ventral lateral complex.[44] Subsidiary foci are also found within the cell-sparse ventral lateral region following injections of tritiated amino acids, an anterograde tracer, into each of the deep cerebellar nuclei. Fibers emanating from tracer injections involving large parts of the dentate nucleus give rise to rodlike aggregations of terminations that are

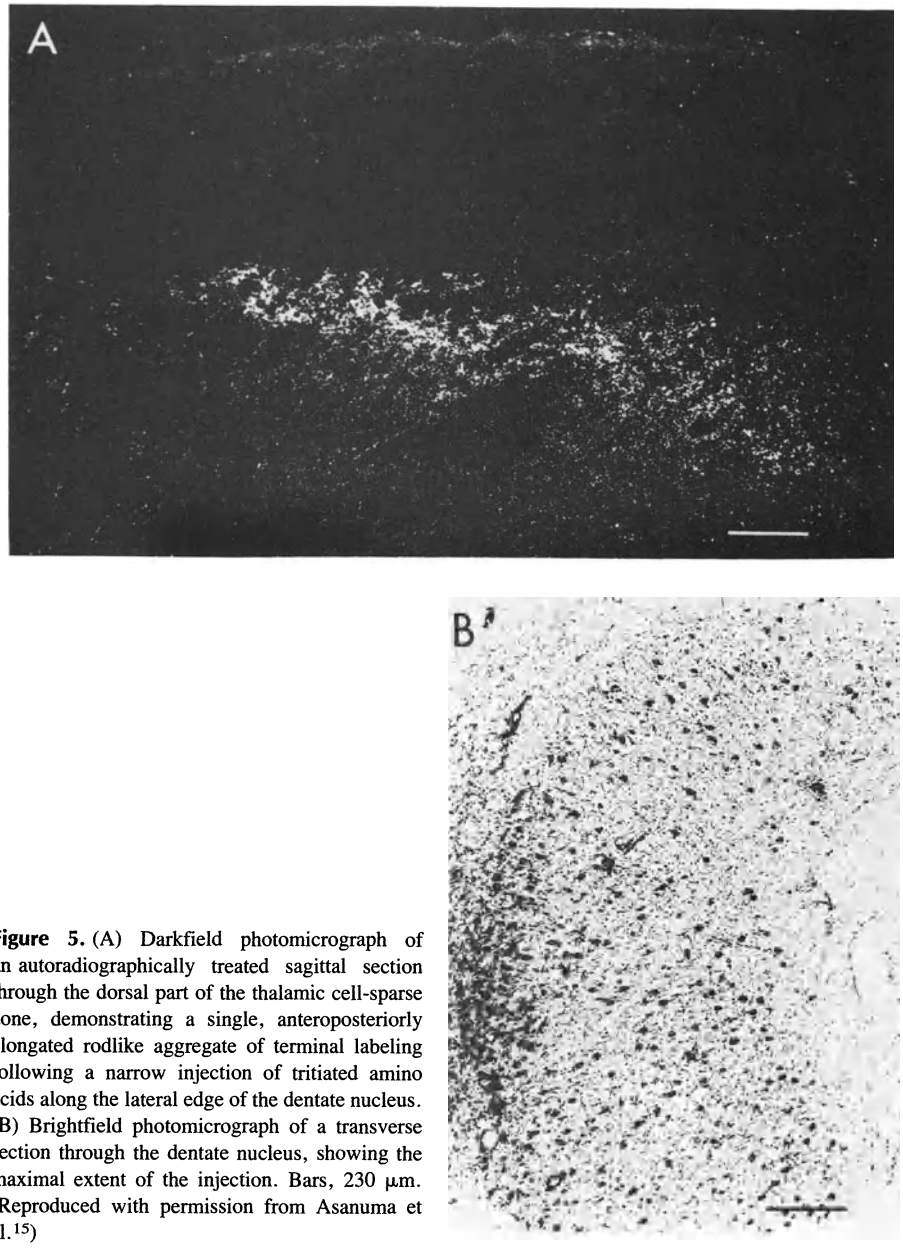


Figure 5. (A) Darkfield photomicrograph of an autoradiographically treated sagittal section through the dorsal part of the thalamic cell-sparse zone, demonstrating a single, anteroposteriorly elongated rodlike aggregate of terminal labeling following a narrow injection of tritiated amino acids along the lateral edge of the dentate nucleus. (B) Brightfield photomicrograph of a transverse section through the dentate nucleus, showing the maximal extent of the injection. Bars, 230 μm. (Reproduced with permission from Asanuma et al.[15])

elongated rostrocaudally and confined within curved lamellae, similar to the orientation of the rodlike aggregations of neurons that project to the motor cortex.[15,72] In addition, a focal injection of the tracer into the dentate nucleus results in the labeling of a single, elongated, rodlike zone of terminations that extends anteroposteriorly through the cell-sparse ventral lateral region (Fig. 5). Different dentatothalamic rods arising in different parts of the dentate nucleus do not overlap with one other (Fig. 6), and the

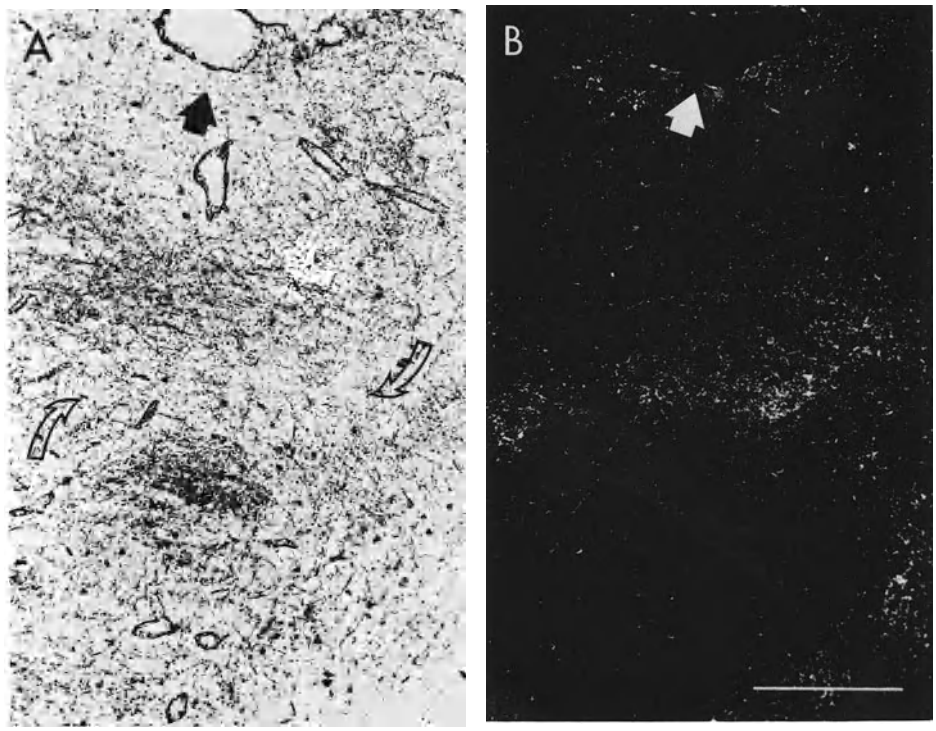


Figure 6. Adjacent parasagittal sections through the thalamic cell-sparse zone in an animal which received a partial lesion of the dentate nucleus followed by a subsequent injection of tritiated amino acids into other portions of the dentate nucleus and into the interposed nucleus. (A) Brightfield photomicrograph of a section treated for silver impregnation of degenerating axons, demonstrating two degenerating dentatothalamic rods; (B) darkfield photomicrograph of an adjacent section in the same region that was treated for autoradiography, demonstrating the independence of the autoradiographically labeled rod from those labeled with the axonal degeneration technique. The solid arrows point to the same blood vessel in each panel. The large curved arrows in (A) indicate the region labeled in (B). Bar, 500 μm. (Reproduced with permission from Asanuma et al.[14])

gaps intervening between dentatothalamic rods appear to be filled by the interpositothalamic, fastigiothalamic, and spinothalamic terminations, which are more punctate than rodlike.[15]

While the significance of these focal domains of afferent terminations and efferent neurons within the caudal ventral lateral complex remains uncertain, what is clear is that the cerebellar projection to the motor cortex in primates is topographically organized with considerable precision, and is focally distributed. It remains to be seen if these anatomical foci represent some fundamental units of movement programming. It should, however, be mentioned that the existence of these focally organized thalamic channels does not necessarily preclude some degree of convergence of the various cerebellar inputs upon some thalamic neurons due to the considerable length and radiating configuration of the dendrites of the large projection neurons in this thalamic

region.[73] Recent experiments in cats (in which the segregation of the different cerebellar inputs within VL does not appear to be complete[74]) indicate that dentate inputs and interpositus inputs do indeed converge on some, though not all, projection neurons.[75–77] The exquisitely precise anatomical organization seen in the afferent inputs to the cell-sparse ventral lateral thalamic region in *primates,* however, implies that neurons in this thalamic region should be more profoundly influenced by one group of topographically specific inputs than another. This, taken together with the focal and topographic manner in which the projection of this thalamic region to the primary motor cortex is organized,[44] indicates that the principal subcortical input to the motor cortex is capable of maintaining body topography in afferent signals while also preserving the integrity of a finer, as yet unidentified, unit in motor programming.

GENERAL FEATURES OF THALAMIC RELAY NUCLEI

Thus far, we have seen that the primate ventral lateral nucleus, like other, more intensively studied thalamic relay nuclei (see Jones,[3] Jones,[9] and Sherman and Koch[78] for review), is organized in a way that allows a faithful preservation of ascending afferent information for its subsequent transmission to the cerebral cortex. This naturally raises the question: "Is the thalamus more than a mere relay center?" While a comprehensive answer to this question remains elusive, our eventual understanding of the "function" of the thalamus may hinge on the identification of organizational features common to all thalamic nuclei. In this section, I will review a few of the more salient features of the dorsal thalamus—features characteristic of most of the nuclei studied thus far. Hopefully these features will prove to be of importance to thalamic function.

In the previous section I have emphasized cytoarchitectural and connectional differences that distinguish thalamic nuclei from one another. There are, however, certain structural features common to most thalamic nuclei. For example, at the ultrastructural level, a distinctive synaptic organization is found within thalamic glomeruli throughout all nuclei of the dorsal thalamus.[79] Large aggregations of dendrites and axon terminals are often virtually completely encapsulated by a wrapping of thin astrocytic processes. The components of these aggregates are the terminal ending of an ascending afferent axon (excitatory, and always presynaptic), the dendritic process of a thalamocortical relay cell (always postsynaptic), and several presumably inhibitory elements (appearing as both presynaptic and postsynaptic profiles), which may be derived from the axons and dendrites of thalamic interneurons[79–92] (see Fig. 7).

The neurons within each thalamic nucleus are overwhelmingly of a single cell type, the so-called "principal neurons."[93] It is these neurons, of course, which send axons to the cerebral cortex. While the presence of thalamic interneurons has been well documented at the ultrastructural level, they have not been consistently seen at the light microscopic level, and even when seen, reports of their numbers have varied from nucleus to nucleus and from species to species.[94–102] The most readily identifiable population of thalamic "interneurons" is actually derived from the ventral thalamus—these are the neurons of the thalamic reticular nucleus.

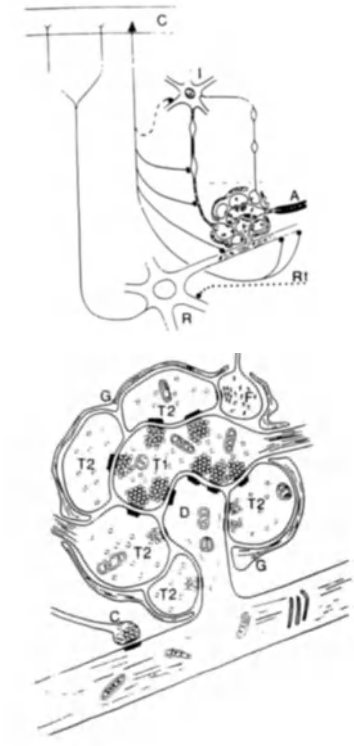


Figure 7. Schematic diagram of the synaptic organization typical of most thalamic nuclei. The glomerular synaptic aggregates tend to be ensheathed in astrocytic processes (G), and contain dendritic protrusions (D) of thalamocortical relay cells (R), receiving terminals (T1) of ascending afferent fibers (A), and presynaptic dendrites (T2) of interneurons (I). Axons of interneurons (F) also terminate upon the intraglomerular presynaptic dendrites. The terminals of corticothalamic axons (C) and reticular nucleus axons (Rt) synapse directly on dendritic processes outside the glomeruli. (Reproduced with permission from Jones.[9])

The thalamic reticular nucleus used to be held as the final "link," en route to the cerebral cortex, in the nonspecific brainstem ascending reticular activating system.[103–105] The thalamic reticular nucleus is a thin, sheetlike layer of neurons that encapsulates the rostral and lateral aspects of the thalamus and thus occupies a potentially pivotal position through which ascending thalamocortical axons and descending corticothalamic axons traverse. This ascending activating system was considered to originate in the brainstem reticular formation and to extend through the intralaminar nuclei of the thalamus to the thalamic reticular nucleus, from which it could directly influence the cerebral cortex. Studies using modern neuroanatomical methods revealed, however, that the thalamic reticular nucleus cannot be the final link to the cortex, since it does not project to the cerebral cortex, but rather projects back into the thalamus[106–107] (see Jones[3] for review). Recent studies have also shown that thalamic reticular neurons receive inputs from collaterals of thalamocortical axons, collaterals of corticothalamic axons, and a cholinergic input possibly arising in the midbrain.[108–110]

Recent immunohistochemical studies localizing the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD) show that the densest concentration of GAD-containing neurons in the thalamus occurs in the thalamic reticular nucleus[111–113] (Fig. 8). That these neurons are inhibitory has also been confirmed electron microscopically by Montero and Scott,[114] who examined the thalamus using the autoradiographic technique at the electron microscopic level following reticular nucleus

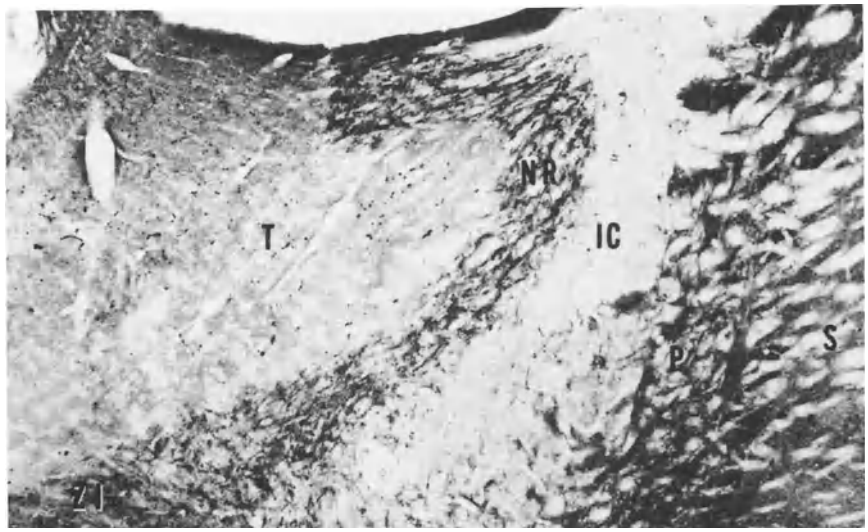


Figure 8. Frontal section through the thalamus of a rat treated immunohistochemically for GAD, demonstrating the dense concentration of GABAergic neurons throughout the thalamic reticular nucleus (T). IC, internal capsule. (Reproduced with permission from Houser et al.[111])

injections of tritiated amino acids. These investigators showed that reticular nucleus axons terminate directly upon the dendrites of principal neurons in the thalamus, and that their terminal boutons contain flattenable or pleimorphic vesicles and form symmetrical synapses, which are usually indicative of inhibitory synapses.[115,116]

This inhibitory property of reticular nucleus neurons, as well as the rhythmic activity in this nucleus that has previously been demonstrated physiologically, has supported the notion that these neurons are involved in the generation of the EEG spindle oscillations thought to originate in the thalamus (e.g., see Steriade and Dêschenes[117] and Steriade et al.[118]). There is, however, a recent physiological study that has yielded some surprising results. This is the work of Llinás and Jahnsen,[119–122] using in vitro thalamic slice preparation (Fig. 9). These studies have shown that the principal neurons of the thalamus have two distinct, voltage-dependent response properties. When a thalamic neuron is near its normal resting potential, or is depolarized, it responds to injected current by firing at a tonic rate. This firing rate is modest, and proportional to the size of the injected current. However, when a hyperpolarized thalamic nueron is stimulated, it fires in an extremely fast burst of spikes, followed by a nonresponsive period of 80–150 msec.

Since the inhibitory reticular nucleus input may function to hyperpolarize the principal cells and, in light of these recent findings, thus "prime" them for a burst of spikes, these results have stimulated interest in and hypotheses concerning the function of the thalamic reticular nucleus. One of the ideas that has received much attention has been the "searchlight hypothesis," which proposes that the thalamic reticular nucleus serves to direct selective attention. This idea was put forth by Crick,[57] and his paper outlines a process by which the reticular nucleus might highlight the activity in specific

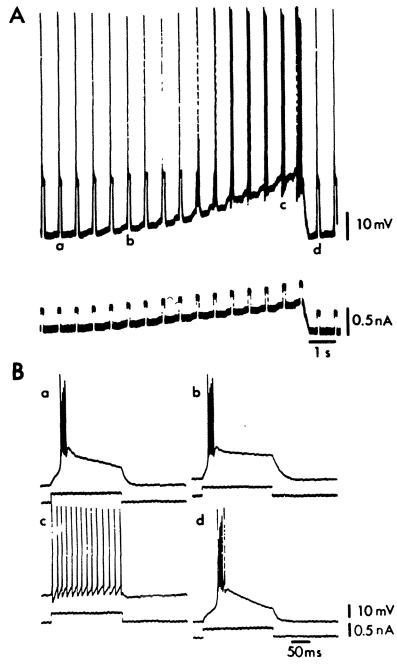


Figure 9. An intracellularly recorded trace (top sweeps) from a thalamic neuron, demonstrating the voltage-dependent switching from burst activity to tonic firing. In (A), a ramp current was injected to slowly depolarize the cell, while applying at the same time brief outward current pulses of constant amplitude (bottom sweeps). The sudden switch from burst responses to tonic responses is evident as the membrane is depolarized at about 10 mV. Some of the responses in (A) are shown at high sweep speed in (B). (From Llinás and Jahnsen,[122] reprinted by permission from *Nature* 297:406–408 © 1982, Macmillan Magazines, Ltd.)

thalamocortical channels by causing foci in the dorsal thalamus to fire in rapid bursts. While highly speculative, this publication has rekindled interest in the thalamic reticular nucleus, and hopefully the resulting experimental work will reveal some clues as to the function of this nucleus that is so intimately associated with the dorsal thalamus.

In conclusion, although we still cannot really say what function the thalamus actually performs, recent research has begun to provide some intriguing clues—clues suggesting that some of the basis for an understanding of the functional significance of the thalamus may lie in intrathalamic integrative processes, and clues that will, undoubtedly, provoke further experimentation.

DISCUSSION

WHAT IS THE ROLE OF THE PULVINAR?

Stein asks what the role of the pulvinar complex might be, and whether the pulvinar complex could be an integrating center for the acquisition of knowledge or for the patterning of cortical activities.

The pulvinar complex is the dominant element in the lateral group of thalamic nuclei and, in nonhuman primates, is subdivided into four nuclei: inferior, lateral, medial, and oral. Although some of these subdivisions receive small amounts of direct inputs from the retina, these nuclei generally receive preprocessed inputs from the superficial or deep layers of the superior colliculus, the pretectum, or the cortex. The inferior and lateral pulvinar nuclei appear to be

concerned with visual processes, while the oral pulvinar nucleus appears to be involved with somatic sensory processes. The functions of the medial pulvinar nucleus are still vague. The cortical interconnections of the medial pulvinar nucleus suggest that it is closely related to those cortical areas that process complex neural processes such as attention, motivation, and memory formation. The medial pulvinar nucleus, along with the mediodorsal nucleus, incidentally, are the nuclei that undergo the greatest phylogenetic development in humans. Because of the multitudes of "associational" cortical areas that are known to be interconnected with the nuclei of the pulvinar complex, this part of the thalamus is thought to integrate and coordinate the activities of associational cortical areas.

Japanese Experience with Pulvinar Destruction for the Control of Chronic Pain

Fukushima indicates that his work for pain control consisted of thalamotomies directed at the centre médian or the subthalamic/parafascicular nuclear complex. Following extensive unilateral or bilateral ablative lesions that also involved the pulvinar, there were transient memory impairments and personality alterations that were always completely resolved within 1–2 months after surgery. Thus, the removal of cavernous hemangiomas from the dorsal posterior thalamus does not appear to have permanent adverse sequelae.

AREA X OF OLSZEWSKI

Carmel asks to have area X clarified: What is area X, and what happens to it in the human?

Olszewski named the rostral part of the caudal ventral lateral complex nucleus X, as it appears to be an isolated, cell-sparse nucleus wedged between the internal medullary lamina and the more laterally located clustered neurons of the VLo nucleus in material sectioned frontally. Since the cytoarchitecture and connectivities of nucleus X resemble its caudally adjoining nuclei—VPLo and VLc—it makes sense to include nucleus X as a component of a common thalamic cerebellar relay nucleus. Nucleus X probably corresponds to the rostralmost part of the nucleus ventralis intermedius in humans.

ASPECTS OF THE THALAMUS

Modular Organization of the Thalamus

Friedman suggests that the modular organization of thalamic nuclei may permit the transmission of a variety of information to the cerebral cortex. Independent X- and Y-cell channels, for example, have been found to underlie the transmission of visual information by the lateral geniculate nucleus, and Friedman wondered if this might also be the case in the motor system.

Multiple thalamic foci are labeled following focal injections of tracers made in either the motor cortex or in the deep cerebellar nuclei. The multiplicity of foci, each representing similar body parts, suggests that multiple channels representing different "modules" of topographically similar information exist in the cerebellothalamocortical system as well. What these modules represent, however, is still a mystery.

Plasticity in the Thalamus

Abrams asks if there is evidence for plasticity in the thalamus. Can the destruction of a small region of the thalamus result in the formation of new connections?

There are few conclusive reports demonstrating alterations in thalamic connections and

functions following partial thalamic lesions in adulthood. The few reports suggesting postlesion changes have been limited to electrophysiological studies, and it is not yet clear if the observed "novel" receptive field properties reflect newly formed connections or simply the "unmasking" of previously undetected response properties. Adult "sprouting" of axons has been convincingly demonstrated in several neural systems, and it is quite possible that this phenomenon occurs in the thalamus as well. This important issue has not received much experimental attention, since the changes may be subtle and difficult to identify with certainty.

Schemes for the Classification of Thalamic Nuclei

Kandel asks if there are any new schemes, based upon transmitter systems, for reassessing thalamic nuclei.

At present, the clearest demonstration of a population of homogeneous, neurochemically specific thalamic neurons has come from the immunohistochemical identification of the presence of glutamic acid dehydrogenase, a precursor enzyme for GABA, within the large neurons of the thalamic reticular nucleus. Specific markers for identifying individual nuclei of the dorsal thalamus have yet to be identified.

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2

Diencephalic Neurology

Hypothalamic Obesity and Emaciation

Gary M. Abrams

HYPOTHALAMIC NEUROHORMONES: AN OVERVIEW

Advances in our knowledge of the mechanism of neurosecretion have provided new insight into neurochemical control of the pituitary gland. Neurosecretory neurons, predominantly in the medial basal hypothalamus, have been shown to produce releasing and inhibitory factors that are delivered to the pituitary gland via the portal vasculature of the median eminence.[1] These neurohormones have generally been characterized as oligopeptides or biogenic amines. While most experimental data have been obtained in the rodent, and species differences do exist, the location and function of these neurohormones in primates is analogous to those in other mammals. Neurons of the hypothalamus project to a wide variety of extrahypothalamic sites. "Hypothalamic hormones" have also been localized in neurons in many regions of the central nervous system that are not generally associated with endocrine or secretory functions. The extrahypothalamic function of neurohormones is uncertain, but they would appear to play an important role in autonomic, visceral, and sensory regulation.

The first hormone system recognized in the hypothalamus was the magnocellular neurosecretory system, emanating from the paraventricular and supraoptic nuclei.[2] These nuclei are the sites of synthesis for *oxytocin* and *vasopressin*. The major projection of these neurons is to the posterior pituitary gland. Neuroendocrine release of oxytocin from the posterior pituitary is an important event in the suckling reflex, and oxytocin is also a potent stimulant of the myometrium. Vasopressin plays a major role in systemic water homeostasis and blood pressure regulation. A second system of parvocellular vasopressin neurons in the paraventricular nucleus projects to the portal capillary system of the median eminence.[3] Vasopressin within this pathway has been

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implicated in the regulation of pituitary secretion of adrenocorticotropin (ACTH), perhaps by potentiating the action of corticotropin-releasing factor (see below). Vasopressin is also located in the suprachiasmatic nucleus of the hypothalamus; the suprachiasmatic nucleus has been associated with the generation of a variety of circadian rhythms, although the role of vasopressin in this process is unknown.[4]

Thyrotropin-releasing hormone (TRH) is the major releasing factor for pituitary thyroid-stimulating hormone (TSH). It is also a potent stimulant of prolactin secretion, being only one of several prolactin-releasing factors. The periventricular nucleus of the hypothalamus is the probable site of TRH neurons that are directly involved in pituitary regulation.[5]

Somatostatin (SRIF) was initially characterized as an inhibitory factor affecting growth hormone release.[5] Somatostatin containing cells in the periventricular hypothalamus give rise to the major projection terminating at the median eminence.[6] Somatostatin is found in other regions of the hypothalamus as well, and somatostatinergic neurons in the hypothalamus project to the brainstem and spinal cord. In addition, SRIF is found in areas such as the basal ganglia, hippocampus, and neocortex.

Growth hormone-releasing factor (GRF) has recently been identified and appears to be predominantly localized in the arcuate nucleus of the hypothalamus. Neurons containing GRF can also be found in the preoptic area. Ectopic production of GRF by human islet cell tumors can lead to excessive growth hormone secretion and acromegaly.[7]

Gonadotropin-releasing hormone (or *luteinizing hormone-releasing hormone,* LHRH) plays a key role in hypothalamic control of gonadal function. In primates, the medial basal hypothalamus is the region containing the neurons that project to the portal capillary system. LHRH neurons are found scattered in the hypothalamus within the periventricular nucleus, supraoptic nucleus, and infundibular and premaxillary regions.[8] Axons from these regions and the preoptic area may contribute to control of pituitary gonadotropin secretion. Restoration of reproductive function in the hypogonadal (HPG) mouse, which is genetically deficient in LHRH, has been demonstrated with transplantation of fetal brain tissue. Donor grafts include LHRH neurons, which reinnervate the median eminence region and are presumably instrumental in the resumption of cyclical gonadotropin secretion. This experimental model illustrates the potential role of transplantation in the treatment of diencephalic neuroendocrine disorders.[9]

Corticotropin-releasing factor (CRF), the most important of several hypothalamic factors involved in the control of ACTH secretion, is primarily located in the paraventricular nucleus of the hypothalamus. Adrenalectomy and stress are associated with histochemical evidence of increased expression of CRF in the hypothalamus.[10] The extrahypothalamic distribution of CRF suggests that it plays a role in the modulation of autonomic function.

Dopamine is a catecholamine that is considered to be the most important regulator of prolactin secretion from the pituitary. Prolactin, unlike other pituitary hormones, appears to be primarily under tonic inhibition by the hypothalamus. Tuberoinfundibular neurons secrete dopamine into the portal system and inhibit prolactin release.[11]

The ability of dopaminergic agonists, such as bromocriptine, to directly inhibit prolactin release has had many important clinical applications in the treatment of hyperprolactinemia due to hypothalamic disease or pituitary tumors.[12] Use of drugs that block dopamine receptors may lead to symptomatic hyperprolactinemia.

Numerous other neuropeptides and biogenic amines have been localized in the hypothalamus and presumably play a role in autonomic and neuroendocrine functions. The integration of these biochemical and anatomical data into an understanding of diencephalic function is a major challenge facing clinical neuroscientists.

THE HYPOTHALAMUS AND NEUROENDOCRINE DISEASE

The diencephalon has long been recognized as playing a pivotal role in the organization of neural information relating to a host of physiological processes. The hypothalamus, which influences virtually all endocrine and vegetative processes, has consistently provided diagnostic and management challenges to the neurosurgeon. This small but vital area straddling the third ventricle on the ventral surface of the brain presents clinicians with signs and symptoms that are unique among neurological diseases. The neurology of the hypothalamus might be broadly summarized as the neurology of (1) food and fluid disorders, (2) growth and development, (3) sexual and reproductive activity, (4) behavioral syndromes, and (5) autonomic and vegetative disorders.

The peculiar manifestations of hypothalamic disease and the relative difficulty in making clinicopathological correlations have limited clinical investigation of the hypothalamus. Paradoxically, the hypothalamus has presented an extremely fertile area of inquiry for the neuroscientist, and advances in the elucidation of the mechanism of neurosecretion have yielded elegant insight into hypothalamic control of the pituitary gland.[13,14] The identification of the various hypothalamic releasing and inhibitory factors has led to sophisticated evaluation of the hypothalamic–pituitary axis and novel approaches to neuroendocrine therapeutics. Endocrine models of brain transplantation, such as the restoration of fertility to the HPG mouse by transplantation of LHRH neurons,[15] promise that the future may also offer new surgical options for the management of diencephalic dysfunction.

Disorders involving caloric regulation represent the type of interdisciplinary problem that characterizes diencephalic neurology. Hypothalamic obesity or emaciation are common manifestations of hypothalamic disease, occurring in more than half of well-documented cases.[16] In fact, the original reports of hypothalamic obesity by Babinski[17] and Frohlich[18] represent some of the earliest documented examples of neuroendocrine disease. A large body of experimental work has firmly established the role of the hypothalamus in caloric homeostasis, and the ventromedial hypothalamus has been classically viewed as the critical center subserving satiety.[19,20] The lateral hypothalamus has analogously been proposed as the feeding center.[21] The importance of projections from the brainstem and other extrahypothalamic regions to the hypothalamus in the maintenance of normal feeding and satiety mechanisms has also been emphasized.[22]

Table 1
Etiology of Hypothalamic Obesity

Tumors	Genetic disorders
Inflammatory lesions	Hydrocephalus
Adipsia–hypernatremia syndrome	Trauma
Basal encephalocele	Syndromes of increased intracranial pressure

Hypothalamic Obesity

Sexual immaturity and hypogonadism, which were observed by both Babinski and Frohlich, are frequently, but not invariably, associated with hypothalamic obesity.[17] This is not surprising, given that sexual dysfunction and diabetes insipidus rank as the most common clinical manifestations of all hypothalamic disorders.[16] In hypothalamic obesity, hypothalamic–pituitary testing yields variable results, depending on the extent of hypothalamic damage. Recognized causes of hypothalamic obesity are listed in Table 1.

Solid tumors invading the ventral hypothalamus are the most common pathologic entity associated with hypothalamic obesity. The neurological presentation is characterized by headache, visual impairment, and cognitive changes. Craniopharyngiomas comprise more than 50% of this group.[23] Additional entities of surgical interest that may lead to hypothalamic obesity are trauma, occult hydrocephalus, and disorders characterized by increased intracranial pressure.[23,24]

The biology of central caloric regulation is complex and incompletely understood. There appear to be short-term and long-term mechanisms for regulation of appetite and caloric intake, possibly based on neural recognition of glucose levels or fat stores.[25,26] The contributions from motivational factors, motor activity, and learned behaviors such as food preference or taste are also very important. The amygdala and limbic centers are cited, not surprisingly, as major anatomical determinants of feeding and satiety. Adrenergic mechanisms, particularly the role of the ventral noradrenergic bundle, are often stressed.[27] The conclusion that the hypothalamus is more likely an integrator of multiple inputs affecting caloric homeostasis, rather than the specific center for this critical function, is inevitable. This observation undoubtedly is true for the majority of hypothalamic or diencephalic functions.

Clinical investigation of hypothalamic obesity is infrequently reported. Considerable evidence from experimental animals would suggest that autonomic dysfunction leading to abnormal regulation of insulin secretion may be an important etiological factor.[28] Patients with hypothalamic obesity fail to suppress insulin levels normally in response to fasting.[23] Early in the development of hypothalamic obesity, a markedly exaggerated insulin response to glucose ingestion has been noted.[29] Additional support comes from the observation that in postoperative craniopharyngioma patients with growth hormone deficiency, excessive somatic growth appears to be due to hyperinsulinism.[30] The abnormality in insulin secretion has been attributed to increased parasympathetic tone resulting from the interruption of hypothalamic projections to or from

the brainstem. The vagus nerve, which directly innervates the beta cell of the pancreas, has been hypothesized to stimulate the excessive release of insulin. In an individual with obesity secondary to traumatic hypothalamic injury, therapeutic vagotomy has been reported to reduce hyperinsulinemia and promote weight loss.[31]

Hyperphagia, which does not invariably accompany hypothalamic obesity, may also be due to a direct effect of insulin on the brain.[28] The role of neuropeptides such as cholecystokinin or the endogenous opioid peptides in the control of appetite has attracted interest. Cholecystokinin may be an important endogenous satiety factor,[32] while the opiate antagonist naloxone has been reported to be a useful adjunctive treatment for hypothalamic obesity associated with trauma.[33] The advent of sophisticated infusion systems for delivery of substances into the central nervous system makes the identification of appetite modulators a potentially rewarding avenue for research.

Hypothalamic Emaciation

Hypothalamic emaciation has rarely been well documented in humans. Profound emaciation in multiple sclerosis was reported to occur in association with demyelination of the lateral hypothalamus.[34] There have been several case reports documenting profound emaciation in association with discrete hypothalamic pathology. White and Hain described an anorexia nervosa-like syndrome which occurred in a 62-year-old woman with a cystic lesion of the third ventricle invading the medial right hypothalamic area at the level of the infundibulum.[35] A similar syndrome was reported in a younger woman with an astrocytoma arising from the ventral surface of the brain, immediately posterolateral to the infundibulum and invading the right tuberal region.[36] There does not appear to be any obvious anatomical correlation among these cases.

The diencephalic syndrome is an uncommon, but interesting, example of hypothalamic emaciation.[37] It usually occurs during the first year of life. Profound emaciation is observed despite adequate food intake and a remarkably cheerful affect. The typical etiology is a tumor arising in the anterior hypothalamic region, but the location of pathology may vary. The interruption of a caudal brainstem projection to the anterior hypothalamus has been proposed as the crucial event.[37] Several reports have noted that growth hormone may be excessively secreted and/or respond paradoxically to various physiological stimuli.[38]

Carmel has reported an interesting case of diencephalic syndrome in which prolonged survival was subsequently characterized by the development of hypothalamic obesity.[39] This observation raises the possibility of a maturational process evolving within the specific hypothalamic axis regulating caloric homeostasis. It is interesting to speculate that there exists a chronologically linked, biological program for caloric intake that may be somewhat analogous to the central nervous system organization for puberty or sexual maturation. Clinical observations made on the unusual, but instructive, manifestations of hypothalamic disease offer excellent opportunities to understand the morphological basis for fundamental neuroendocrine systems characterizing our species. Continued progress in surgical management of disorders of the third ventricular region will inevitably contribute greatly to advances in this area.

HYPERPHAGIA AND ANOREXIA FOLLOWING EXTENSIVE THIRD VENTRICULAR SURGERY

Long cites the case of a teenage girl who had a mild excessive-eating disorder before surgery for a craniopharyngioma and who suffered large intraventricular extension and severe hyperphagia postoperatively such that she gained several hundred pounds in one year. Abrams adds the report by Bucher in the 1983 *New England Journal of Medicine,* which cited instances of hyperphagia and obesity in postoperative craniopharyngioma patients. I am familiar with only one patient with hyperphagia and obesity unrelated to surgery. His weight doubled in the course of a year and became almost life threatening.

Patterson remarks that although weight gain postoperatively isn't uncommon, he had not observed postoperative cachexia.

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3

Neuropathological Considerations in Management of Deep-Seated Gliomas

Peter C. Johnson

INTRODUCTION

Simultaneous developments in microneurosurgical techniques, neuroradiology, and neuropathology offer hope that in the future effective treatment strategies may be developed for a disease currently with a poor prognosis—deep-seated glial tumors of the brain. The purpose of this report is to communicate our recent findings from a study that utilized a newly developed technique involving magnetic resonance imaging (MRI), followed by pathological analysis, of postmortem brain specimens harboring these neoplasms.[1] I will discuss our results in light of current and prior related studies and then postulate possible future avenues for study.

With the advent of MRI, it is now possible to document the presence of, and potentially treat, deep-seated mass lesions at stages far earlier than was previously possible.[2] It is not known whether early surgical extirpation, with or without radiation therapy, of such lesions might produce longer remissions or perhaps even a cure. The invariably bad outcome for patients with deep-seated gliomas at this time obliges us to seek new forms of therapy, particularly now that we can identify the lesions earlier. Currently, a major impediment to our treatment of such patients is our inability to adequately delineate the limits of the tumor so as to provide an exact localization of the field requiring therapy.

We recently reported studies[3] in which analysis of postmortem MRI and subsequent pathological analysis was performed on brains from elderly patients to determine the nature of the so-called "little bright objects" or incidental lesions that are fre-

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quently found in the white matter, periventricular zones, and basal ganglia of elderly people. In this study we found that these bright objects, best seen on T_2-weighted images, represented pathological abnormalities long recognized in the brains of the elderly, namely: (1) état criblé, or the dilatation of the perivascular space of Virchow-Robin; (2) état lacunaire, a small microinfarct usually related to hypertension and usually in the basal ganglia and subcortical white matter; and (3) loss of myelinated nerve fibers accompanied by an increase in extracellular water in the angles of the lateral ventricle. The common denominators resulting in the increased signal on T_2-weighted images were the loss of myelinated nerve fibers and an increase in extracellular water.

In our study we first established the feasibility of doing postmortem MRI that allows exact pathological correlation with whole-brain sections cut at the same plane as the MR-image cuts. We then decided to perform postmortem MRI studies on the brains of individuals who died with glioblastoma multiforme tumors. Our goal was to correlate the extent of the radiographic abnormality with the extent of the pathological abnormality as determined by microscopic examination. The results among cases of untreated glioblastoma are preliminary because of the small number of cases, but indicate that the extent of tumor visualized on the postmortem MR scan slightly underestimates the extent of the infiltrating tumor as seen microscopically. However, MRI appears to be more sensitive than computed tomography (CT) was previously found to be.[4–7] For tumors in remission, the MRI lesion appeared larger than the actual tumor due to surrounding white matter edema, while in the case of recurrent tumors, the individual tumor cells found throughout both hemispheres (Fig. 1) were often unassociated with other changes in the white matter, such as edema, and were therefore undetectable with the present MRI technology (Fig. 2A).

One negative finding of our study was an untreated case of glioblastoma in which there were infiltrating tumor cells in the cerebral cortex that were undetected with the MR scan. This is not unexpected, since the MR scan mainly detects differences in water distribution and edema does not accompany tumor infiltration into gray matter. The fact that some of these tumor masses were 8 cm or more from the main tumor mass and 4–5 cm from a satellite nodule suggests that in cases of multifocal glioma, current MRI will not be able to pick up such gray matter multifocal or infiltrative lesions (Fig. 2B, C).

On a more hopeful note, our one case of untreated anaplastic astrocytoma, in which the postmortem MRI and the histopathology showed an almost exact correlation, offers hope for a successful surgical approach to such deep-seated lesions.

POSSIBLE APPLICATIONS OF MAGNETIC RESONANCE IMAGING TO MANAGEMENT OF DEEP-SEATED GLIOMAS

An interesting point taken from our studies is the apparent existence of a window of opportunity in the management of deep-seated tumors. This follows surgery and radiation therapy, when the tumor is in remission and sufficiently reduced in size for surgery or local interstitial radiation therapy to make total extirpation possible. The

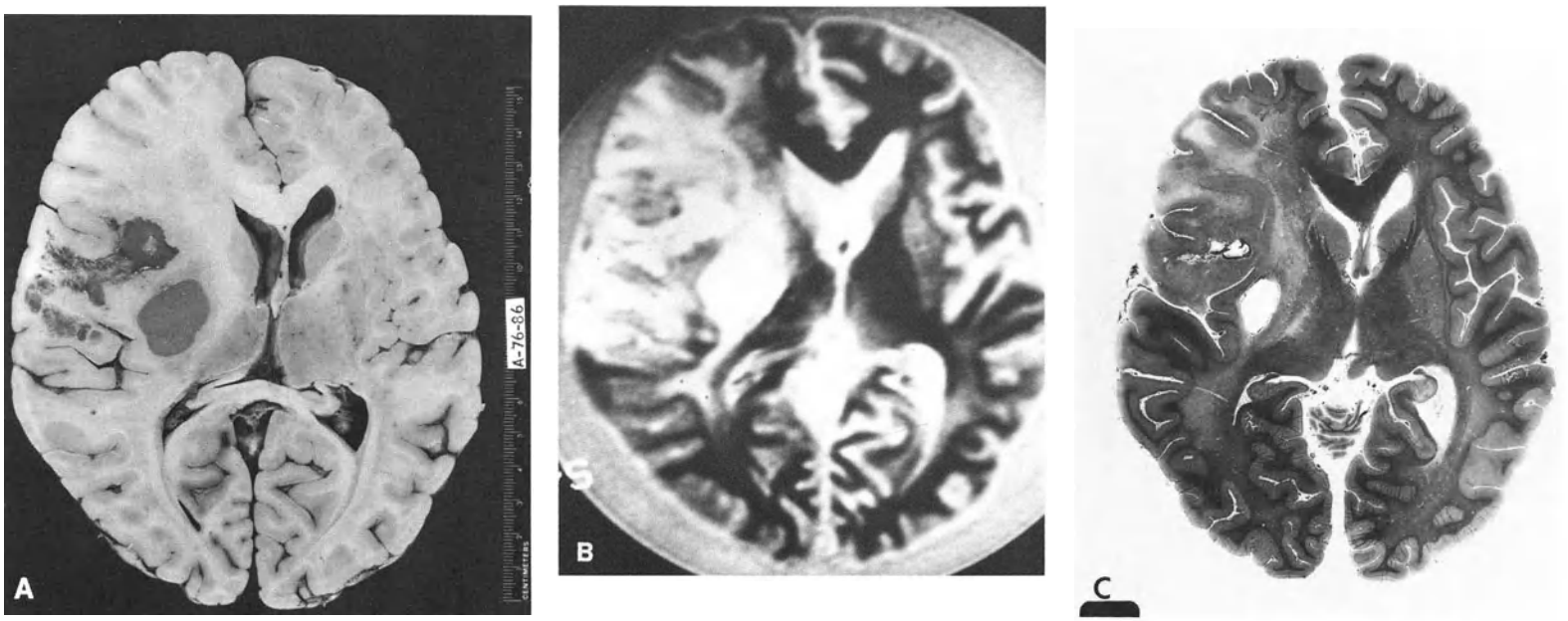


Figure 1. Recurrent glioblastoma multiforme: Tumor cells are found throughout both hemispheres. The MRI underrepresents the extent of the ''corona'' since the tumor cells are present far beyond the limits of edema. (A) Gross brain; (B) the MR image; (C) Weil's myelin stain.

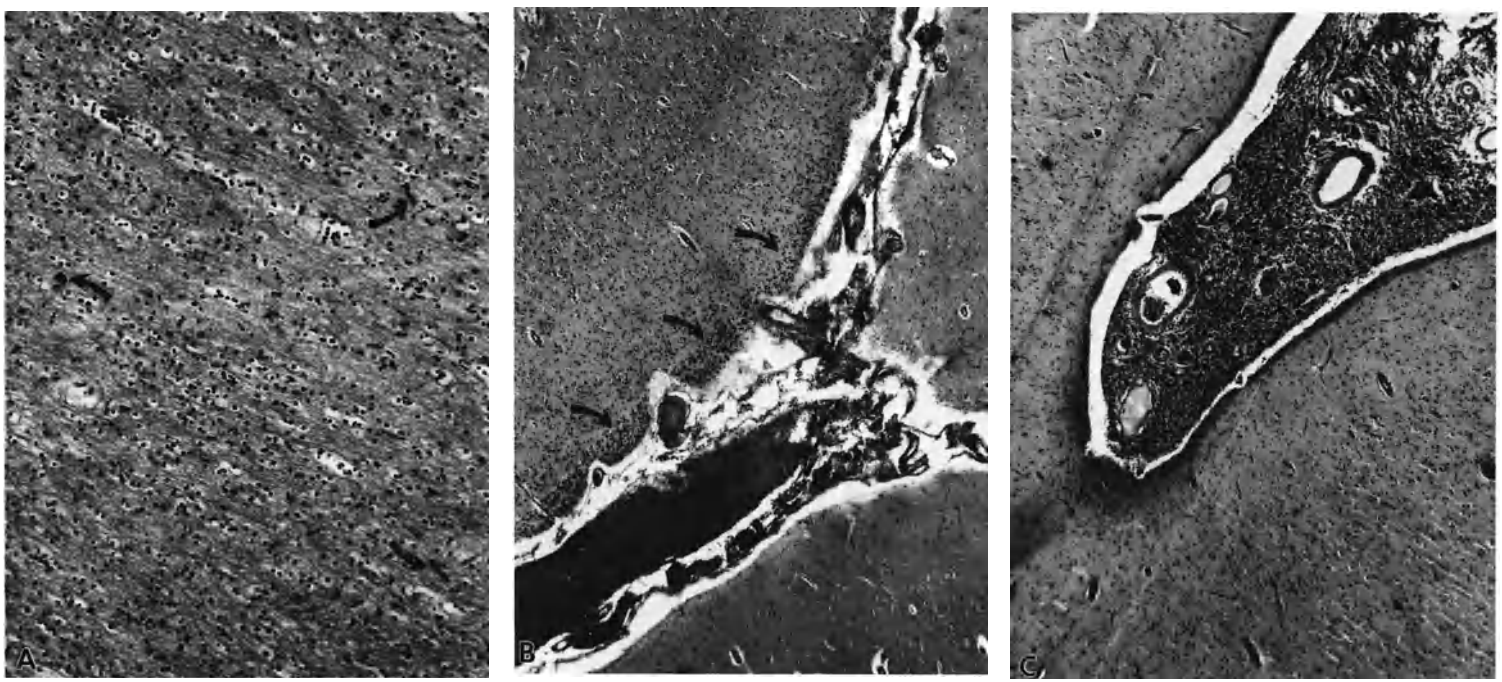


Figure 2. Undetected by MRI were infiltrating single cells without edema (A), subpial spread (B), and small subarachnoid metastasis (C).

determination of tumor extent necessary for such extirpation would require stereotactic needle biopsies for staging. The reports of Kelly[8,9] and his colleagues in the Mayo Clinic have offered an innovative and promising approach to the management of deep-seated glial tumors. From a staging and planning approach, stereotactic biopsies are performed around the periphery of the CT/MRI localized tumor in order to document the extent of the tumor. But a refinement is necessary in this technique. As I tell my students when I teach them neuropathology during their second year of pathology, "the brain is not a liver." That is, the brain is not homogeneous structurally but is exquisitely complex; this complexity is reflected in patterns of tumor growth. Of significance here is the fact that tumor cells and, interestingly, the edema that often accompanies them (an association of possible significance in terms of future therapy), mainly travel in local white matter tracts. This constitutes what we call the tumor corona, after the radiation of the sun. While these rays (tumor cells and edema) sear through white matter tracts, nuclear masses such as those in basal ganglia are hardly invaded. Perhaps this relates to the fact that extracellular space in the gray matter of nuclear masses is essentially nonexistent. Perhaps the tumor cells do not percolate through the gray matter as they do through the white matter because of their large size and their lack of plasticity and mobility.

My proposal for the treatment of glioblastoma and anaplastic astrocytoma is to use MRI to modify the Kelly approach in staging these tumors. Using a needle biopsy technique, these biopsies must be specifically directed to the white matter tracts involved near the tumor. Surrounding nuclear structures can be considered to be scarcely invaded or perhaps invaded proportionately to the amount of white matter they contain. Consequently, we cannot plan our stereotactic biopsies as being of uniform distances from one another but rather they must be concentrated in the white matter tracts, with only a few biopsies in the nuclear masses (those close to the radiographic tumor core).

A final consideration is that glial tumors vary in their infiltrative extent, some growing as a localized mass lesion while others, particularly low-grade astrocytomas, infiltrate extensively, a fact long recognized[10] and recently reemphasized.[8,11–13] Localized tumors are potentially curable with local extirpative therapy, while widely invasive tumors are so admixed with normal brain that any local treatment is useless and harmful. At present there are no known methods for distinguishing tumors with different growth patterns—this needs to be addressed. Perhaps by utilizing special morphological techniques that determine cellular DNA ploidy, nuclear size, and nuclear contour index, some other cytological feature will be identified that is predictive of tumor growth pattern when correlated with neuroradiology. Being able to predict the growth pattern will be useful in planning the stereotactic biopsy field.

CONCLUSION

In summary, our studies of postmortem MRI of brain specimens from patients with deep-seated glial tumors would indicate that the MR scan of untreated tumors closely reflects the pathological extent of tumor, while in tumors in remission following radiation therapy the neoplastic cells are considerably less widespread than is the

MR abnormality. Recurrent tumors are much more extensive than is the radiographic abnormality. I propose for the management of deep-seated tumors (for example, those in the basal ganglia) obtaining stereotactic three-dimensional reconstructions of the MR images of these tumors. From these images the pertinent white matter tracts and their coordinates could be determined. In order to plan the surgical extirpation, stereotactic needle biopsy study of the white matter tracts traversing the area around the tumor should be performed to determine the tumor corona, or infiltrating edge. Treatment of deep-seated tumors, with modern microsurgical techniques, may actually benefit from the circumscription provided by the surrounding nuclear masses. Once the white matter corona is identified using stereotactic biopsy, it is possible to proceed with tumor extirpation.

DISCUSSION

MULTIFOCAL GLIOMAS AND TRACKING

Apuzzo inquires as to the confidence of neuropathology in evaluating tracking, suggesting that neuropathologists might be missing tracks between multiple lesions.

The lesions presented here are multifocal on separate sections. It is unclear if they communicate, as serial sections were not done to determine whether these were truly multifocal and primary in and of themselves. In all probability they are related to the main tumor mass and represent small fingerlike projections of tumor. The important point here is that from a radiographic standpoint it appeared as though there was a solitary mass, whereas pathological investigation showed additional focal tumor infiltrates that the MRI did not pick up.

STEREOTACTIC BIOPSY AND THE MAGNETIC RESONANCE IMAGING APPEARANCE OF A TUMOR

Apuzzo offers that if we try to relate a CT scan to an MRI scan and take assays in the obvious tumor burden area, and then take biopsies from a T_2-weighted image, we will get tumor tissue from the tumor area. From biopsies in the T_2-weighted image area a pathologist can generally identify tumors 75% of the time. From "clean areas," for example, areas that appear to be unaffected on MRI, we can occasionally pick up cells by Dumont's methodology that are not normal cells. Are these reactive astrocytes?

Carmel points out that one is looking at a pixel on an MR image, measured in millimeters, and at fingerlike projections—perhaps even at some distance—that are measured in small aggregates of cells (e.g., microns). Given a microgenerating pixel size on an MR image one can see a border more precisely, but as long as one is averaging the border and has, for example, 4% tumor cells and 96% nontumor cells, that will average out in the pixel as nontumor.

Apuzzo's response is that the issue is how much of a case can be made for treating the tumors in a local fashion, whether it's LAC cells or interstitial brachytherapy, or whatever. The issue relates to what the imaging tells us about the extent of the tumor; what we are seeing is that 5–7 cm away from the tumor, in remote areas on the MR image, we will biopsy cells that are very bothersome in their "malignantlike" appearance. Lucien Rubenstein has said that Dumont's methodology is ironclad, but nobody has had the opportunity to really recap her work.

Pixel size is probably not important here if one is looking for water. If there is no disturbance in water distribution associated with infiltrating tumor cells, it doesn't matter which pixel size one has. What is needed is a technique that is going to detect DNA abnormalities. Many of these tumors are euploidic and so it may be difficult to detect such abnormalities.

Dumont made a point that echoes what people have thought for a long time, namely, that different tumors have different infiltrative characteristics. Some are diffusely infiltrative and infiltrate normal brain, while others are sharply circumscribed. The problem is how to define which tumors are sharply localized and not diffusely infiltrative, and are therefore amenable to local therapy.

ONCOGENICITY AND TUMOR INDUCTION

Edwards raises the argument that the factors causing or inducing cancer may exist throughout the brain. Why then should it be assumed that they exist only in one localized area of the brain? We often view them as localized tumors, and in many instances we treat them as localized tumors—we're trying to define the extent of disease. Yet, it is not very surprising to think that whatever starts the malignant process in the brain may exist throughout the brain tissue, such that at the time of the patient's demise or at the time of tumor recurrence in the face of treatment failure, we find tumor throughout the brain just as one finds distant metastases with glioblastomas in approximately 20% of cases at postmortem examination. We certainly don't treat these tumors as we would medulloblastomas with primary and distant metastases.

Edwards raises a second point relating to the process we have termed "tracking." This may not be the pathogenetic process, but rather *induction* of tumor cells. Rather than cells actually growing and moving through white matter tracks, malignant cells may have the capability to induce cells in their vicinity to become malignant.

Apuzzo responds that there may indeed be an induction process rather than a growth process. However, the issue remains, can we rule out the fact that a track is not there?

There is an epicenter of tumor cells that are highly concentrated around the original tumor bed, and there is a graded decrease in the number of tumor cells as one proceeds centrifugally. In the one untreated case presented here, the tumor cells were much more highly restricted. The idea that these tumor cells might be becoming neoplastic remote to the tumor epicenter is not very likely. The induction of normal glial cells by infiltrating tumor is entirely possible, but that still does not negate the concept of local disease spreading peripherally.

Leeds emphasizes that the neuropathologists are giving the neuroradiologists and the neuroimagers a lot of credit. Those in neuroradiology do not feel that they can identify the limits of a given malignant tumor. He reports that in his review of 100 gliomas of the brain, it was possible to grade the lesions by their associated degree of edema. He feels it is impossible to tell where the tumor ends and the edema stops: There is tumor both within the edema and outside the area of edema. Some tumors, such as oligodendroglioma, clearly demonstrate the coexistence of tumor and edema.

Leeds continues, in regard to Carmel's point about pixel size, that pixel size is irrelevant. MRI is the equivalent of gross pathology. We don't see a microscopic specimen. MRI is very sensitive, but it is not very specific.

Dolenc remarks that the findings of Kelly, who has been biopsying the brain both in front and behind a given tumor's radiographic borders, point strongly to the existence of malignant cells as far away as 7 cm. (Of course this kind of study is limited by the sampling via tiny biopsies as opposed to a postmortem specimen, in which everything can be seen.)

THE QUESTION OF WHOLE-BRAIN RADIOTHERAPY

Carmel notes that the information provided here would cause us to step back in time to giving patients whole-brain radiotherapy, whereas the RTOG carefully studied this question and showed that there was absolutely no improvement in survival rate given whole-brain radiation versus focal radiation with a boost to the primary tumor site. This throws a paradox into the neuropathological studies on treatment of the tumors that are based primarily on the histological features reported by Kelly. Carmel concedes that there may be tumor cells elsewhere, but is not sure how we should deal with this in the clinical management of patients.

My own experience indicates that whole-brain radiotherapy would not be applicable to the treatment of localized tumors. My studies—traditional studies, without MRI—would indicate that gliomas are a localized disease process until their late stages, and whole-brain radiotherapy makes little sense until the late stages of tumor growth and invasion.

Patterson questions the reliability of seeing one black elongated pyknotic nucleus. How reliable is a pathologist's conclusion that this is a neoplastic cell? One wouldn't make that diagnosis in a patient who has not got a known primary focus of malignancy; on needle biopsy of a brain, a single atypical nucleus would not serve as the basis for a pathologist calling it a glioblastoma cell. However, if the patient has a known glioblastoma and one finds a scattering of remote nuclei that appear malignant, the pathologist may consider infiltrating malignant cells. Patterson perceives this inconsistency as a problem with Kelly's studies.

The fact is that one doesn't see these malignant cells in other studies. The present case is part of a large study of whole-brain MRIs of other neuropathological conditions. We looked at a lot of brain tissue and felt that we could see these neoplastic cells. We didn't include the so-called small-cell glioblastoma because it is often too hard to tell infiltrating cells from normal glial cells. This study was restricted to those tumors with obviously pleomorphic cells, where there was no question that they were infiltrating tumor cells.

THE RADIOGRAPHIC SIGNIFICANCE OF VASCULAR ENCASEMENT

Difficulties with the Use of Radiotherapy in Low-Grade Gliomas

Leeds presents the MR images of a lesion that looks like a pituitary tumor (Fig. 3). The lesion is a sphenoid sinus carcinoma. The right cavernous carotid artery is narrowed and displaced, while the left is normal (Fig. 3B,D). The encased carotid, with vasoconstriction and decreased flow, can be compared with the normal, pointing up the value of MRI as an angiographic technique providing us with a great deal of information. The high-intensity signal within the lesion is indicative of tumor bleeding (Fig. 3A,D). The key to diagnosis is that this tumor is growing from the sphenoid sinus forward into the sella turcica and then into the nasopharynx.

A second case of arterial encasement is seen in a young woman who developed headaches and decreasing vision. A large lesion was found filling the suprasellar cistern, enhancing uniformly and demonstrating calcification. The lesion traversed the suprasellar cistern and crossed the carotid fissure to the frontal region. On MRI, one can see the midline location of this lesion in the suprasellar cistern, the carotid encasement, and the growth forward into the frontal lobes (Fig. 4). There is distortion of the choroidals, the posterior communicators, and the carotid, but the lesion appears particularly uniform with its encasement of the A_1, M_1, and supraclinoid segments of the carotid.

There has been some difference of opinion as to the nature of this lesion. It spared the sella

turcica and there were portions with a decreased density. Of note is the extent of this lesion around the third ventricle.

Leeds notes that when a suprasellar lesion has uniform density and crosses the carotid fissure it has the appearance of a meningioma. When calcification is present it looks like a craniopharyngioma. However, a tumor occupying the suprasellar cistern with encasement of both A_1 segments, a radiographically normal optic nerve on the unaffected left side, and an enlarged optic nerve on the right, points to the diagnosis of either an optic nerve glioma or a hypothalamic glioma with extension into the optic chiasm.

Post operated in this case and found significant changes in the subfrontal cortex. The pathological diagnosis was low-grade astrocytoma; it was not certain whether the lesion originated in the optic nerve or the hypothalamus. Post raises the issue of the advisability of irradiating a low-grade astrocytoma of the hypothalamic region.

Apuzzo responds that he doesn't believe this lesion is low grade and suggests that one could get a more accurate assay of tissue with an imaging-guided stereotaxy than on open biopsy. With the imager one can select an area, then take a specific piece of tissue. The images presented in Post's case are not completely uniform in their entire extent. Apuzzo claims that in his experience, if the lesion is not completely uniform one of the areas which appears "fluffy" will show a higher grade of neoplasia.

Post responds that if it were a higher grade all would agree that radiation therapy would be necessary. Yet, what if it were uniformly a low-Grade I–II glioma—would you irradiate it promptly or would you watch it? Does the lesion have to show characteristics of a Grade III tumor for you to request radiotherapy?

Apuzzo declares that the terms Grade I, II, and III are not used on his service. Instead, the terms astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme are used. If a lesion falls into the category of the middle grade he would irradiate it. Apuzzo submits again that more precise sampling is obtained by stereotactic biopsy than by open biopsy: In this way, one can pinpoint the zone of tumor one wishes to biopsy on the image, whether it be an area of puddling of dye on CT scan or a fluffy-looking area on MR, and the incidence of high tumor grade in those areas is significantly greater. We know that the lesion will evolve with time. Despite the fact that we may take a trillion samples demonstrating a low-grade tumor, within 2–3 years the lesion will evolve. This is commonly seen in middle-aged patients.

Post agrees that a more malignant area of tumor may be missed on open biopsy, but asks again: If the lesion is all low grade would you irradiate it?

Tew responds "Yes."

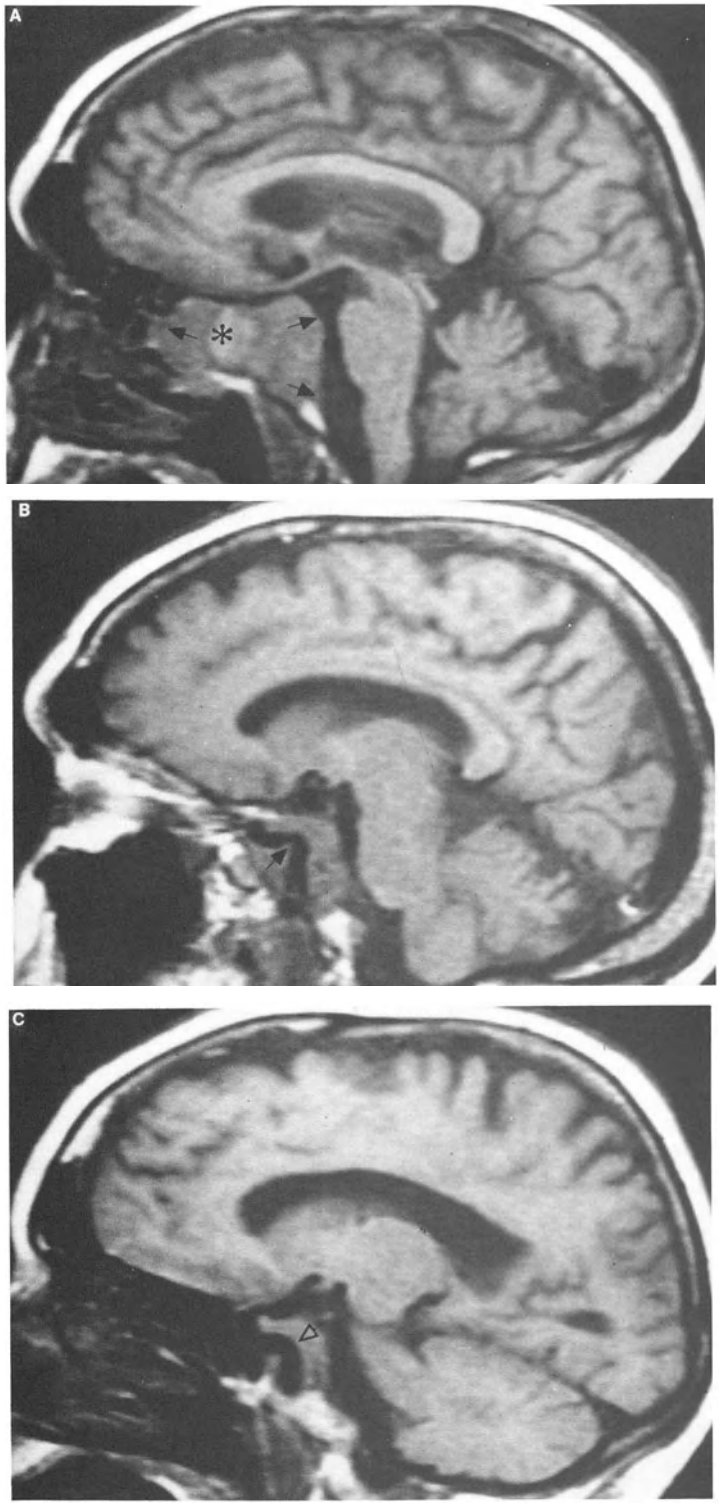
Apuzzo claims it's "a roll of the dice." There is no valid data to help one arrive at the decision to irradiate such a lesion. He does not believe Post will find support for a decision to irradiate.

Post continues that both high-grade and low-grade gliomas are being radiated. He claims to want to assess the number of opinions that there isn't a large body of support for giving radiotherapy for low-grade gliomas.

Tew maintains that there is some good data on radiation of gliomas of the cerebral hemispheres.

Fukushima reports that the University of Tokyo's Brain Tumor Group has a definite policy on giving chemoradiotherapy. He personally does not give radiation to gliomas classified as Grade I or II, but just watches them. A large number are stable for many years. He cites a few cases where there was worsening after radiotherapy.

Apuzzo remarks that he suspects Post has raised this issue because his situation is such that, if he sends his patients for radiotherapy they all receive radiotherapy.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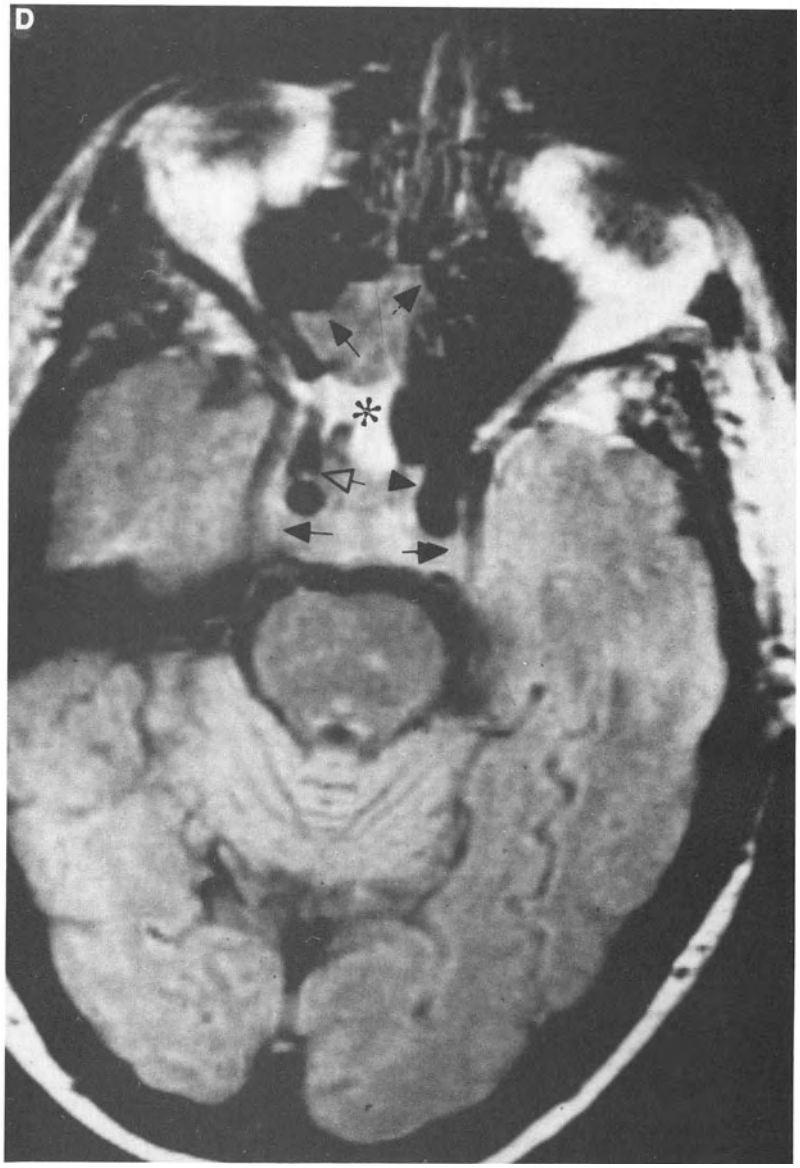


Figure 3. Sphenoid sinus carcinoma with cavernous carotid encasement and displacement. (A) Sagittal-plane spin echo T_1 in midline, revealing large isointense tumor in sphenoid sinus (arrows). Hyperintense zone is seen in center (asterisk), and represents blood (methemoglobin); (B) sagittal-plane spin echo T_1 to right of midline, showing encasement of cavernous carotid artery (arrow) by tumor; (C) sagittal-plane spin echo T_1 to left of midline, demonstrating a normal cavernous carotid artery (open arrow); (D) Axial-plane proton-density image reveals isointense tumor in sphenoid sinus (arrows) and central zone hyperintensity (asterisks), representing blood (methemoglobin). The right cavernous carotid artery (open arrows) is narrowed and displaced, while the left (arrowheads) is normal.

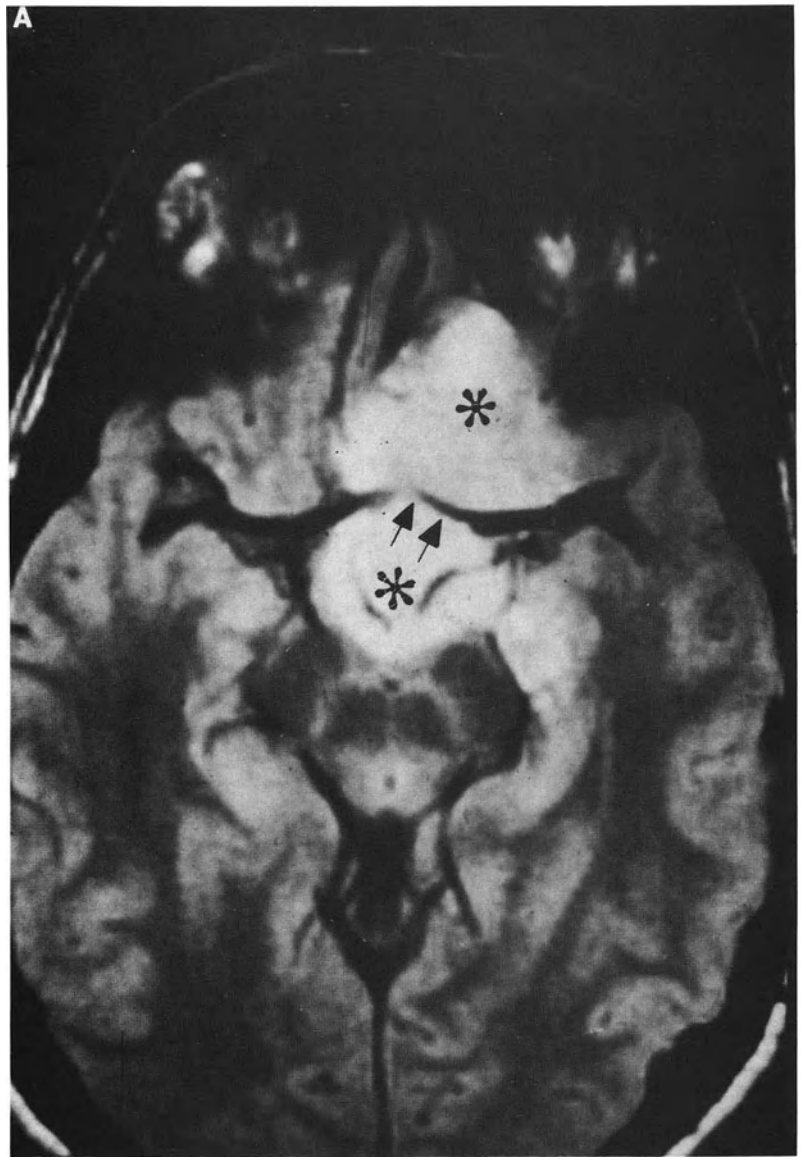


Figure 4. Hypothalamic glioma with arterial encasement. (A) Axial section through suprasellar cistern on spin echo proton-density imaging reveals a large hyperintense tumor occupying the suprasellar cistern and extending forward to midline and left frontal region (asterisks). The tumor surrounds and constricts the left A1 (arrows); (B) coronal section through suprasellar cistern in spin echo T_2, showing hyperintense tumor (asterisks) in same areas as on axial section, with addition of tumor in left temporal region and vasoconstriction of both anterior cerebral arteries (arrowheads), left middle cerebral artery (arrow), and left supraclinoid carotid artery (open arrow).

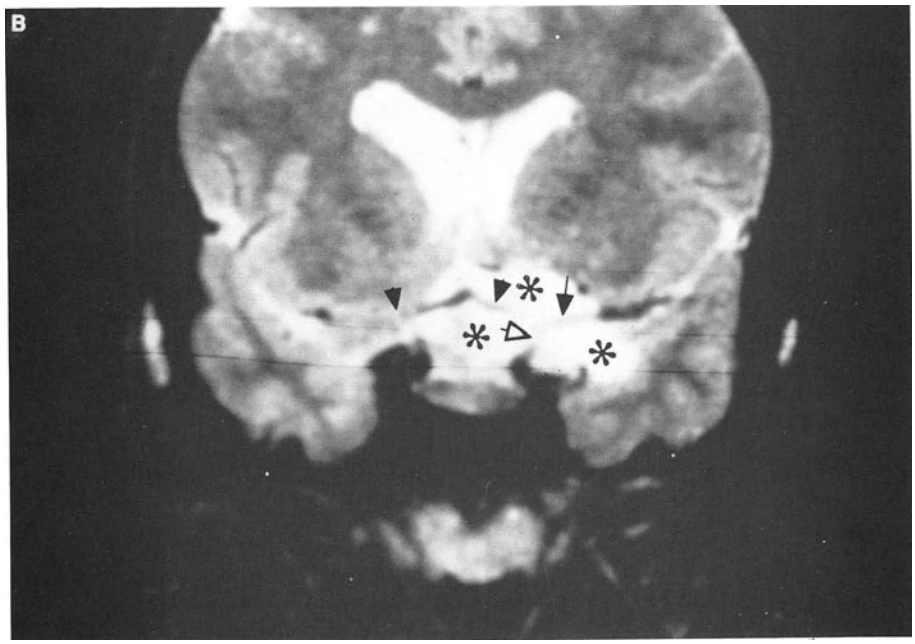


Figure 4. (*Continued*)

Fukushima emphasizes that we can follow our cases closely with MRI or CT. If there are any signs of rapid growth then we can use radiotherapy.

Apuzzo adds that if one looked at the data concerning patients with a low-grade glioma over the age of 35, one would opt to treat such a patient with radiotherapy, whereas one might not treat an individual in the age group 18–22 years.

Tew inquires as to why this is so. Are the tumors more potentially malignant in the older age group?

Apuzzo responds that the older patients will more commonly show changes in their tumors in 3–5 years.

The Radiographic Determination of Intra- and Extraaxial Lesions

Leeds presents a patient with seizures. CT scanning (Fig. 5A) and MRI (Fig. 5B,C,D,E) reveal a low attenuation in the medial temporal lobe and hypothalamic region. The diagnosis of temporal lobe glioma with extension into the hypothalamus was made in this case. One can observe the extent of this lesion from the medial temporal lobe into the suprasellar region compressing the brainstem.

Leeds believes that this is not a glioma, but rather an extraaxial lesion. On the T_1-weighted images the lesion is hypointense, while on the T_2-weighted images it is hyperintense. This is characteristic of an epidermoid, which was confirmed on contrast cisternography. One can appreciate the frondlike characteristics of an epidermoid intruding into the contrast-opacified cisterns (Fig. 5E). In addition, the fact that the lesion is hyperintense on the T_2 and hypointense on the T_1 indicates mainly cerebrospinal fluid (CSF), not fat. It is not a dermoid. There is no fat

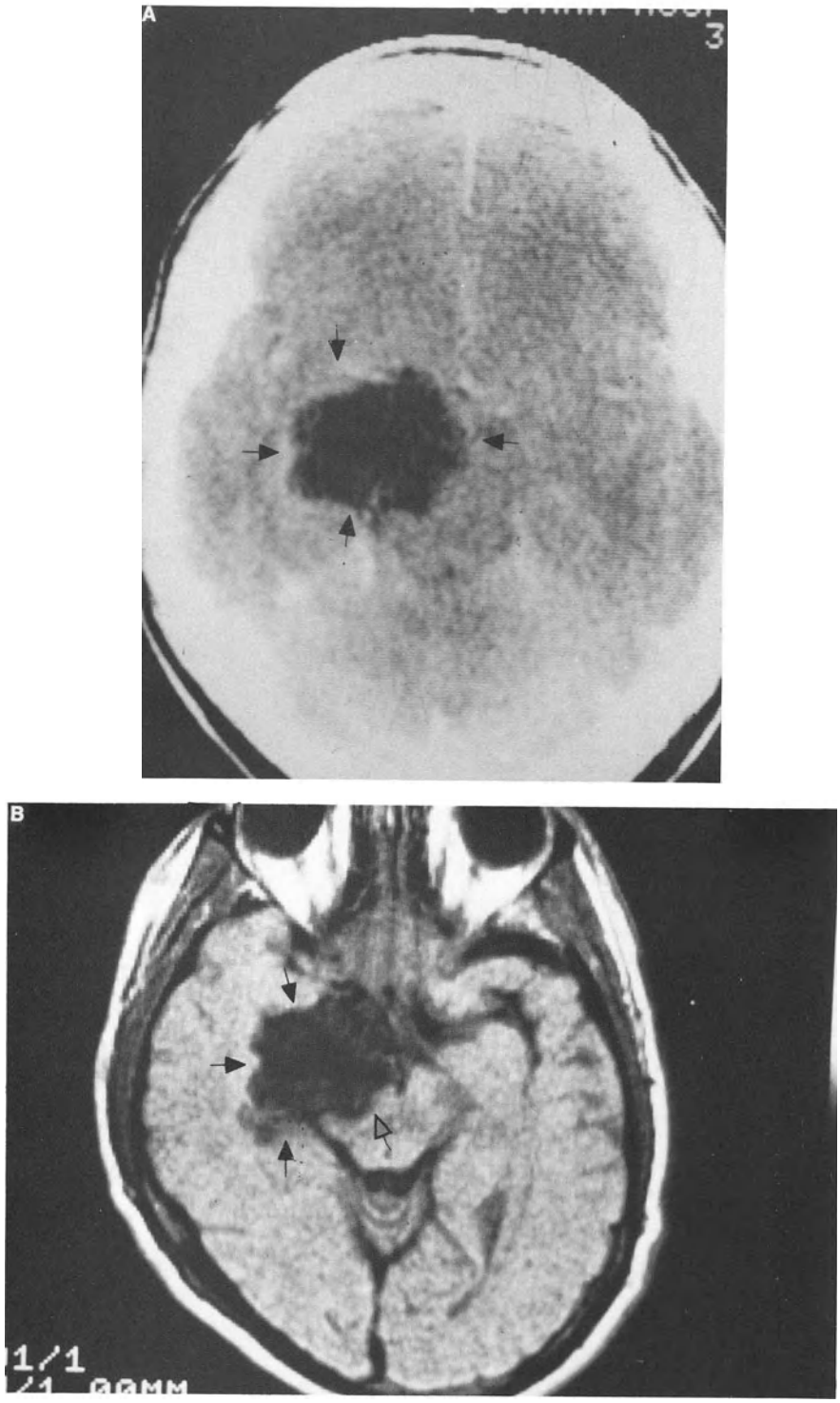


Figure 5

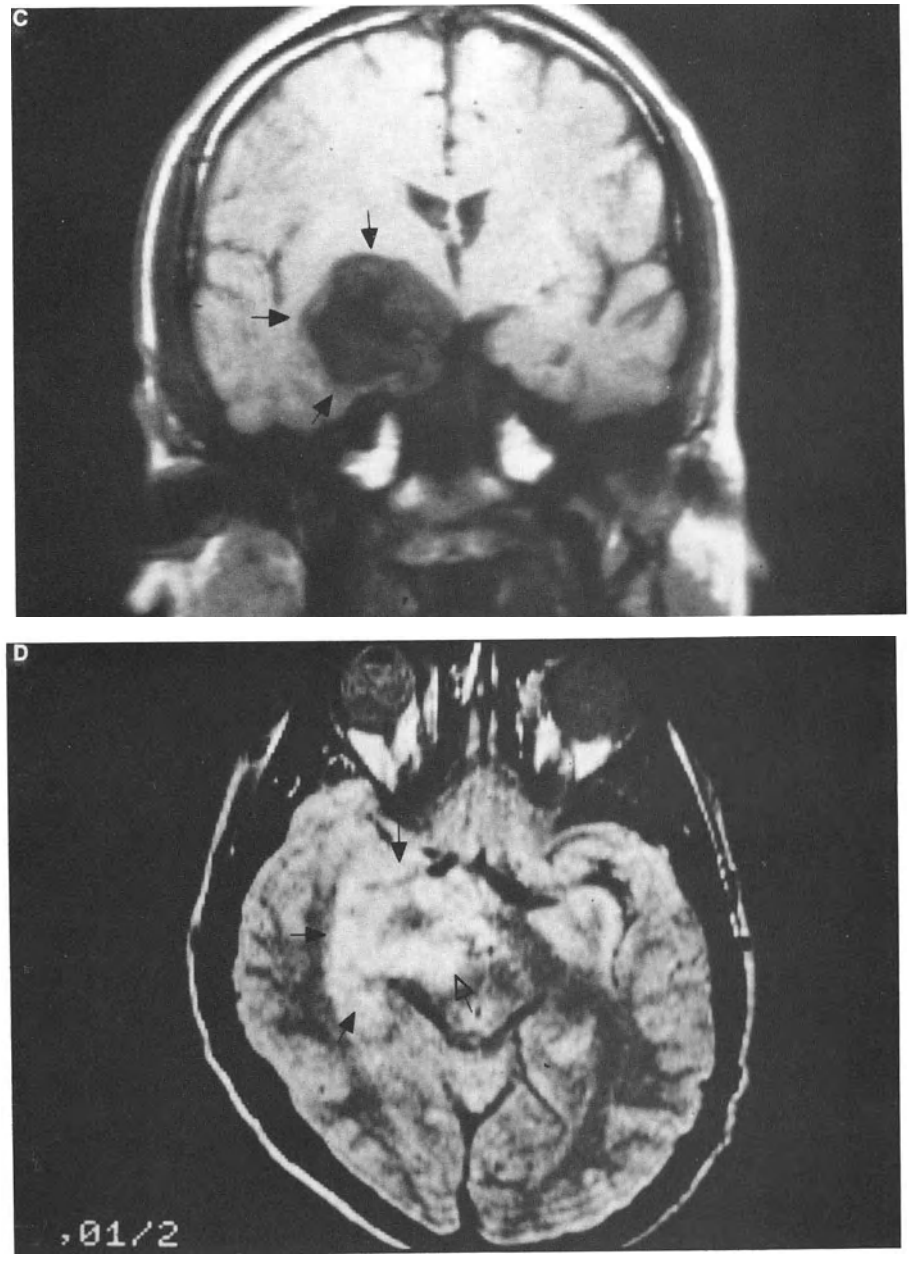
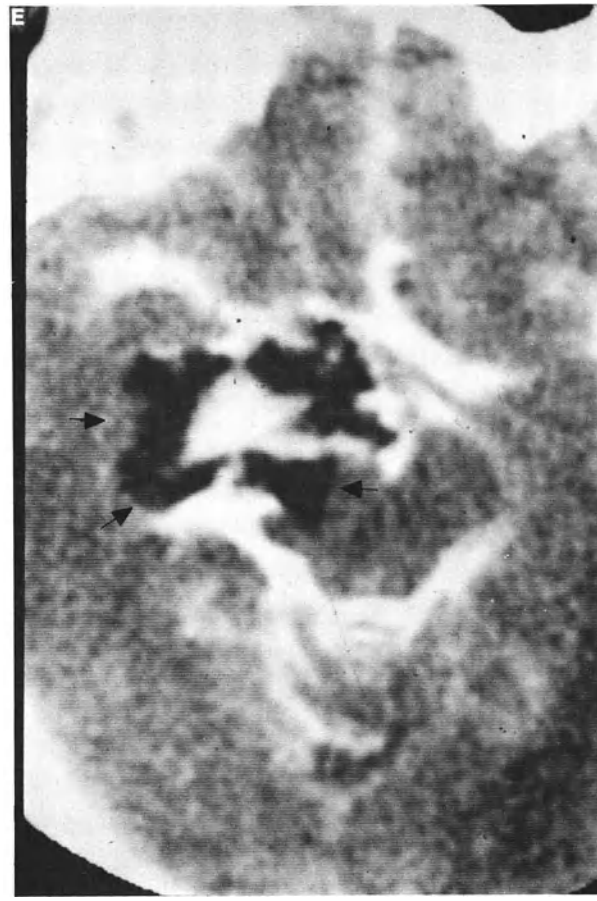


Figure 5. Epidermoid in a 32-year-old patient who presented with seizures. (A) Axial CT scan following intravenous contrast administration, revealing a sharply defined low-attenuation lesion with lobulated borders (arrows) in the right medial temporal region juxtaposed to the suprasellar cistern. The lesion was considered to be intraaxial by the original examiners, but in reality is extraaxial in location; (B,C) MRI at the base of the brain with spin echo T_1-weighting in axial (B) and coronal (C) planes, showing a sharply defined lobulated hypointense lesion (arrows) juxtaposed to the suprasellar cistern. On the axial view (B), the right



cerebral peduncle is focally compressed (open arrow); (D) spin echo T_2 in axial plane, revealing lesion to be hyperintense (arrows), with compression of right cerebral peduncle (open arrow). Similar to B except for variation in intensity due to relaxation time; (E) axial section through the suprasellar cistern after CT cisternography with nonionic contrast. A frondlike low-intensity lesion is seen partially filling the suprasellar cistern and extending to the right lateral aspect (arrows).

in it. That can be effectively demonstrated on MRI, which shows fat to be hyperintense on the T_1-weighted images.

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4

Neuroradiology and Neuroimaging of the Diencephalon

Norman E. Leeds

INTRODUCTION

This chapter begins with something old and proceeds on to something new in the neuroimaging of the diencephalon. In this regard it is pertinent to look at the angiographic anatomy and pathology visualized just a few years ago in the radiographic examination of the thalamus. In retrospect, it is amazing how well neuroradiologists performed in the past without the newer imaging techniques of today.

Figures 1 and 2 of this chapter, on the neuroanatomy of the thalamus, will serve as an introduction. The details of the brain are readily visualized on MRI slices (Fig. 1). White matter is quite bright on T_1-weighted images and decreases in intensity on T_2-imaging. The thalamus stands out because of its density variation—MR images of the thalamus may even appear slightly better than actual anatomical sections. It is very important for the neuroradiologist to identify the normal anatomical structures of the brain. The MR images in Fig. 2 demonstrate the anatomy in great detail, including the retropulvinar cistern (or what used to be called the ambient wing cistern) defining the pulvinar, the anterior commissure extending across the midline, and the various thalamic nuclei in between (Fig. 2A). T_2-imaging is outstanding for the demonstration of pathology, but not as good for anatomy. For anatomical detail, one uses either T_1 images or proton-density imaging. We have been using MRI as we would CT, but MRI is not really like CT. One is able to glean a great deal more information using various pulse sequences. In addition to the advantages of a variety of pulse sequences and multiple planes (e.g., coronal and sagittal as well as axial), reduced flip angles provide information more rapidly with subsequent shortening of scan times. In this manner, information is being acquired that was not previously obtainable. We may look at

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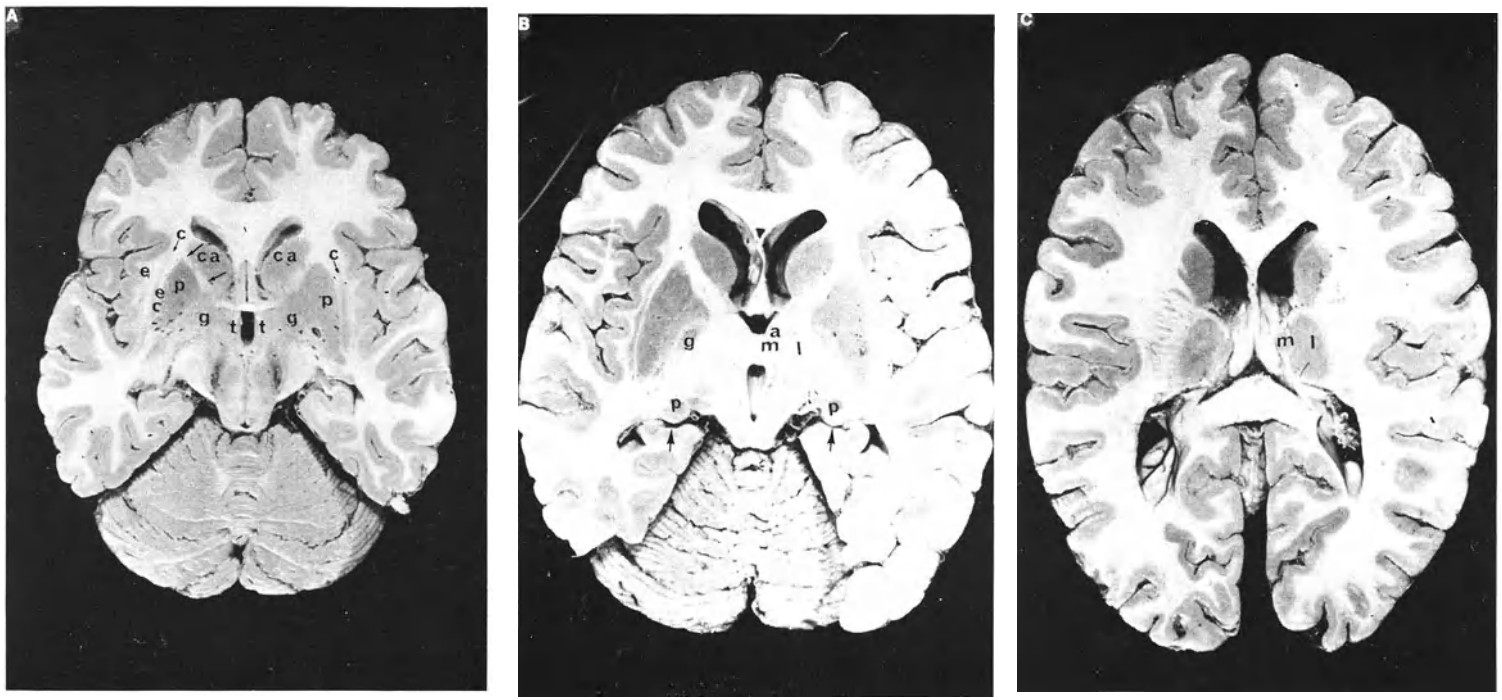


Figure 1. Neuroanatomical brain slices in the axial plane. In (A) the following anatomical structures are highlighted: e, extreme capsule; c (arrow), claustrum; ec, external capsule; p, putamen; g, globus pallidus; arrows, internal capsule; t, thalamus; ca, caudate nucleus. In (B) the thalamic nuclei may be identified: a, anterior nucleus; m, medial nuclei; l, lateral nuclei; p, pulvinar (one of lateral nuclei); arrow, retropulvinar cistern; g, globus pallidus. In (C) medial (m) and lateral (l) nuclei are well seen.

chemical shift imaging also. In other words, we may acquire both biochemical and anatomical information.

The thalamus is very nicely seen in the coronal plane (Fig. 2C). Again, we had been using the axial plane as for CT, but now we are doing more coronal sectioning because in MRI the coronal section is of equal quality to the axial sections. Variations in the density of the thalamus occur because it has a little more fat deposition and is not purely a gray matter structure.

OLDER STUDIES IN NEUROIMAGING

The older neuroradiological studies involved visualizing the vascular supply of the thalamus, for which one needs to look at the posterior circulation. Figure 3 shows the anterior thalamoperforators arising from the posterior communicating artery. Note that they go around the optic tract, penetrate through the midbrain, and then ramify within the thalamus. The posterior thalamoperforating arteries arise from the tip of the basilar artery. The vessels that come off laterally from the posterior cerebral artery, just before the origin of the posterior medial choroidal artery, are called the thalamogeniculate arteries and their branches penetrate the thalamus in the region of the geniculate body—so the blood supply of the thalamus actually originates from the posterior circulation. This includes the posterior communicating artery, the tip of the basilar artery, and the posterior cerebral artery. The posterior medial and posterior lateral choroidal arteries are also very important vessels.

Normal anterior and posterior thalamoperforators ascend posteriorly at about a 45° angle and undulate as they course posteriorly and superiorly (Fig. 3).

Figure 4 demonstrates an arteriovenous malformation in the thalamus, supplied by the anterior and posterior thalamoperforating arteries, the thalamogeniculate arteries, and the medial and lateral posterior choroidal arteries.

Figure 5 illustrates the fascinating case of a 1-year-old child who presented with a hamartoma, located at the base of the brain, that was totally removed by Dr. Kenneth Shulman. The main finding is the stretched vessels, including penetrating ganglionic branches, the thalamoperforating arteries, the thalamogeniculate arteries, and the posterior medial and lateral choroidal arteries extending around the medial posterior aspect of the tumor.

Figure 6 shows a patient with a malignant lymphoma deep within the hypothalamus that is supplied by the posterior communicating artery and the anterior choroidal artery, with an extensive (arterial) blood supply and early venous drainage.

Figure 7 represents a patient with a unilateral thalamic glioma. The lateral vertebral arteriogram was normal. On the anterior–posterior views the medial and lateral posterior choroidal arteries are perfectly normal on the left, but on the right the thalamic neoplasm distorts these choroidal arterial branches. In another patient with a hypothalamic glioma (Fig. 8), note the marked stretching of the posterior lateral and medial choroidal arteries, while the thalamoperforating arteries are perfectly straight. The thalamoperforating arteries reveal the inferior extent into the hypothalamus, while the posterior choroidal artery displacement indicates the thalamic involvement.

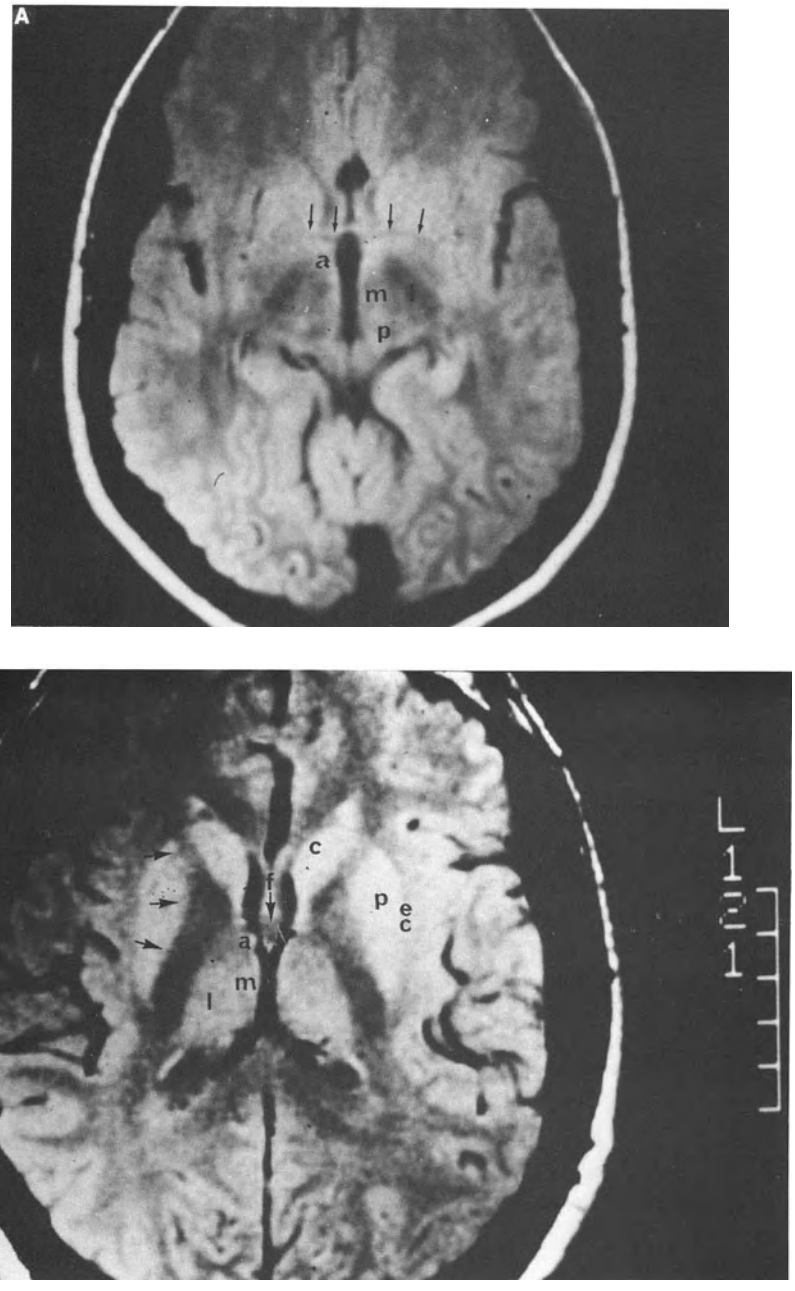


Figure 2. MRI slices of normal anatomy in the axial and coronal planes. (A) Axial section through thalamic nucleus, showing: a, anterior nucleus; m, medial nuclei; l, lateral nuclei; p, pulvinar (a lateral nucleus); arrows, anterior commissure. (B) Axial section 5 mm higher than in A, illustrating: c, caudate nucleus; arrows, internal capsule; p, putamen; ec, external capsule; arrow, fornix. Thalamic nuclei shown include: a, anterior nucleus; m, medial nuclei; l, lateral nuclei. (C) Coronal slice through the thalamus (arrows): m, medial nuclei; l, lateral nuclei.

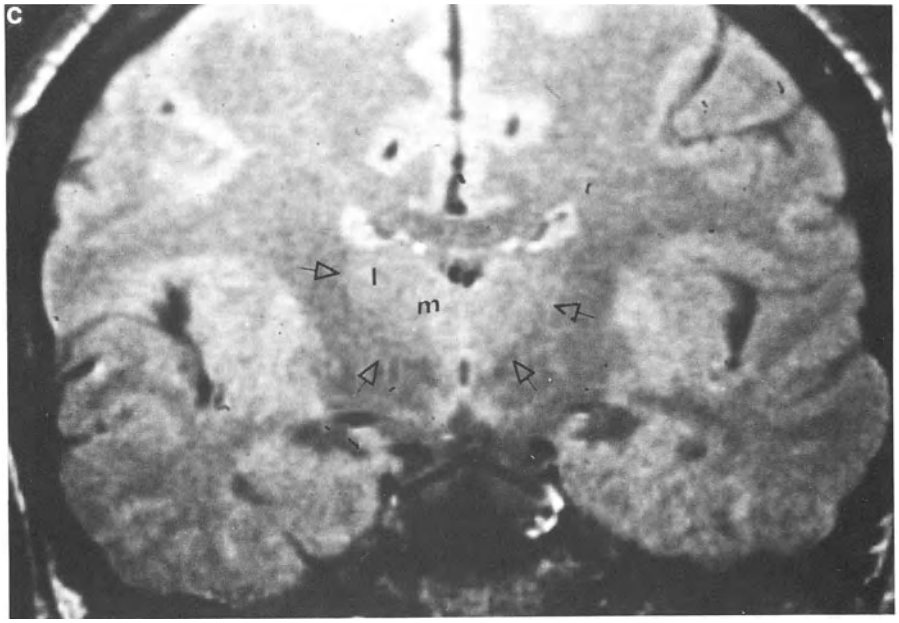


Figure 2. (*Continued*)

These cases represent older studies in neuroimaging. Although some angiography is still done today, other studies, such as CT and MRI, yield relatively more information.

MORE RECENT STUDIES IN NEUROIMAGING

Figure 9A shows another patient with a thalamic neoplasm; if we look very carefully on the midline sagittal T_1-weighted image we see that the tumor extends posteriorly, indenting the quadrigeminal plate cistern and involving the periaqueductal gray matter. It is seen again a little bit more laterally, very irregular and with a permeative pattern. Note that in the axial plane one can see the entire extent of this lesion (Fig. 9B). This is a pineal region neoplasm that, in this case, is a thalamic glioma.

A mixed component is present on the T_1 image, but on the T_2 images one cannot be sure. This illustrates that MRI is very sensitive, but not very specific. One is able to identify this particular lesion and its extent: It is bilateral, penetrates into the mesencephalon, and, judging from the tissue pattern, probably is a recurrent neoplasm.

Some of the problems neuroradiologists face are illustrated by the case shown in Fig. 10. This lesion is also in the thalamus, and on both the proton-density images and the T_2 images it is bright white. This is multiple sclerosis (MS); we know it is MS because it has all the findings associated with MS. Our team has seen three cases of such

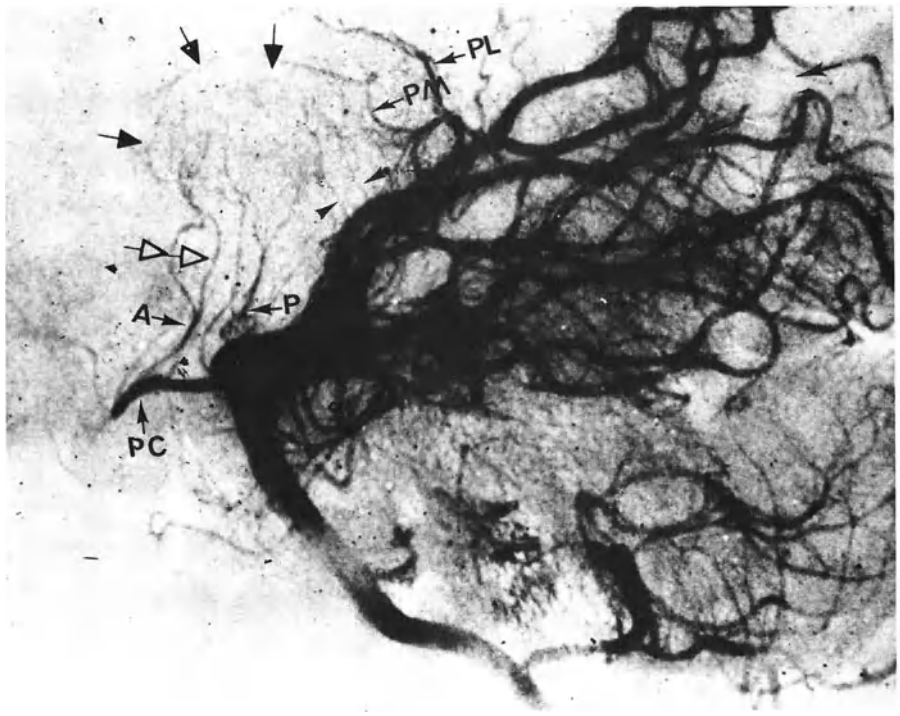


Figure 3. Normal lateral projection in arterial phase of vertebral angiography. The anterior thalamoperforating arteries arise from the posterior communicating artery (PC), ascend at a 45° angle, pass around the optic tract (A), penetrate the midbrain (open arrows), and then ramify in the thalamus (arrows); the posterior thalamoperforating arteries (p) arise from the basilar artery and take a similar course, except that they are not related to the optic tracts. The thalamogeniculate arteries are more posterior and penetrate the thalamus laterally (arrowheads); the posterior medial choroidal artery (PM) has the course of a figure three in the midline posterior to the third ventricle, and the posterior lateral choroidal artery (PL) is more lateral and lies between the thalamus and floor of the lateral ventricle.

lesions in the thalamus. In addition, there have been a couple of unidentified bright objects (UBOs) in the white matter. UBOs may be the result of a variety of possible changes in the parenchyma; it is a mistake to attribute them to MS unless they occur in association with white matter foci, are periventricular in location, are associated with corpus callosal atrophy, and the patient is in the appropriate age group. The lesion shown in Fig. 10, a large lesion, represents our third such case. The fact that this is a true example of MS was established by cerebrospinal fluid (CSF) findings and the clinical course and outcome. Another advantage of MRI, then, is that we now have a noninvasive examination for the periodic assessment of patient outcome in cases of MS.

Some interesting concepts relevant to this case can be presented. In an article from the University of Pennsylvania, for instance, gadolinium diethylenetriaminepentaacetic acid (DTPA) was reported to have been used to define active plaques in MS. We are not totally convinced of the authors' observations. We believe the rings report-

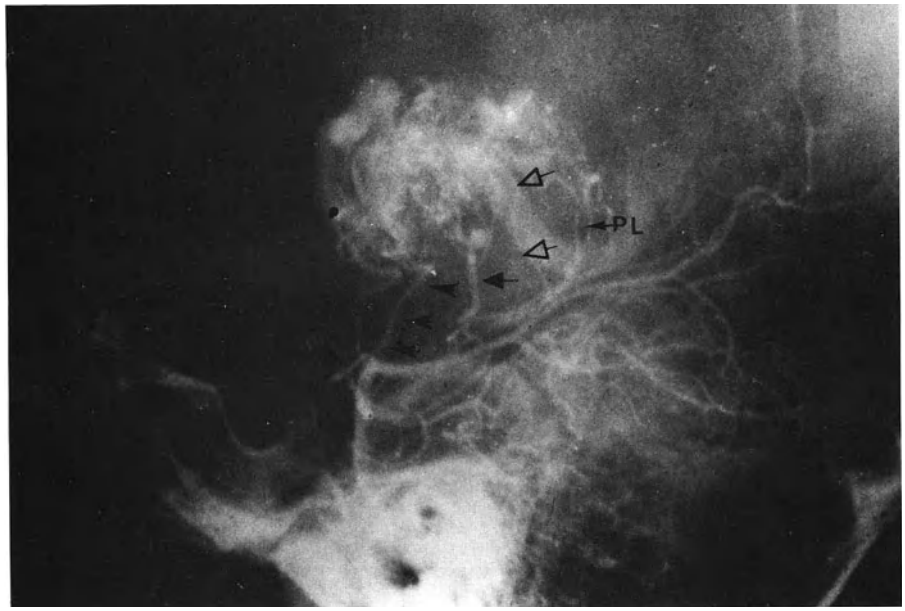


Figure 4. Thalamic arteriovenous malformation. The supply to this malformation is from the thalamoperforating arteries (arrowheads), thalamogeniculate artery (arrow), posterior medial choroidal artery (open arrows), and posterior lateral choroidal artery (PL).

edly formed may result from various stages of activity of the lesions. One thing we have learned from CT scanning is that often the lesions revealed are not necessarily located at a site comparable to the presenting clinical symptomatology.

Figure 11 illustrates another case involving a thalamic lesion, this one an infarct. This lesion is slightly irregular and has a haze surrounding it. This was an early infarct in the posterior cerebral artery distribution extending into the thalamus.

Figure 12 is from a very interesting case referred to Dr. Bennett Stein for surgical treatment. The patient had recently come to the United States from Israel for MRI testing, having brought her CT scans with her. She was 21 years of age, presented with intense headaches, and was quite ill. She was treated with steroids. The lesion in Fig. 12 was seen on the CT scan. The MR we obtained showed the lesion to be very bright on the T_1-weighted images, suggesting that it might contain fat. One must note the fluid level as well. The cyst wall is hyperintense on varying images. The first image was gotten at a TR of 600 msec. We then used a shorter TR of 300 msec, which produced an even clearer image. We then did a short T_1 inversion recovery (STIR) pulse sequence, which is a fat-suppressed sequence, which showed that hyperdensity was still present in the lesion, although the border was isointense. Therefore, the bright signal seen on T_1-weighted imaging was not fat, but more probably either blood or protein aggregate in a cyst of the pineal region. It was unlikely to be a teratoma, in view of the absence of fat within the lesion. It could have been a cystic astrocytoma with blood inside it. We've imaged a number of pinealocytomas and the imaging does

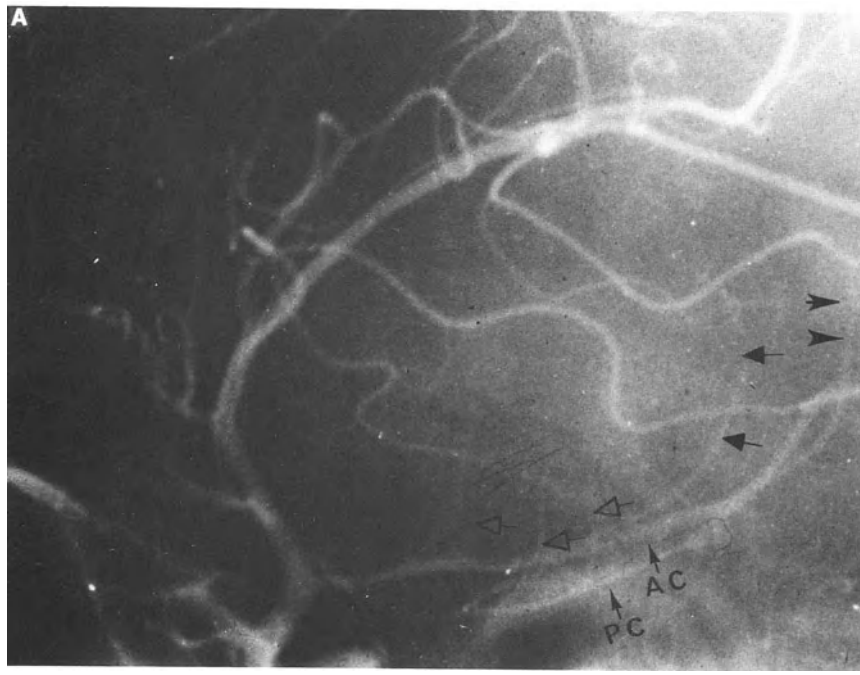


Figure 5. Hamartoma at the base of the brain, affecting hypothalamus and thalamus, in a 1-year-old. (A) Lateral projection after injection of the internal carotid artery. The anterior choroidal artery (AC) and posterior cerebral artery (PC) are stretched and inferiorly displaced. The penetrating ganglionic branches, including thalamoperforating and thalamogeniculate arteries, are stretched and elongated (open arrows). The medial (closed arrows) and lateral (arrowheads) posterior choroidal arteries are also stretched about the mass. The middle cerebral artery is markedly elevated. (B) Lateral projection after injection of the vertebral artery. The anterior (two open arrows) and posterior (four open arrows) thalamoperforating arteries are markedly stretched and elongated. The medial (arrows) and lateral (arrowheads) posterior choroidal arteries are also elongated and stretched as they define the posterior and medial margins of the tumor.

not look very different from that of an astrocytoma. In fact, our experience has been that one cannot distinguish pinealocytomas from astrocytomas on MR images. At surgery this particular lesion was found to be an ependymoma with hemorrhaging within its matrix.

Figure 13 shows another patient with large ventricles. This was a dysgerminoma, which is obviously a more common pineal-region neoplasm, with calcifications within the tumor. The neoplasm responded to radiation and shunting with a marked decrease in tumor size after 3 months (Fig. 13B).

Figure 14 displays a large neoplasm, found in a young child, which turned out to be a glioma in the basal ganglia and thalamus.

The case represented in Fig. 15 is fascinating because one can identify a hemorrhage in the thalamus and, aside from mass effect, only minimal changes are evident. The arteries do look slightly prominent as they penetrate the thalamus, but this may just

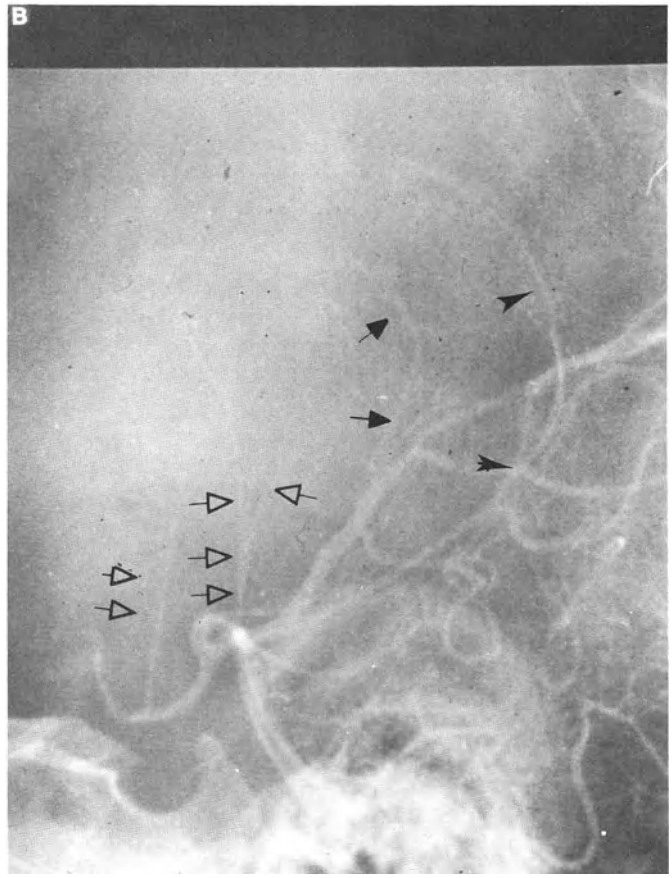


Figure 5. (*Continued*)

represent hyperemia since there really doesn't appear to be any connection with the thalamic hemorrhage. During the venous phase, the venous angioma accounting for this thalamic hemorrhage can be recognized. Venous angiomas may often be observed with MRI and CT; they occur incidentally in the region of the thalamus and posterior fossa.

The last patient represented (Fig. 16) came for MRI because he was losing vision. The report from the neurologist was that he had a "normal computed tomography." The MRI revealed what appeared to be a craniopharyngioma (Fig. 16A–C) and the CT scan, in retrospect, was positive (Fig. 16D), demonstrating the cyst and calcification within the suprasellar cistern. The MRI revealed a high-protein cystic mass in the suprasellar region, with a normal anterior pituitary and posterior pituitary gland. In addition, one may observe the expanded suprasellar cistern and the compression of the optic nerves.

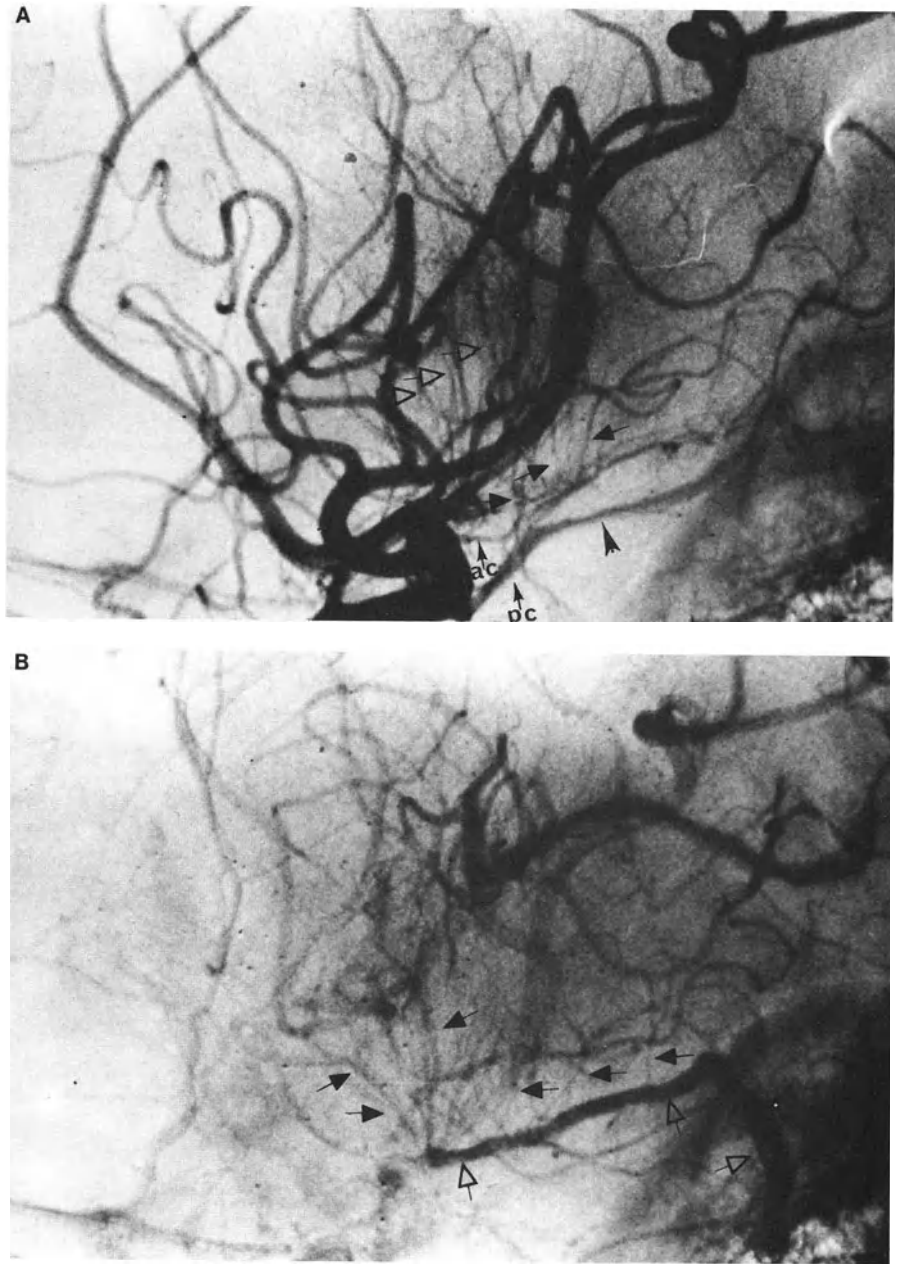


Figure 6. Hypothalamic lymphoma. (A) Lateral projection in the arterial phase. Vascular supply is observed (open arrows and closed arrows) arising from the posterior communicating artery (pc), posterior cerebral artery (arrowhead), anterior choroidal artery (ac), and middle cerebral artery. (B) Lateral venous phase. Many abnormal medullary veins (arrows) are observed draining the neoplasm and emptying into an enlarged deep middle cerebral vein (open arrows).

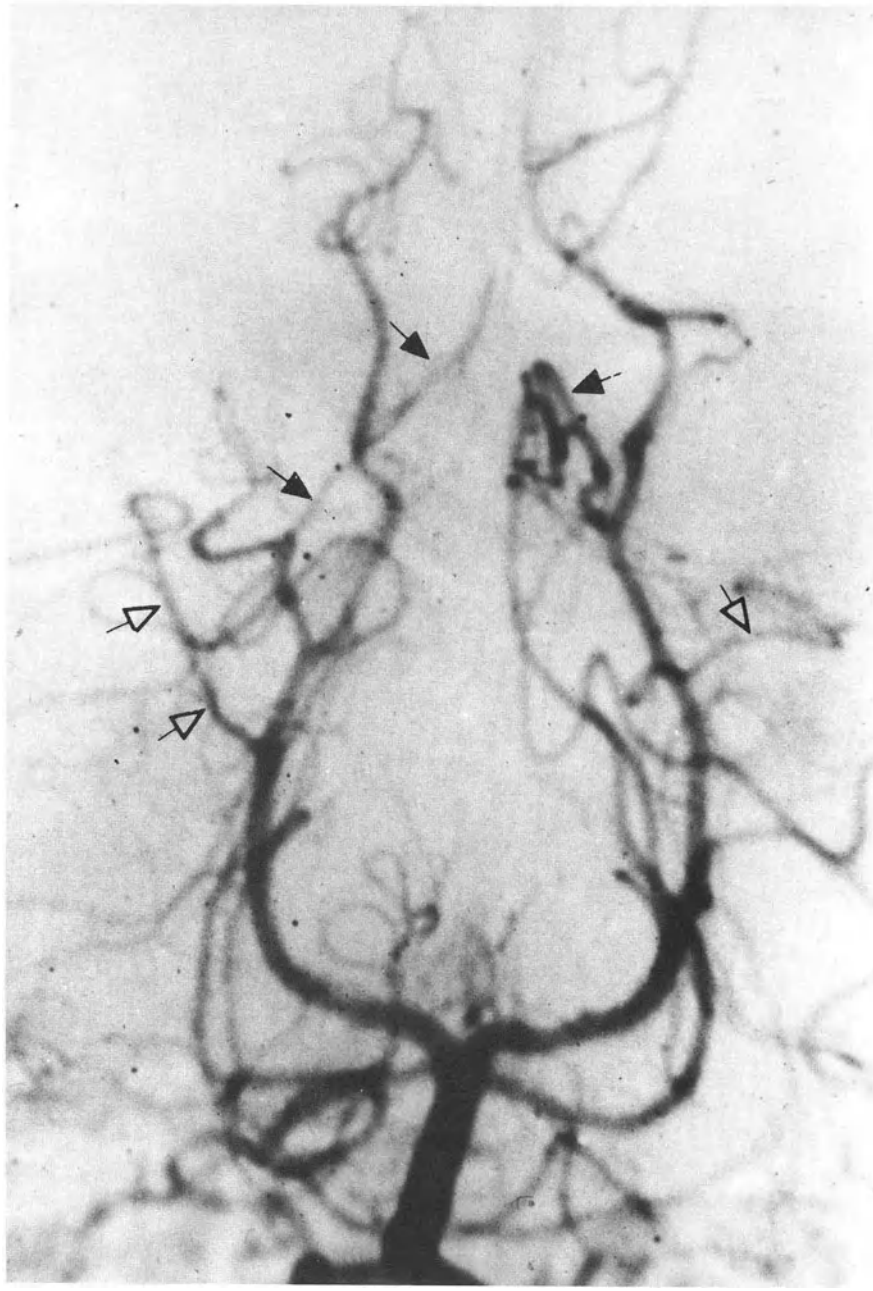


Figure 7. Right thalamic glioma. Anterior–posterior projection in the arterial phase of vertebral angiogram shows the left lateral (open arrow) and medial (closed arrow) posterior choroidal arteries are normal; their counterparts on the right lateral (open arrows) and medial (closed arrows) are stretched and displaced by the thalamic neoplasm.

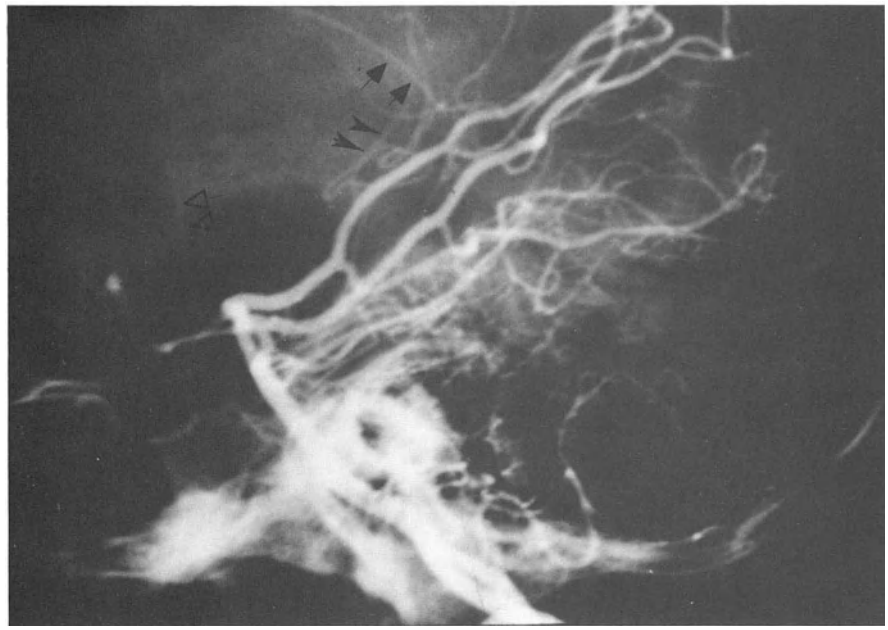


Figure 8. Hypothalamic–thalamic glioma. Lateral projection in the arterial phase of vertebral angiogram shows the anterior thalamoperforating arteries are elongated, stretched, have lost 45° angulation, and are not undulating (open arrows). The medial (arrowheads) and lateral (arrows) posterior choroidal arteries are markedly stretched and displaced by the tumor.

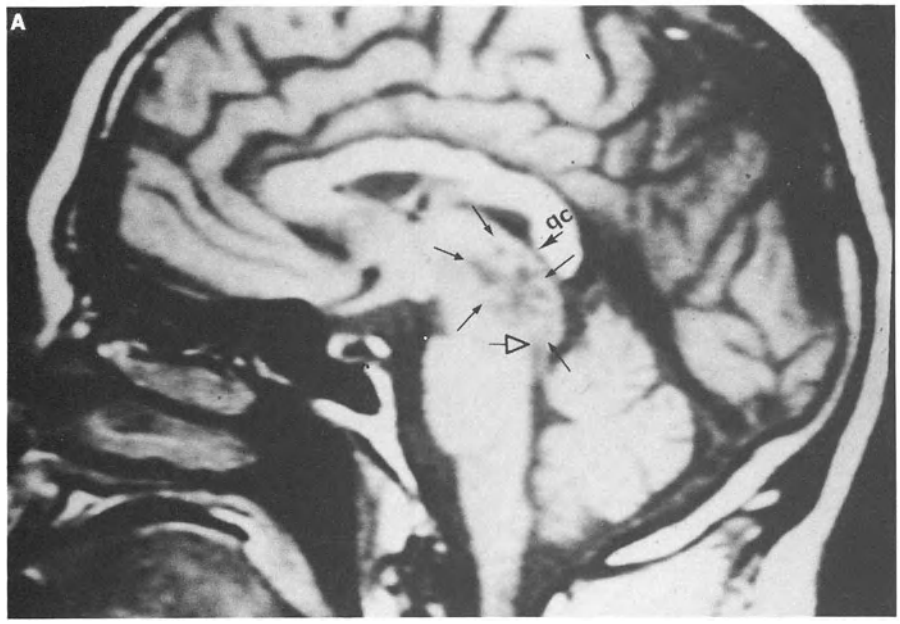


Figure 9

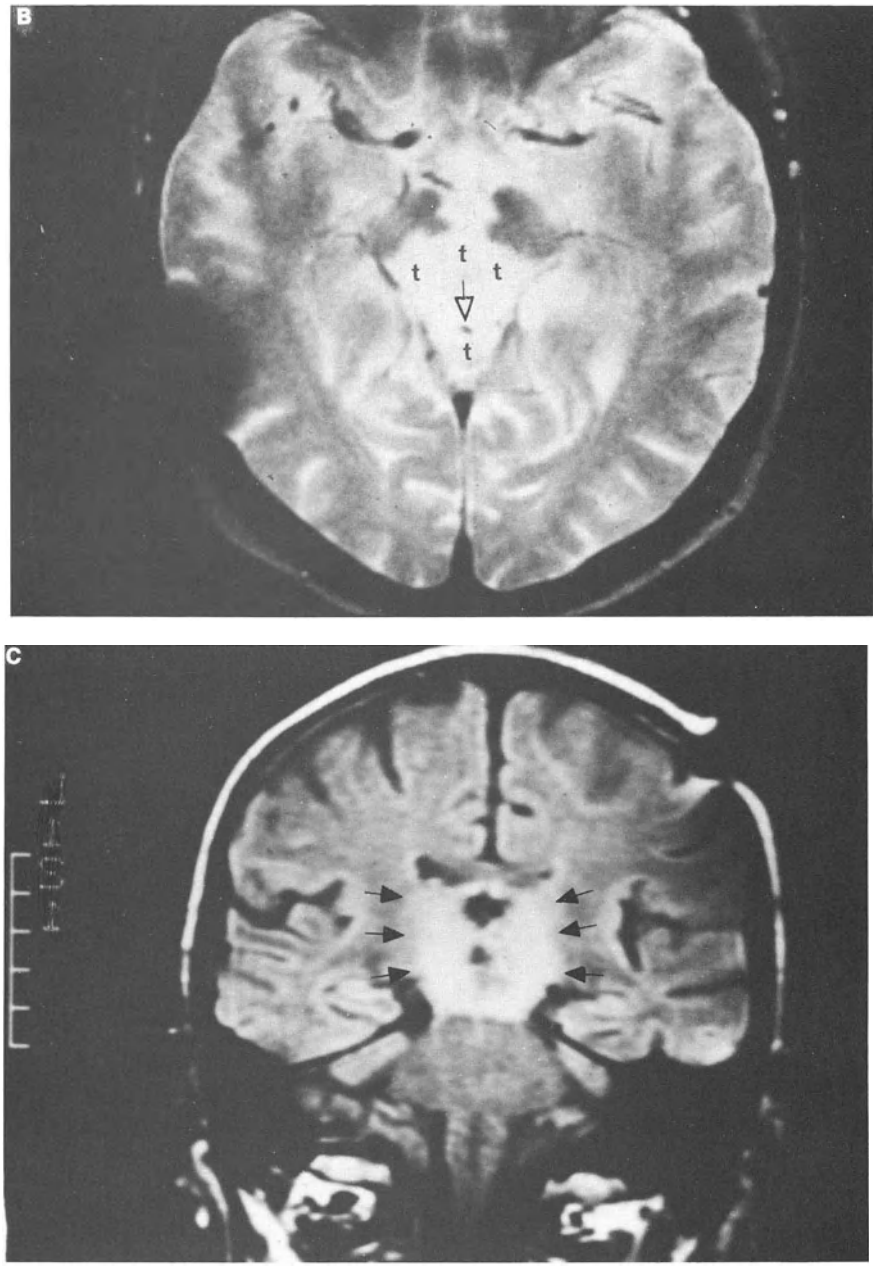


Figure 9. Thalamic glioma in the pineal region, periaqueductal in location and invading quadrigeminal plate. (A) T_1 image in saggital plane, revealing hypointense permeating neoplasm in thalamus, periaqueductal region, and quadrigeminal plate (arrows). The quadrigeminal plate cistern (qc) is stretched. The aqueduct has been interrupted by the neoplasm (open arrow). (B) T_2 image in axial plane. The tumor is hyperintense and affects the thalamus (t's) and encompasses the aqueduct (open arrow). (C) Proton-density image in coronal plane. The bilateral midline hyperintense thalamic neoplasm (arrows) is again seen.

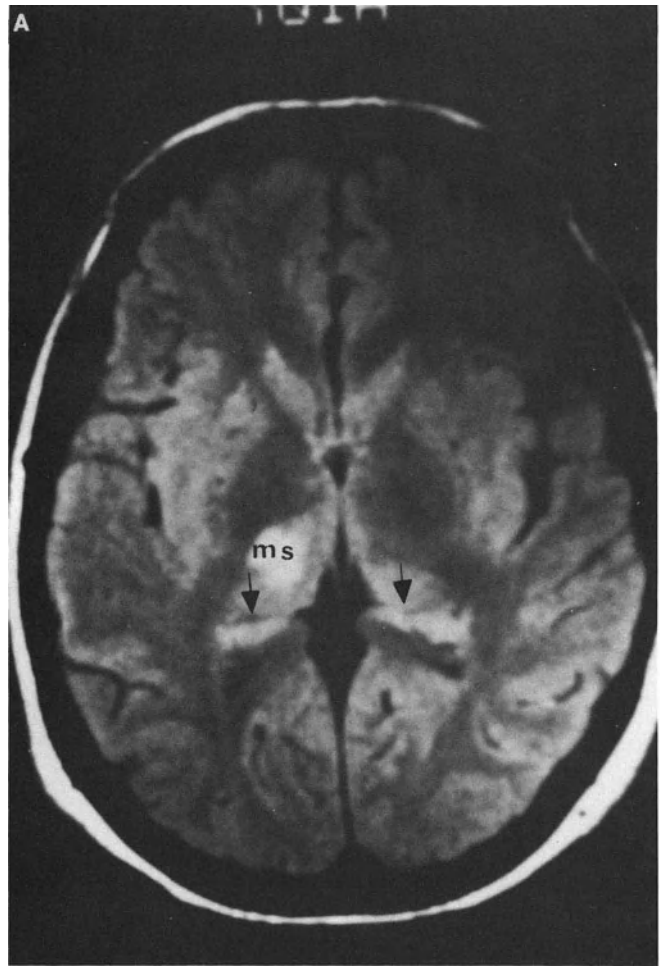


Figure 10. Multiple sclerosis plaque in pulvinar of the thalamus and midbrain. (A) Proton-density axial image. A hyperintense nodular density (ms) is seen within the pulvinar of the thalamus; the retropulvinar cisterns (arrow) are seen. (B) T_2 axial image. Nodular hyperintense image (ms) in midbrain is defined posteriorly by quadrigeminal plate cistern (arrow); the substantia nigra (open arrow) and red nucleus (arrowhead) are seen because of paramagnetic effects of iron on T_2 images.

CONCLUSION

In summary, angiography was and continues to be an excellent technique of particular usefulness in the thalamic region because of the attention that one can pay to specific blood supply. CT scanning added a great deal of information, but MRI has moved us a step further, since it has very high sensitivity. However, its specificity has yet to be fully determined. The newer pulse sequences and shorter flip angles, as well

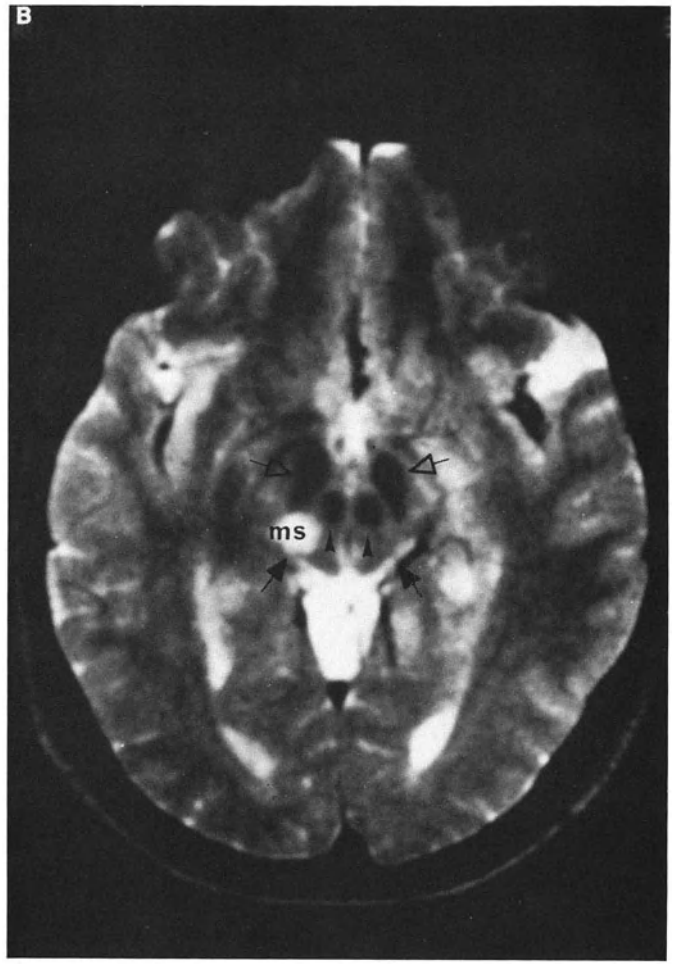


Figure 10. (*Continued*)

as chemical shift information, may provide improved specificity and biochemical and physiological data. Finally, MRI allows visualization of blood vessels, which may obviate the need for angiography in some cases.

DISCUSSION

MAGNETIC RESONANCE IMAGING DOCUMENTATION OF MICROADENOMAS OF THE PITUITARY

Fukushima asks how often microadenomas can be demonstrated with MRI. Edwards reports that 70% of cases of Cushing's disease—basophilic adenomas—were detectable on MRI

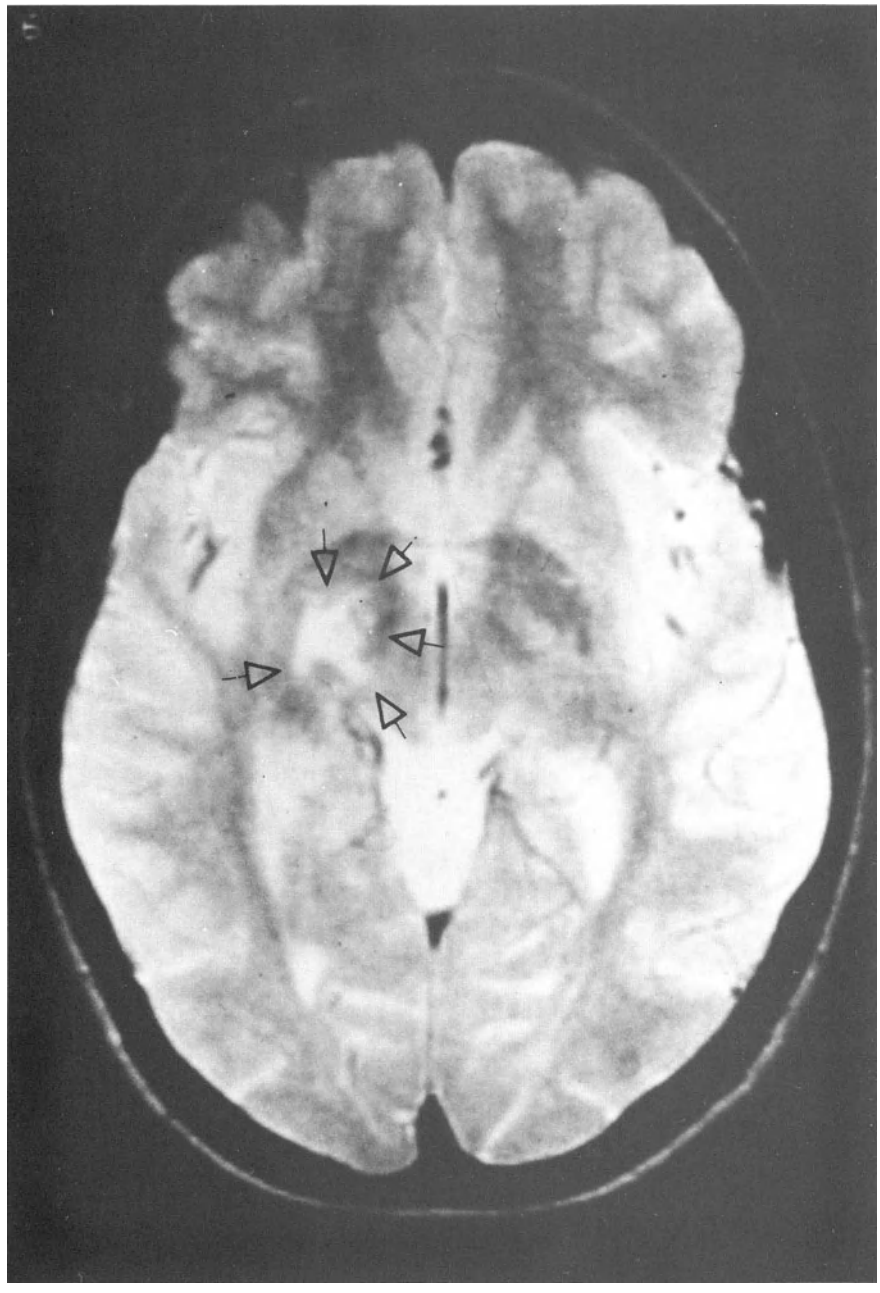


Figure 11. Thalamic infarct. T_2 image in the axial plane shows a hyperintense irregular image (open arrows) with hazy borders in the lateral nucleus of thalamus.

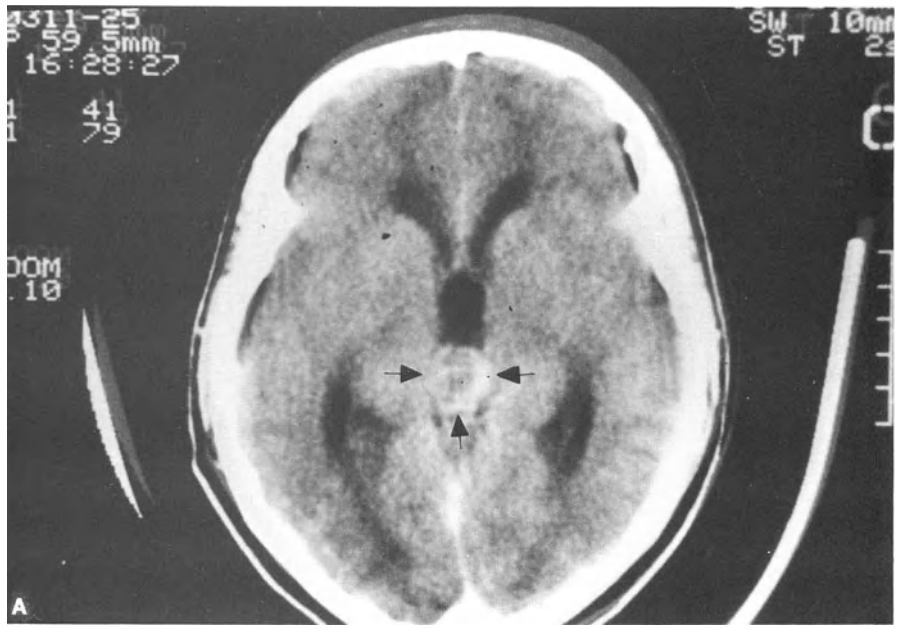
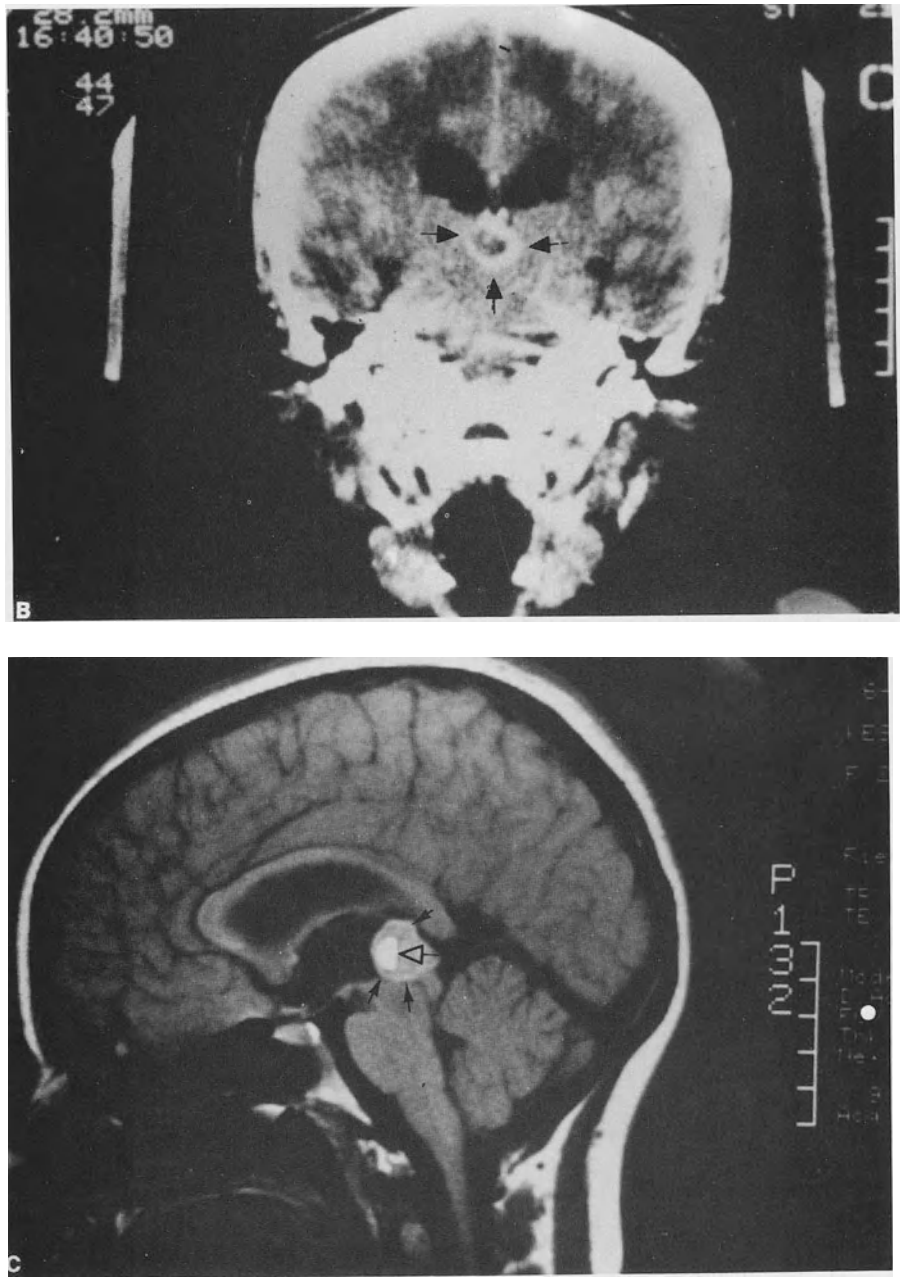


Figure 12. Pineal-region ependymoma with hemorrhage. (A and B) Axial (A) and coronal (B) CT scans following intravenous contrast. In A, a circumscribed, well-defined ring lesion is seen in the pineal region (arrows). (C) Sagittal T_1 image at a TR of 600 msec. An isointense pineal-region nodule is seen containing a hyperintense lesion with a fluid level (open arrow). The borders of the neoplasm are hyperintense (arrows). The lesion indents the posterior third ventricle and compresses the proximal aqueduct. (D) Sagittal T_1 image with a shorter TR of 300 msec. The findings are similar to those in C, but hyperintensity of the borders of the lesion (arrows) and the hyperintense lesion with fluid level (open arrow) are accentuated. (E) Inversion recovery with fat suppression, in the sagittal plane. The hyperintense density with fluid level is still hyperintense (open arrow), while fat is suppressed and border of lesion becomes isointense (arrows). (F) Proton-density image in the axial plane. The pineal-region tumor is seen again, with a hyperintense semicircular component with a fluid level having a black inferior border (arrows) as a result of heterogeneous magnetic susceptibility. (G) T_1-density image in the coronal plane. The lesion has a hyperintense margin (arrows) and a center that is mixed iso- and hypointense.



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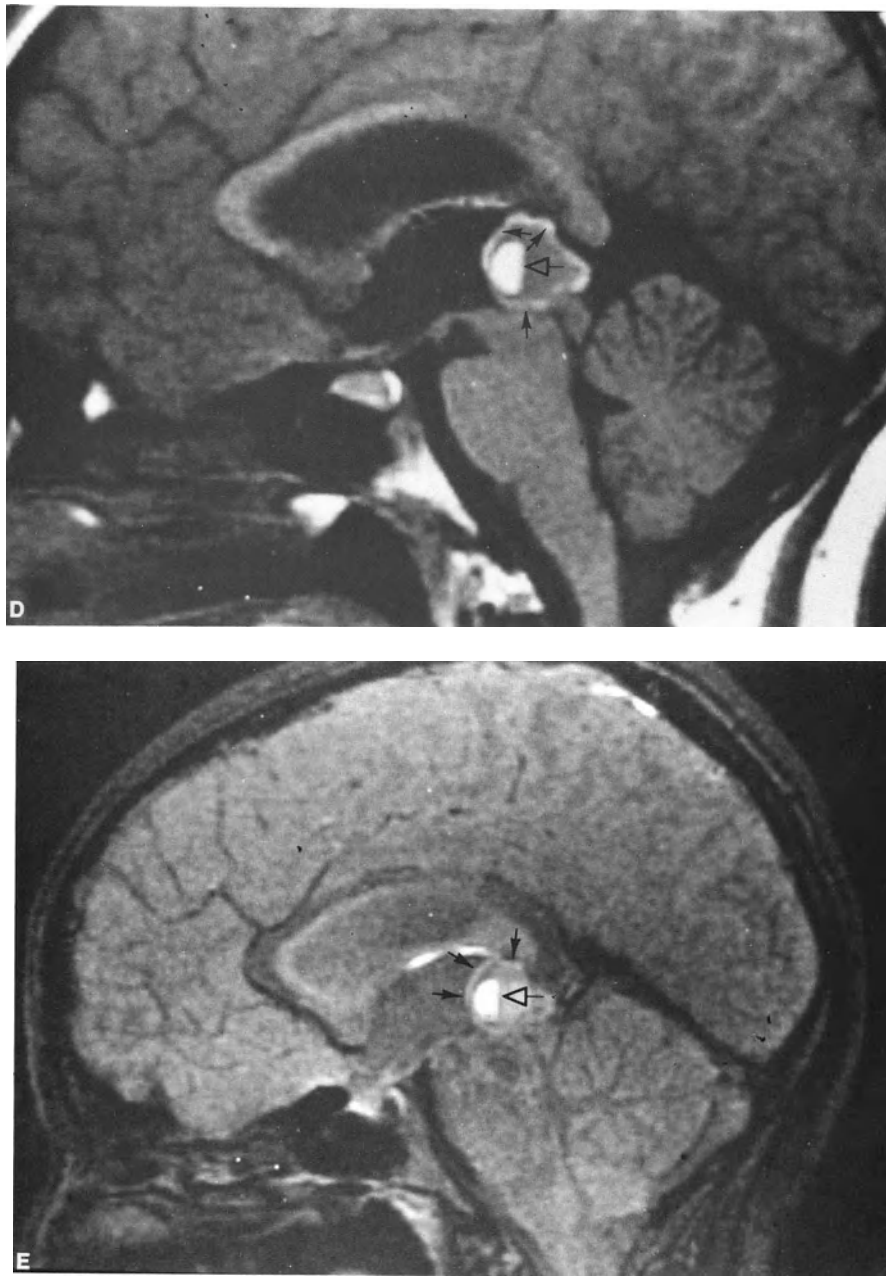

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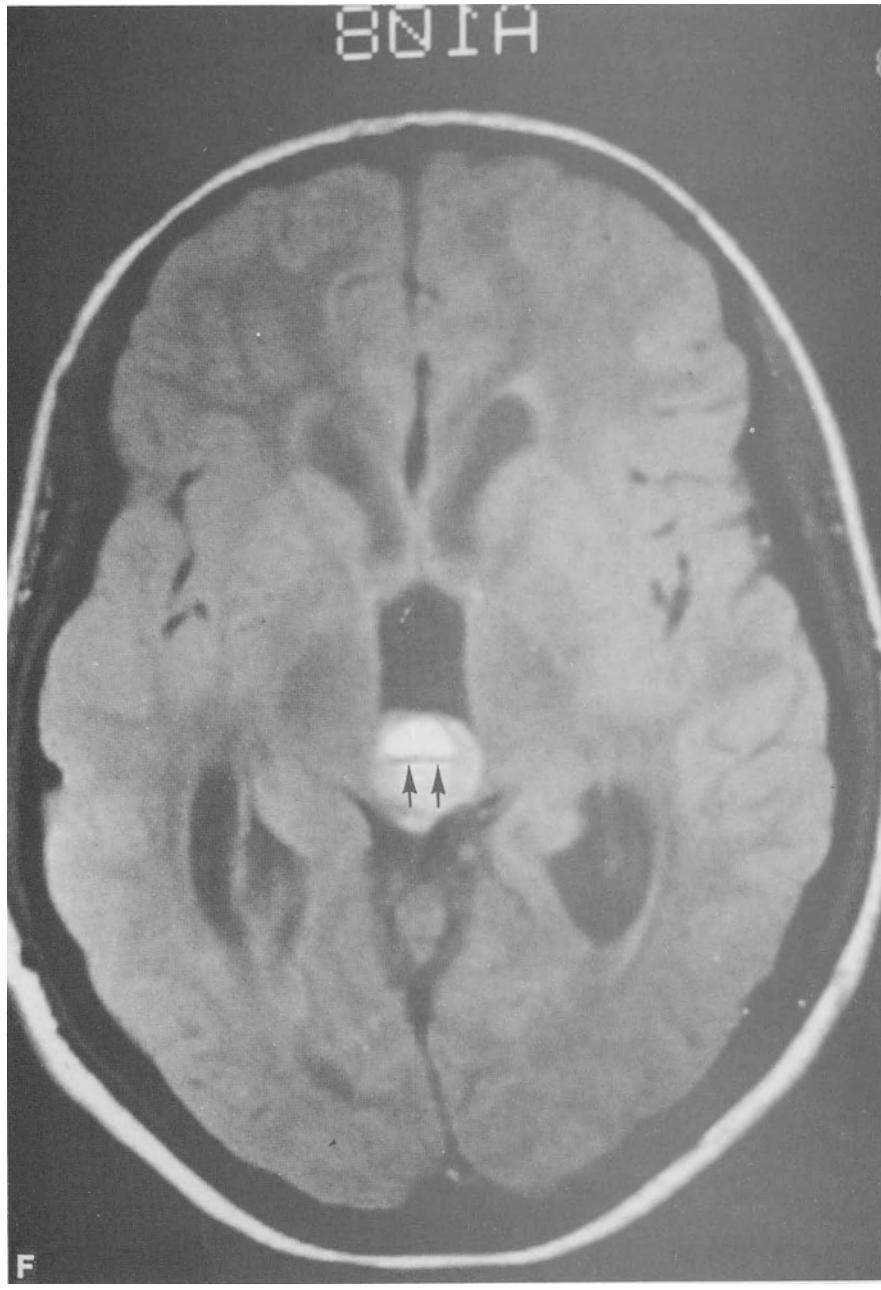

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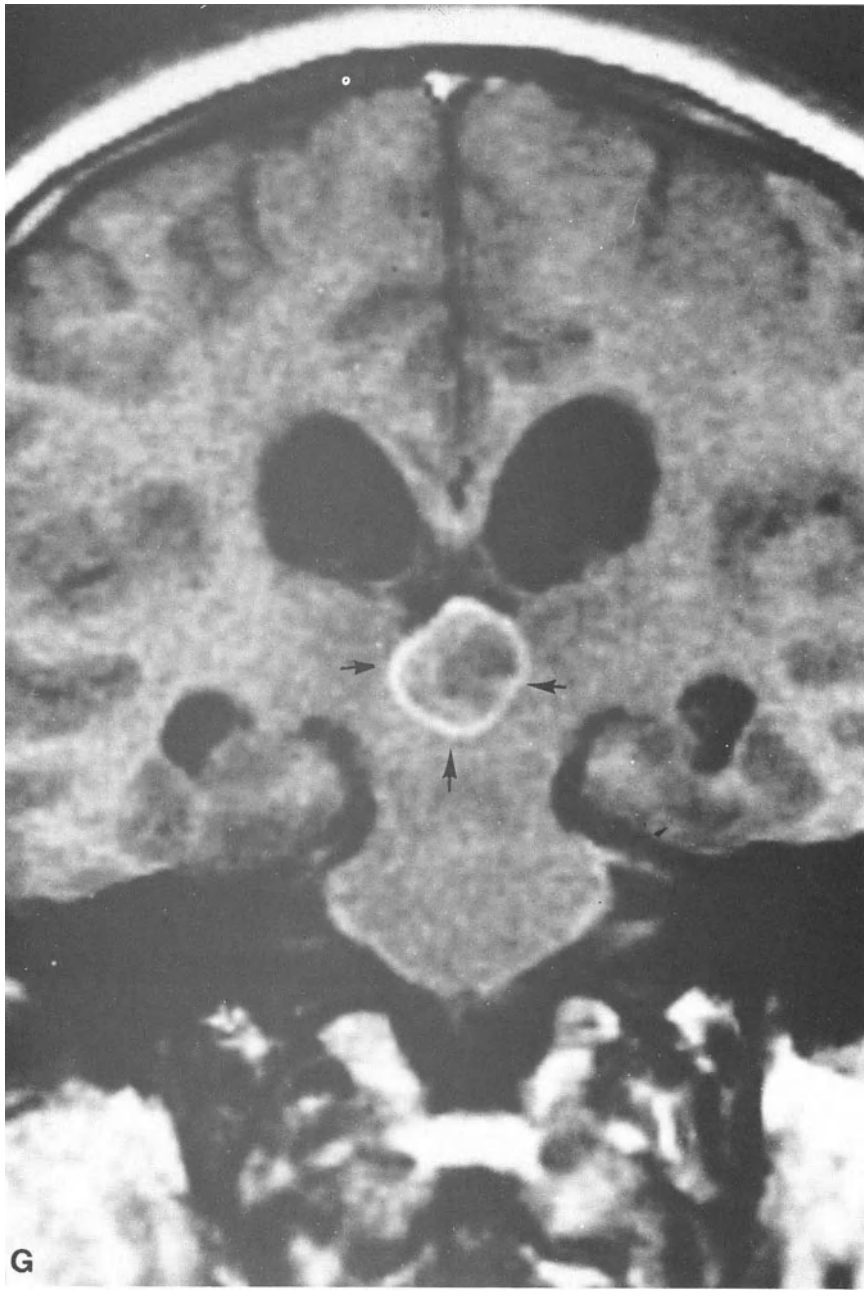

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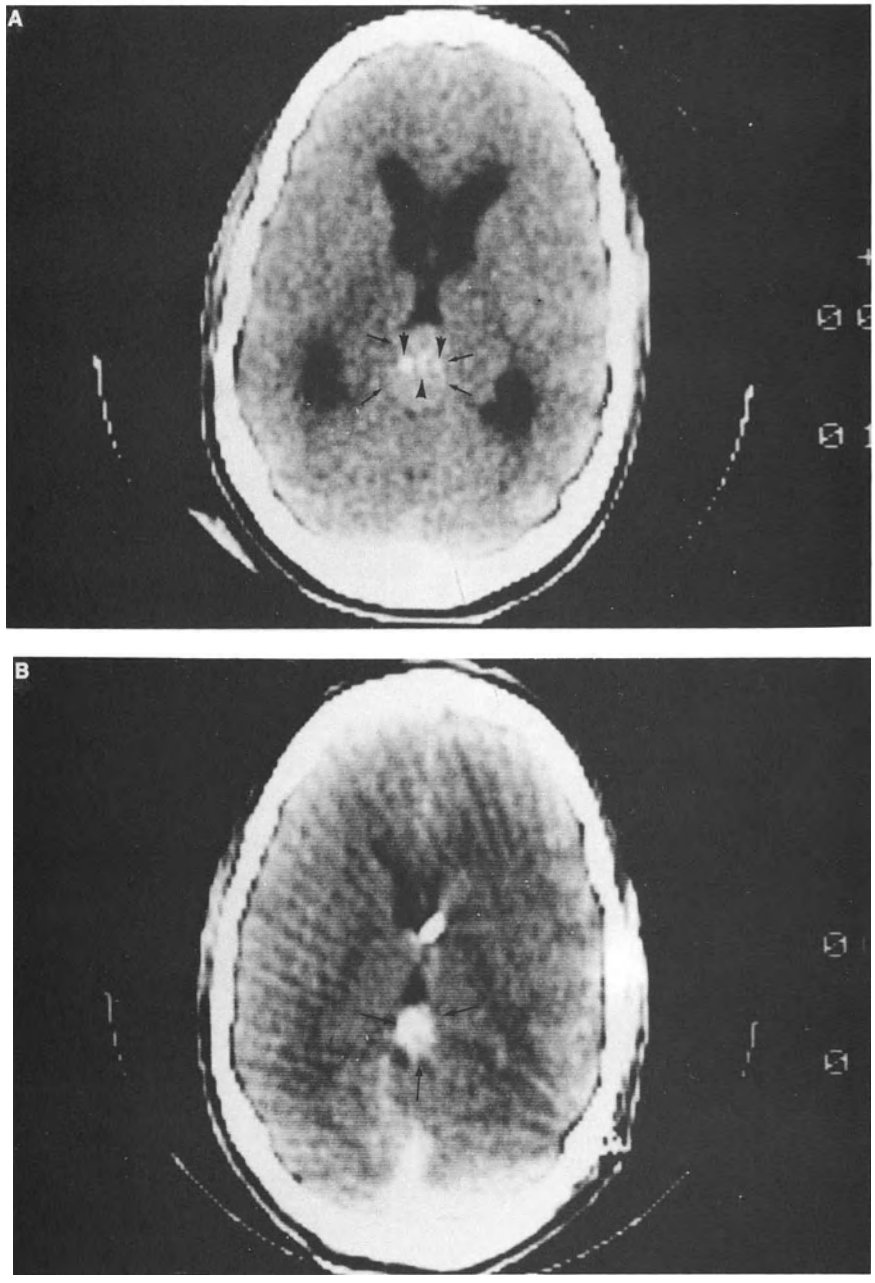


Figure 13. Pineal-region dysgerminoma. (A) Axial CT scan without contrast material. Note the large, slightly hyperdense oval lesion (arrows) in the pineal region with several nodular calcifications (arrowheads). Ventricular enlargement is present. (B) Axial CT scan following intravenous contrast infusion, shunt procedure, and radiation therapy 3 months later. Ventricles are decreased in size following shunting and the contrast-enhanced neoplasm (arrows) is reduced significantly in size.

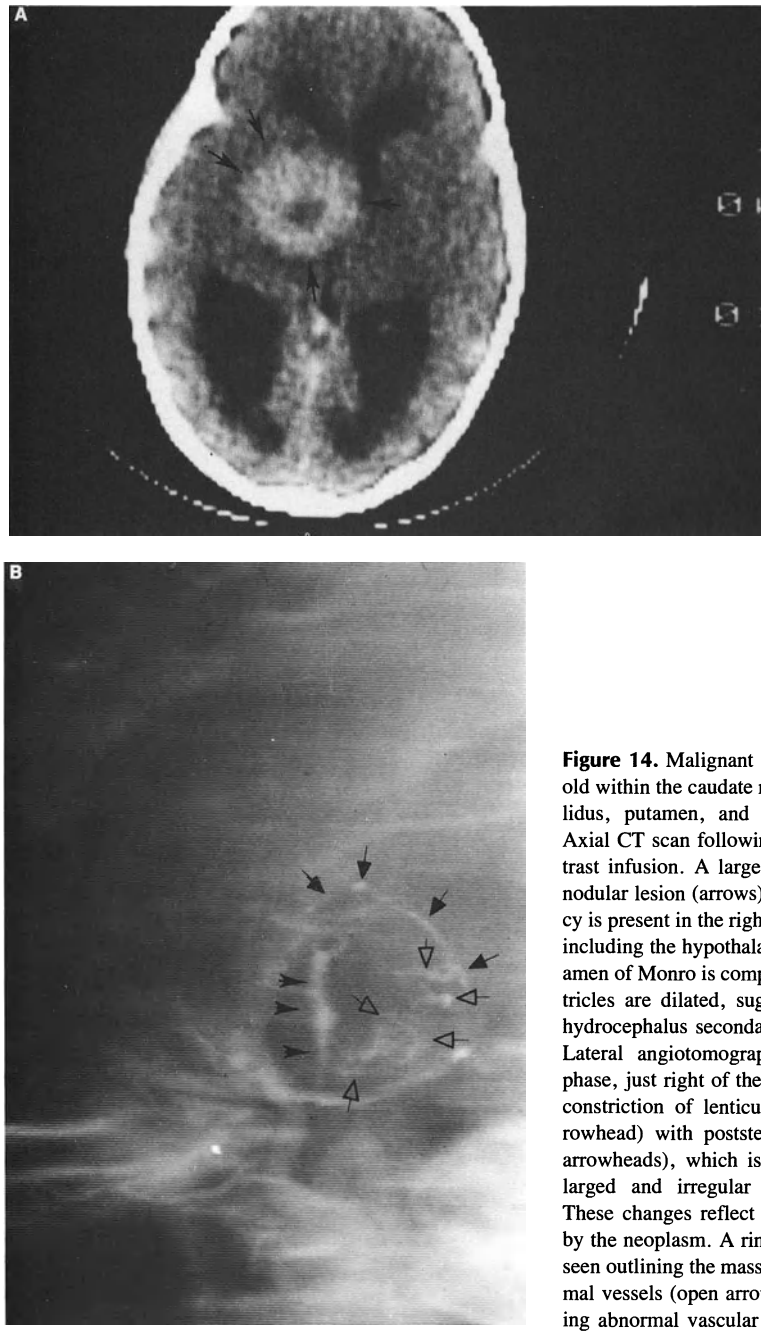


Figure 14. Malignant glioma in a 3-year-old within the caudate nucleus, globus pallidus, putamen, and hypothalamus. (A) Axial CT scan following intravenous contrast infusion. A large contrast-enhancing nodular lesion (arrows) with central lucency is present in the right ganglionic region, including the hypothalamus. The right foramen of Monro is compressed and the ventricles are dilated, suggesting obstructive hydrocephalus secondary to the mass. (B) Lateral angiotomography in the arterial phase, just right of the midline. Localized constriction of lenticulostriate artery (arrowhead) with poststenotic dilation (two arrowheads), which is also markedly enlarged and irregular (two arrowheads). These changes reflect arterial encasement by the neoplasm. A ring lesion (arrows) is seen outlining the mass. A tangle of abnormal vessels (open arrows) is seen, reflecting abnormal vascular supply.

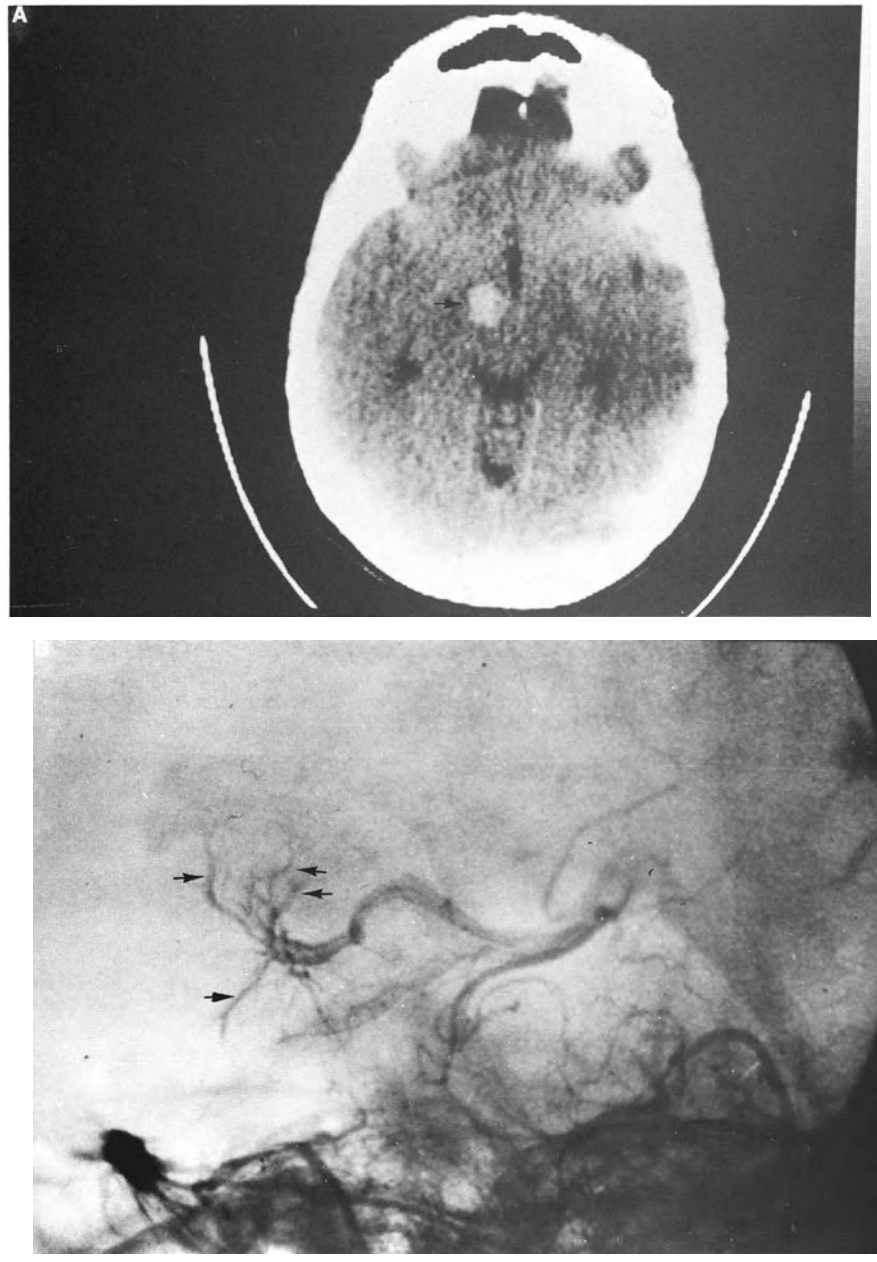


Figure 15. Venous angioma with hematoma. (A) CT-scan section at the level of the third ventricle, revealing a hematoma within the right thalamus (arrow), with minimal compression of the third ventricle. (B) Venous-phase right common carotid arteriogram, confirming the presence of venous angioma with enlarged thalamic and caudate veins (arrows).

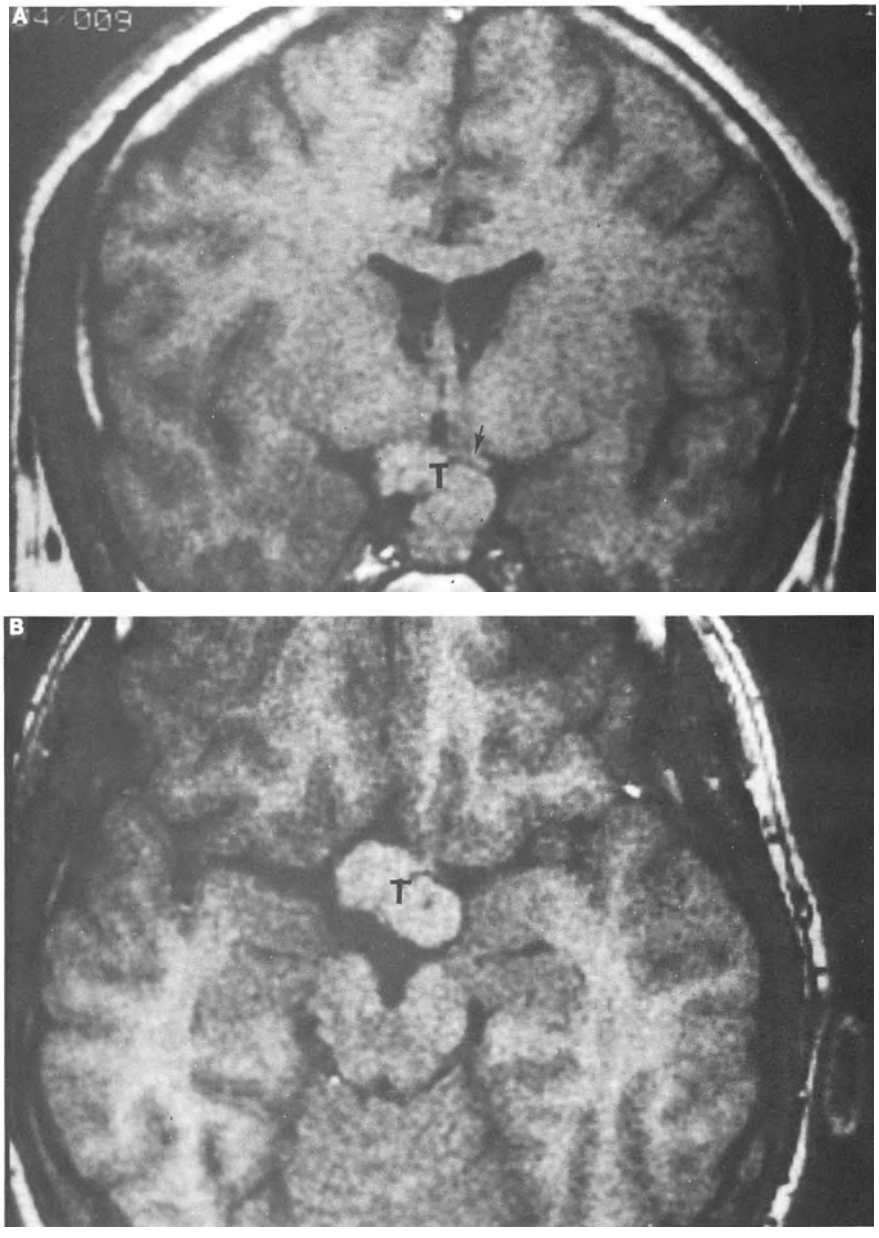
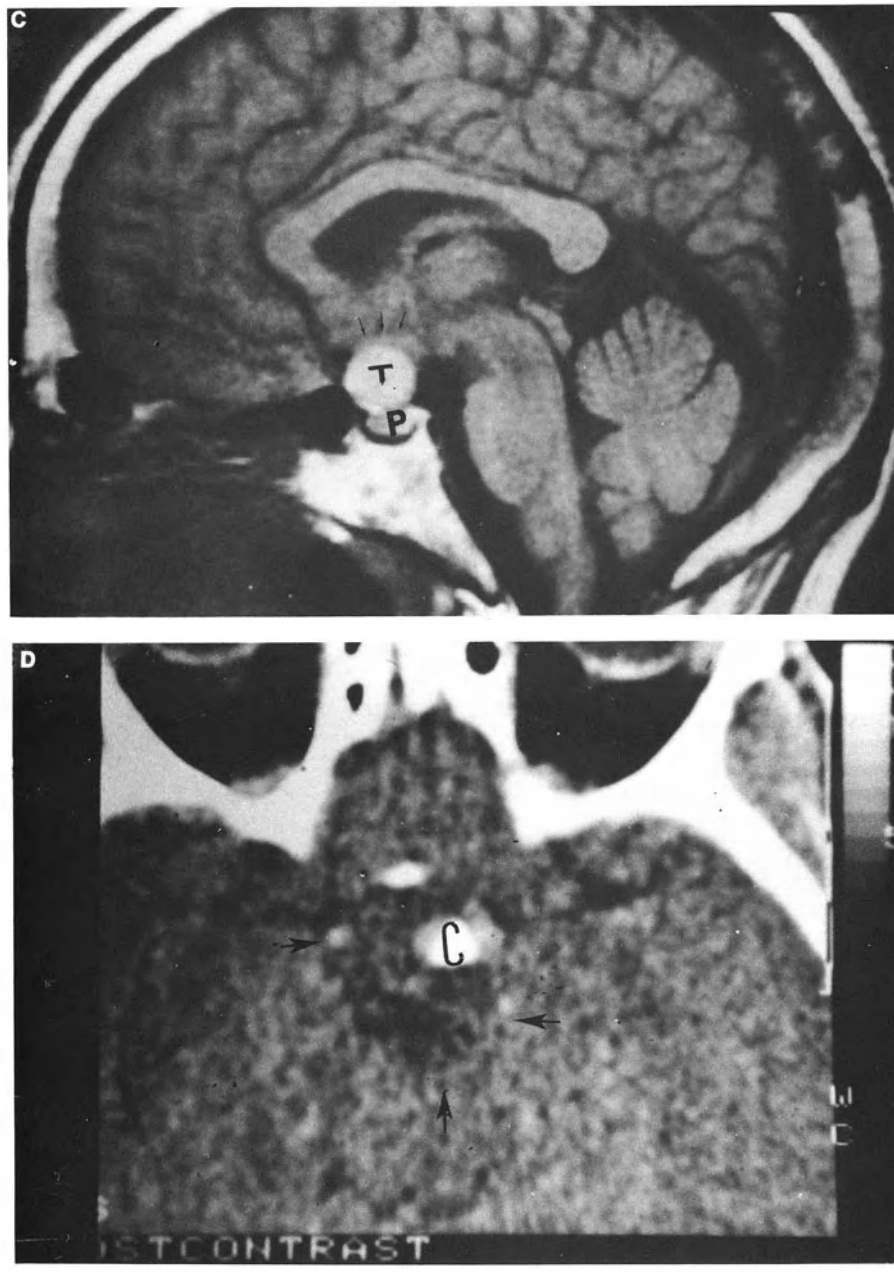


Figure 16. Craniopharyngioma. (A) Coronal slice, spin echo T_1-weighted (TR, 600 msec; TE, 20 msec), showing a bilobed, sharply circumscribed suprasellar mass (T) that is slightly hyperintense minimally compressing the left optic nerve (arrow), with obliteration of the right optic nerve. (B) Axial slice, spin echo T_1-weighted, showing again bilobed suprasellar tumor (T) that is slightly hyperintense expanding the suprasellar cistern. (C) Sagittal midline section, spin echo T_1, revealing an oval, sharply demarcated,



hyperintense suprasellar mass (T) compressing the optic nerves and chiasm (arrows). The pituitary gland (P) is normal. (D) CT-scan slice through suprasellar cistern, revealing an expanded, enlarged cistern (arrows) and calcification (c) in the tumor.

and were localized appropriately in the gland. The use of paramagnetic agents has also increased the sensitivity a bit. The adenomas were all hypointense on the T_1-weighted images. Adenomas with hyperintense T_1-weighted images were reflective of associated hemorrhage or pituitary apoplexy. In Edwards' experience, intrasellar craniopharyngiomas were always associated with a high T_1-weighted image.

If the MRI unit has a good magnet, there is a very high likelihood of being correct. Magnets less than 1.5 Tesla require more time to obtain the same quality of image that a 1.5 Tesla magnet obtains. Therefore, blur occurs and any blur will result in the loss of an image. If one is dealing with a small image, and if one's study takes more than 8 or 9 min, the likelihood is great that the patient will move and motion artifact will result in blur and loss of the image.

High-resolution MRI units allow faster scanning and the ability to obtain thin slices of 3 mm. In the future, it should become possible to look at the pituitary gland and tell what its makeup is by the chemical shift of the image, thereby distinguishing a prolactinoma from a basophilic adenoma.

II

The Diencephalon and Pain

5

Diencephalic Surgery for the Relief of Pain

Donlin M. Long

INTRODUCTION

Diencephalic surgery for the purpose of relieving pain has a long history and has not been an unqualified success over this time.[1,2] There are several reasons for this. Stereotactic surgery, before CT and MRI, depended upon anatomical localization first by intraventricular air study and later by positive contrast. Large ventricles could be confounding, particularly if the third ventricle was wide. The anatomy defined by this technique, while satisfactory in a practical sense, was often obscured by many things (lack of ventricular filling, poor definition of commissures, thalamic assymetry). As a result, much of the localization and many of the results reported are difficult to interpret now because it is very hard to know exactly where electrodes were and where the lesions were. Lesions tended to be large; they were frequently placed somewhat arbitrarily without very good anatomical delineation. Furthermore, the pain pathway was not well understood, so thalamic lesion making did not have much chance of success. Most of the literature on diencephalic surgery and pain dating from the 1950s and 1960s is, therefore, very difficult to interpret. The lesions were made in a wide variety of places, the most common targets being the centrum medianum, the parafascicular nucleus surrounding it, and specific thalamic sensory nuclei. The relevant papers are difficult to review. Most do not prove the localization of the lesion because the patients survived and histological specimens were not available. The size of the lesion is hard to determine given the rather crude lesion-making techniques of the time, and the criteria for the success of pain relief were indefinite at best. In fact, records show that the average follow-up duration for stereotactic pain surgery at that time was 3 months, so it was impossible to determine whether there was any long-term effect upon pain. Only a small amount of destructive thalamic surgery has persisted into this era. What we now know about the pain pathway might make a rebirth more fruitful,

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but most have stayed with stimulation rather than attempting to go back to destructive lesions. Some of the ideas presented in this volume may cause surgeons to rethink that position.

THE ASCENDING PAIN SYSTEM

The ascending nociceptive tract is now much better understood than it was in 1950.[3,4] The contralateral anterior spinothalamic tract is well known to all. In the early 1960s, brainstem collaterals were demonstrated by Nauta. This discovery generated a new interest in the pain pathway. It is now known that there are also terminations in the posterior ventral and intralaminar thalamus. The ventral posterolateral nucleus, the general target for stimulation, has a somatotopic relationship that is similar to that throughout the pain pathway. Contrary to findings in many lower animals, in humans and in primates there are very sparse nerve endings in the parafascicular and centrum medianum area. Most of these come from the midline reticular system and their importance in pain perception is still not entirely understood. There are additional supplementary tracts connecting throughout the brainstem reticular formation that do reach the centrum medianum and parafascicular nuclei. It is now well understood that there is a major contribution from the thalamus to sensory cortex and back.

Thus, there is a contralateral ascending pain system that goes directly into the specific thalamic nuclei and subsequently to both primary and secondary sensory systems. There are significant connections throughout the brain-stem reticular formation, and in the midline nonspecific reticular thalamus as well. This ascending system has multiple contributions throughout the reticular system of the brainstem, hypothalamus, posterior hypothalamus, and midline thalamus. Cortical connections are not proven in man, but it is probable that they do exist in humans as they do in lower animals.[3,5,6]

To summarize, there is a specific ascending sensory system, carrying both pain and nonpain, which bypasses the midline reticular system and goes through specified thalamic nuclei. It is in these nuclei that one type of stimulating electrode is placed. This neospinothalamic tract carrying pain parallels the nonpain fibers and has a similar somatotopic relationship in the thalamus. What was earlier termed the paleospinothalamic system has multiple connections in the brainstem reticular system, medial thalamus, and hypothalamus. A cortical connection, if it exists, is probably mediated through the limbic system, dorsomedial nucleus, and frontal lobe, especially the inferofrontal connections. There are two surgical targets: the ventralis posterior and periaqueductal gray area. The ventralis posterolateralis (VPL) has the reticular thalamic nuclei capping it. The internal capsule is lateral; this nucleus is the basic target in the specific sensory nuclei. The reticular system is closely related to the VPL. These relationships are important because with a large electrode in such a nucleus it is extremely difficult to be certain that the only thing being stimulated is in the specific nucleus. There is a somatotopic relationship, so the position of the electrodes utilized in this location can theoretically be localized to provide stimulation in any part of the body. It is rare to produce paresthesias in the whole body, but it is possible by

Table 1
Pain Perception Pathways and Stimulation

Pain perception pathway	Stimulation type
Ascending	
Peripheral receptor	Transcutaneous electrical stimulation (TENS), peripheral nerve stimulation
Peripheral nerve	
Dorsal horn	Spinal stimulation
Anterior spinothalamic tract	
Brain stem reticular system	Periaqueductal gray stimulation
Reticular thalamus	
Limbic lobe	
Thalamus	Thalamic stimulation
Nucleus ventralis	
Posterolateralis, mediatlis	
Cortex	
Descending	
Cortex	
Thalamus	
Brain stem reticular system	
Dorsolateral quadrant of cord	
Dorsal horn	

manipulating the stimulation so as to stimulate the specific portion of the body that is painful. The ventralis lateralis is the primary target for movement disorders; the VPL is the primary target for body pain, and, farther forward and more medially, the ventralis posteromedialis is the primary target for facial pain. The electrode position can be judged to accommodate any portion of the body where stimulation is needed.[4] (See Table 1.)

The centrum medianum, its capping parafascicular nucleus, and the remnant of the thalamic reticular system have also been targets in destructive surgery.

STEREOTACTIC TECHNIQUE

Techniques in my own hospital have changed significantly since the early days of diencephalic surgery. Both Brown–Roberts–Wells and Leksell frames are now used without modification. Procedures are carried out in real time in the CT scanner. A stereotactic operating room was built around a CT scanner in the Neuroradiology Department, where all the stereotaxis is done. This gives adequate localization for placement of electrodes in a structure as large as a specific thalamic nucleus, or for placement in periaqueductal gray matter. It is not adequate, however, to carry out precise electrode placements, and certainly not adequate to do destructive lesions. The next step will be to build a cap for the patient that will allow MRI, positron-emission

tomography (PET), and CT to be used interchangeably with the stereotactic frame in place, and to be used to provide midline and diencephalic localization as well as functional studies. Final surgery is done in the CT scanner, where the electrode is placed along the predetermined course under direct monitoring.

THALAMIC STIMULATION FOR PAIN RELIEF

The History of Thalamic Stimulation

The history of brain stimulation for pain relief has included stimulation in sensory radiation subcortical tissue (this is a good way to cause seizures, but not a very good way to reduce pain), the internal capsule, both medial and lateral portions of specific thalamic nuclei, periaqueductal gray matter, and a few attempts at specific stimulation in the interlaminar nuclei of the thalamus.[7–14] The large electrode with which most of the early work was done is now outmoded. New electrodes with multiple combinations of stimulating points are in common use. The combinations are important because they allow one to stimulate in a somatotopic way; the new systems are dramatically better than anything available before. The number of stimulating combinations, irrespective of parameters, varies with the cube of the number of points one has available. Thus, if one has four electrodes, the number of stimulating combinations is 50, a sizable number, but if one has eight electrodes, there are 6050 combinations. Then, it becomes very difficult to go through all the possible combinations. As the number of stimulating points has increased from two to four to eight, our laboratory computerized all of the choices so that choosing stimulus parameters is now done automatically. The patient and his or her stimulator sit down with a computer and the computer runs through the several thousand combinations possible for testing. This advance, engineered by Dr. Richard North, has brought a real improvement over the days when one put in the electrode, turned on a device, and it either stimulated or it didn't.[15] In addition, many of the new stimulators allow changes in the parameters of stimulation. Hosobuchi has demonstrated that ramping is important, but we have shown that pulse, width, and rate and pulse shape all have important roles in changing what the patient perceives and, therefore, change pain relief.[15]

Brain stimulation is not at all new. As early as 1957, it was suggested that supraoptic and septal area stimulation would produce pain relief in humans.[16] The spinothalamic fasciculus was stimulated in 1960.[13] Hosobuchi and Adams began to stimulate in the thalamus in the late 1960s and began reporting in 1973–1975.[7–12] In 1974, Adams reported internal capsule stimulation,[7] and periaqueductal gray stimulation was proposed in humans or in animals as early as 1969.[4] Work in humans was not reported until much later.[17,18]

In 1975, I reviewed all the material available at that time for the first Congress on Pain, and at that point stereotactic surgeons as a group were reporting that 60–70% of patients treated with internal capsule stimulation or sensory thalamic stimulation received adequate pain relief.[19] In the posteromedial thalamus–periaqueductal gray area, Adams and Hosobuchi reported figures approximately like these.[7,9–12] Our own suc-

cess was significantly less—less than 50%—but we dealt almost exclusively with thalamic syndrome. At that time, I concluded that brain stimulation was an excellent technique for the treatment of central pain (what has been termed deafferentation pain) and at Johns Hopkins did not apply it for anything else. Since then, those criteria have been modified to include a wide variety of problems. Periaqueductal gray stimulation has received the greatest amount of publicity in the recent past.

Recent Issues in Brain Stimulation

I would like to make several points about brain stimulation. First, in our experience a unilateral stimulation routinely has bilateral effects, and it is unusual to have to place or use two bilateral electrodes when stimulating in the periaqueductal gray area. There is a descending inhibitory pathway that begins in that general area of the upper midbrain and descends in the reticular system.[3] The relays are not clearly known in man. Once this tract reaches the spinal cord, it is well known that it is in the dorsolateral quadrant in most animals, and it is also known that this system does not relate to the opioids: This is a serotonin–norepinephrine system, and does not depend upon opioids for its inhibitory effect. There is still considerable uncertainty about whether periaqueductal gray stimulation in man is reversed by naloxone. It clearly is reversed in some experimental animals, but not in others; the evidence in man is still quite controversial, and opinions are equally divided between those who believe that this is an opioid system and that stimulation analgesia is reversed by naloxone, and those who believe that it is not an opioid system and that none of the current stimulation techniques are reversed by naloxone.[22–29] That naloxone does not cause reversal can be said with certainty for peripheral nerve stimulation, spinal cord stimulation, and stimulation with sensory thalamus.[30–35] That statement is less secure for periaqueductal gray matter, for which data are contradictory and definitive studies still need to be done. It has been reported that there is tolerance to stimulation in periaqueductal gray matter; that appears to be very definite. A cross-tolerance to morphine has also been reported; what is less certain, and the most controversial of all, is whether or not there is elevation of β-endorphins in the cerebrospinal fluid with stimulation.[28,36–38] This question is still open and remains to be proven by multiple laboratories and multiple techniques of measurement. The fact that unilateral stimulation has bilateral effects has been said by some to suggest a humoral effect, but all of these reticular systems are bilateral. They have multiple cross-connections at multiple levels throughout the reticular system and the brainstem throughout the thalamus, and this could easily be not a humoral effect, but simply related to the fact that one is affecting the system bilaterally by direct electrical stimulation. The prolonged analgesic effect, often persistent hours after stimulation, is also unexplained.[16,38,39]

Another point is the effect of electrical stimulation on the nervous system.[40] It has been said that this is neuroaugmentation. Ray and Burton used that term routinely; however, there is no evidence that this is neuroaugmentation aside from the possibility that there is β-endorphin induction. Quite the opposite is true. Stimulation in the nervous system is usually synonymous not with activation, but with temporary cessation of function. In thalamic surgery for movement disorders, stimulation stops the

movement to prove the electrode is in the right place, then a lesion is made to duplicate the stimulation. The same is true of pain. When stimulation is in the appropriate area in the thalamus, the pain is temporarily abolished. That is the way to search for the appropriate place to make the lesion. It is still a technique used to find the appropriate place to leave an electrode. There may be an augmentation aspect to stimulation, but this remains unproven at the present time.

Results of Brain Stimulation

Young has recently reviewed the reported results from 13 centers comprising 698 patients who have had some form of brain stimulation.[20,21] He estimates from those studies that 57% of the patients have achieved long-lasting, adequate relief of pain. The reported figures for the thalamus vary between 50% and 80%, for periaqueductal gray matter they run from 0–90%, and for cancer pain, the figures are equally good—70–75%.

The composite complication rate indicates a thalamic hemorrhage in 2–4% of the patients. Mortality rate has ranged from 0–2%. These are highs and lows, respectively, not averages. Infection occurred in 3–6% of patients. Extraocular movement abnormalities occurred in 2–4%, but we now know we can avoid this completely if we don't go below the iter of the aqueduct from the third ventricle. There is also a hardware failure rate that is persistent and gets bigger the longer one follows the patients. All of these patients are told that their hardware will last 3–5 years and then will have to be replaced. Fortunately, it is usually not the electrode that causes problems. Usually the cause is the rest of the device, which is relatively easy to change.[31]

CRITERIA FOR BRAIN STIMULATION

Our current criteria for the use of diencephalic stimulation are stringent.[42] First, there must be an objective basis for pain. The point that must be made is that the majority of patients referred to us complaining of incapacitating chronic pain have no discernible organic basis for that pain; in our opinion, these suffer primarily from psychiatric disease or a personality disorder. It is extremely important, before using a potentially dangerous surgical technique, to establish that there is an objective basis for the pain that is clearly demonstrable—a diagnosis other than a complaint of intractable pain.

Secondly, alternative therapies must have been exhausted or, for some reason, found unacceptable. Treatment is never given anybody complaining of pain without first administering a complete psychiatric evaluation. This is true even for those with a clearcut, objective basis for pain, because it is quite common that such patients have become seriously depressed, chronically anxious, or intoxicated with medications. Also, cross-tolerance or not, if a patient is addicted to narcotics, it is difficult to determine whether he or she has pain relief. We make a strong point of detoxifying all patients well before stimulation, and we require that they remain off narcotics for up to 6 months before they have a stimulator; for the less invasive stimulators, 2–3 months

are required. The things mentioned—depression, anxiety, intoxication, and addiction—all need attention before it is possible to determine how effective pain therapy has been. Much of the confusion concerning chronic pain in the United States is secondary to failure to differentiate those people with an objective, organic pain problem from those with personality and psychosocial abnormalities not generally amenable to any form of direct pain therapy.

Finally, pain must be in a location where stimulation can be obtained. This is particularly important for peripheral nerve or spinal stimulation, and not so important for thalamic stimulation. For deafferentation pain, irrespective of its location, it is our practice to place bilateral periaqueductal gray electrodes. We normally expect to use only one (nearly always the left one) but both are placed and then stimulated alternately until it is clear which one is going to be effective. Approximately 90% of the time it is the left electrode that is effective (in fact, we recently stopped putting both in initially). We prepare for this, but we put in the dominant electrode and then stimulate. If the pain is strictly unilateral, a contralateral periaqueductal gray electrode is placed, along with a sensory thalamic electrode if the pain is not clearly central nervous system in origin. There is nothing specific or correct about this technique. It is our practice: With unilateral pain both periaqueductal gray and sensory thalamus are assessed, and with deafferentation pain bilateral periaqueductal gray stimulation is employed, most commonly on the dominant side.

USES OF BRAIN STIMULATION

Brain stimulation is used in the treatment of a variety of ailments. Thalamic syndrome and anesthesia dolorosa, principally of trigeminal origin, are our most common nervous system problems. Others include: postherpetic neuralgia (only a small number of patients are so seriously incapacitated that they need this); phantom-limb pain; postcordotomy dysesthesias; spinal cord injury (this is valuable only when the injury is partial); and severe brachioplexopathy. Some patients with chronic low-back syndrome are candidates. Most have arachnoiditis, and not simply the chronic low-back syndrome. These are people with multiple operations—our average number is six. They have demonstrated arachnoiditis and have failed all other forms of therapy, including spinal cord stimulation. Some patients with cancer pain, particularly those with bilateral pelvis or plexus involvement, and a rare patient with chronic visceral pain of some origin other than cancer are candidates.

OTHER FORMS OF DIENCEPHALIC THERAPY

There is another form of nondestructive therapy that will be employed much more in the future: There is now available a totally implantable, externally fillable, programmable pump that is a versatile device. The pump can be interrogated by telephone to determine how much drug it is giving. The prescription can be changed in the same way. The device can give a regular readout of how much drug it still has available, how

much it has been using, and can predict for the patient how long to go before filling. The pump was built for morphine, but is made universal so that any suitable drug can be employed. Currently, it is in clinical use in diabetes, being implanted for the delivery of insulin. One of the most important future uses for diencephalic surgery may involve delivering, by this technique, the drugs that are important substrates of physiological activity in the thalamus, the walls of the third ventricle, and the upper brainstem. Rather than putting adrenal medulla into the caudate nucleus, it might be reasonable to put a catheter such as this into the appropriate area of the third ventricle or lateral ventricle near the thalamus and to give the drugs one is attempting to induce by adrenal transplant, in order to determine if there is a physiological effect and to determine dose responses. The future is bright for this technique; as more is learned about the pharmacology of the diencephalon and its immediate surrounding environment, it will be possible to devise many kinds of drugs that can be used to modify function.

Stimulation was thought from its inception to be a temporary phase in functional surgery. I never thought it would last this long, but it has been nearly 20 years now; my view in 1975 was that it would probably be supplanted by something else in 10 years. This has not proven to be the case. Thalamic stimulation for the relief of pain continues to have a role, in the hands of experts, in the treatment of carefully chosen patients. It can be of great benefit to many patients with otherwise untreatable pain syndromes. Nevertheless, the future probably lies in pharmacological manipulation of the same systems.

DISCUSSION

VARIOUS ASPECTS OF THE EXTERNALLY FILLABLE PROGRAMMABLE PUMP

Patterson inquires as to how the pump is powered. The answer to this question is that the power is derived from a lithium cell. The first device we made was rechargeable and was made for stimulation primarily so that one didn't have to operate every 3 years or so and implant a $5000 device. The power requirements for this device are so small that it basically has an infinite life span in the average patient. The estimates are at least 20 years, depending on what type of infusion is being performed. Everything here is positive: This pump doesn't depend upon vapor pressure, as some of the pumps do; it doesn't have a diaphragm that must be depressed; it's an elegant computerized device that has some fail-safes built in—it can only fail to function, it can never deliver an extra amount of drug. This unit was derived in part from technology available at NASA.

Abrams asks if the delivery mode is pulsatile or continuous? The fact is that one could have anything one wants. Big pulses. Little pulses. It can give one pulse every minute or a single pulse per year. It can be programmed to give a continuous infusion.

Tew asks when it will be available for protocol. The device is currently approved for use in diabetes and is probably in ten patients right now. We have approval for use with morphine, but haven't begun as yet. When the diabetes trial is over, if it has functioned well and there aren't any problems, then it's probably going to be made generally available.

Some concepts discussed have included the pump's use for delivery of anticonvulsants and psychotropic medication, and for long-term anticoagulation. The limiting factor is the form in

which the drug can be prepared. The pump has been in animals for 4 years now without a single failure, so chances are good that it's going to continue to work.

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6

Brain Stimulation for Pain Control

Yoshio Hosobuchi

INTRODUCTION

Electrical stimulation of specific anatomical sites in the human brain has been used to obtain relief or suppression of pain since 1960, when Heath and Mickle reported suppression of pain in patients by stimulation of the septal area.[1] Others subsequently used therapeutic stimulation of subcortical areas, such as the median forebrain bundle[2] and the caudate nucleus,[3] but, for more than a decade, little attention was paid to these sporadic clinical efforts.

In 1973, Mazars and colleagues[4] and our group at the University of California at San Francisco[5] reported independently that electrical stimulation from electrodes permanently implanted in the region of the sensory thalamus satisfactorily alleviated deafferentation pain, a syndrome caused by damage to the peripheral or central nervous system that generally responds poorly to opiate analgesic agents.[6] These findings led to the commercial manufacture of a stimulation system consisting of an implantable electrode made of an inert metal (gold or platinum) connected to a radiofrequency-coupled transcutaneous stimulation device. On the basis of studies by Reynolds[7] and others[8,9] showing the behavioral antinociceptive effect of stimulation of the periaqueductal gray region of the brain in animals, this system was assessed to determine the therapeutic efficacy of stimulation of the comparable area of the human brain. The encouraging preliminary results were reported in 1977 by our group[10] and by Richardson and Akil.[11] Since that time, clinical evidence has established that stimulation of the somatosensory area of the thalamus is effective in the control of deafferentation pain or neuropathic pain,[12,13] syndromes that may be refractory to conventional opiate medication, and stimulation of the periaqueductal gray region is effective for pain syndromes responsive to opiates.[6,12]

It would appear that the analgesia and suppression of pain produced by stimulation in the septal and subcortical areas of the brain are related to the rewarding

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properties of the stimulation. Although consensus is lacking on the question, it seems probable that the mechanism of response to stimulation in those areas is different from that governing the pain suppression and analgesia achieved by stimulation of the somatosensory system or the periventricular gray region and medial brainstem. It is these latter two anatomical systems that are the focus of present investigations into the mechanism and effects of brain stimulation, both in humans and in experimental animals. They are, therefore, the focus of this discussion regarding the clinical applications of electrical stimulation of the brain, its efficacy, and issues regarding this therapeutic modality that have not yet been resolved.

SELECTION OF PATIENTS FOR THERAPEUTIC ELECTRICAL STIMULATION OF THE BRAIN

Patients who suffer severe and chronic intractable pain that cannot be controlled by medication, including opiates in large doses, may be considered candidates for the electrical stimulation procedure. For many such patients, the brain-stimulation technique affords a favorable alternative to ablative surgical procedures, which may be ineffective in the treatment of certain pain syndromes and entail a high risk of a neurological deficit more devastating than the original pain.[14,15]

Stimulation of the somatosensory area of the thalamus is effective in the control of deafferentation pain or neuropathic pain,[6,12] syndromes that may be refractory to conventional opiate medication. Stimulation of the periaqueductal gray region is effective for pain syndromes that are responsive to opiates.[12,16] Specific pain syndromes that can be treated effectively with electrical stimulation are described shortly, in the section reviewing the series of patients treated at our institution. Although some patients suffering from pain associated with cancer may benefit from periaqueductal gray stimulation, they generally are poor candidates for this procedure because the efficacy of this stimulation depends greatly upon the nutritional status of the patient.

Screening Tests

Patients with chronic pain often manifest varying degrees of depression, anxiety, and somatization, but it appears that such a psychological profile does not influence the success or failure of electrical spinal cord or brain stimulation for pain control.[17,18] Although all patients in this series underwent psychometric and psychiatric testing, the results of these tests were evaluated solely to exclude patients who had obvious thought disorders or were not capable of operating the self-stimulation device. With these exceptions, patients' scores were not considered a criterion for selection. In contrast, the morphine intravenous infusion test was exceedingly helpful as a screening test for patient selection.[16] The test is performed in the hospital with the patient lying in bed. Morphine sulfate is administered through an indwelling intravenous catheter in a double-blind fashion; saline is used as a placebo. The drug is given stepwise in 5-mg increments to a total of 30 mg within 30–45 min, while the heart rate and blood pressure are monitored frequently. The patient's subjective evaluation of the pain relief obtained during the infusion is scored on a visual analog scale of 0 to 10 (0 = no pain,

10 = maximum tolerable pain). When possible, a subjective report of pain is confirmed with an objective test, such as straight-leg raising, to assess the degree of analgesia achieved. After the patient has received 30 mg of morphine, the opiate antagonist naloxone (0.2–0.8 mg) is given intravenously in a double-blind manner to determine whether the response to the opiate is reversible.

The patients' response to this screening test determines not only their selection for electrical brain stimulation, but also the area of the brain in which the electrode will be implanted. Patients who experience total relief of pain with less than 10 mg of intravenous morphine are excluded from the group selected for electrode implantation. This threshold has been selected arbitrarily as the level at which the chronic pain is considered manageable by conservative means. Such patients are encouraged to follow a regimen consisting of nonnarcotic medication, physical therapy, and the use of a transcutaneous nerve stimulator.

Patients who obtain total pain relief with 10–30 mg of morphine are selected for implantation of an electrode in the periaqueductal gray region. Those who do not experience total pain relief with 30 mg of morphine may have deafferentation pain, may have developed tolerance to opiates, or may have both of these problems in combination. To differentiate these subgroups of patients, the diagnosis of deafferentation pain is based on a clinical picture that clearly indicates such a syndrome,[12,14,15] such as a brachial plexus injury, postcordotomy dysesthesia, or thalamic syndrome.

Patients judged to have a deafferentation syndrome are selected to have an electrode implanted in the region of the contralateral somatosensory thalamic nucleus. The patients in the remaining subgroup are considered tolerant to the analgesic effect of 30 mg of morphine and continue in the selection process: They are treated daily with L-tryptophan (4 g) and are encouraged to decrease their opiate intake for 4 weeks,[19] after which time the morphine infusion test is repeated. After following this regimen, patients who have developed tolerance tend to respond to morphine in a more clearly dose-dependent manner.[19] In this series, most of the patients in this subgroup underwent implantation of an electrode in the periaqueductal gray region. In some cases, however, the L-tryptophan regimen did not produce complete reversal of tolerance, suggesting that a component of the patient's pain was probably attributable to an additional deafferentation syndrome. In those cases, the patient received an electrode in the periaqueductal gray region and another in the somatosensory area of the thalamus, both of which were connected to a dual-channel radiofrequency receiver to allow the patient to stimulate the two brain loci simultaneously.[20]

Computed tomography is required as an additional selection procedure for patients who have a thalamic syndrome, in order to confirm that they have an adequate anatomical substrate for the stimulation.

IMPLANTATION OF A BRAIN-STIMULATION SYSTEM

The Electrode

The electrode used for electrical brain stimulation that is presently available commercially is made of pure platinum. It consists of four wires that are entwined, terminating with the individual wires separated from one another to form four 1-mm-

long loops (0.8 mm in diameter). These constitute four separate contact points. They are 2 mm apart, as measured from the midpoint of each contact. The electrode contact points are labeled 0, 1, 2, and 3 by the manufacturer, 0 being the most inferior contact point. The loop of the most inferior contact (0) facilitates the insertion of the electrode into the central gray matter by encircling the tip of the special tool that is used to insert the electrode into the brain.

Operative Procedure

Implantation of the electrode is accomplished by means of a stereotactic neurosurgical procedure. Local scalp anesthesia is used. A standard stereotactic apparatus (such as the Leksell, Riechert–Mundinger, or Todd–Wells apparatuses) serves satisfactorily for this operation, although I prefer to use the Leksell apparatus.

The patient is placed in the semisitting position on a specially designed operating table. The head is shaved, washed with Betadine soap and water, and painted with Betadine solution. The head rests on a small suboccipital cup support. First, the stereotactic head frame is positioned and supported using calibrated ear plugs, and the midline of the apparatus (Z axis) is carefully approximated to the midsagittal plane of the head. Three entry zones on the scalp are selected for the placement of three skull pins that will be screwed into the outer table of the skull. These scalp areas are generously infiltrated with local anesthetic. The hole for the anterior skull pin is placed just behind the hairline of the forehead (for naturally bald patients, this site is approximated as closely as possible). The other two sites are positioned approximately 4 cm behind each external auditory meatus. A guiding tube that pierces the scalp is inserted at each of these three sites, and is firmly fixed to the pericranium. Then, a skull pin is inserted into each of the three guiding tubes and is screwed into the outer table of the skull using a special drill.

The surgeon, at this point, must make certain that the frame is firmly fixed to the patient's skull. The head and frame are then partially draped, leaving the patient's face exposed. The location for two separate scalp incisions are marked so as to bisect the coronal suture on each side, 2.5 cm from the midline, and the scalp is infiltrated with local anesthetic. Bilateral, paramedian, pericoronal burr holes are made 1 cm anterior to the coronal sutures and 2.5 cm from the midline. It is critical that the burr holes be made in precisely this location. (In the case of brachycephalic or dolichocephalic patients, the burr holes are moved in either an anterior or posterior direction so that the line connecting the burr holes to the posterior commissure will form an angle of 60° to 70° to the intercommissural line.) Since the target points in either the periaqueductal gray region or the sensory thalamic nuclei are located within 5 mm of the X and Y axis (the anteroposterior axis and ventrodorsal axis, respectively), this trajectory offers the maximum probability of the electrode contact points being placed in the region that will produce therapeutically effective stimulation.

After the burr holes are appropriately placed, the dura of the right burr hole is opened in cruciate fashion and is coagulated. The cortical surface is inspected carefully so that a major sulcus is not encountered in the trajectory. The surface of a gyrus is cauterized, a small cortical incision is made using a no. 15 blade, and the right lateral ventricle is cannulated with a Scott cannula. The tip of the cannula is aimed toward the

contralateral angle of the mandible so that the catheter can be advanced to the third ventricle through the foramen of Monro. At this time 2 ml of air is introduced into the ventricle, and x-ray films (anteroposterior and lateral views) are obtained to verify the location of the catheter. If necessary, the catheter positioning and x-ray exposure factors are corrected. Ventriculograms are then obtained in the anteroposterior and lateral projections using 3 ml of Conray contrast medium mixed with 7 ml of ventricular cerebrospinal fluid. These ventriculograms should delineate the foramen of Monro, the third ventricle, and the anterior and posterior commissures.

In my opinion the use of the CT scan in combination with the stereotactic apparatus for the electrode implantation procedure is unjustifiable, not only because of the expense of the scanning process but more importantly because CT scanning cannot provide the surgeon with sufficient information for accurate determination of the site of electrode implantation.

Target Regions in the Brain

Periaqueductal Gray or Periventricular Gray Regions. For X and Y coordinates, the iter of the aqueduct is selected. The laterality of the Z coordinate is therefore not influenced by the width of the third ventricle, as the target is caudal to this structure. The shape of the aqueduct is oblong in the ventral and dorsal axis at the iter, and the laterality of the target is determined by the ventral–dorsal diameter of the aqueduct at the iter, which is almost always less than 2 mm. Consequently, in most cases, the target laterality (Z coordinate) is 3 mm from the midline for the insertion tool. Since the electrode is always inserted in a position lateral to the insertion tool, the tip of the electrode usually lies 2.5–3.5 mm lateral from the midline of the iter of the aqueduct. The target point is marked on the ventriculogram; this point is projected perpendicularly to the reference scale of the frame, and the X, Y, and Z coordinates are calculated.

Implantation may be performed either unilaterally or bilaterally, although in my experience better analgesia is produced (by a 9:1 ratio) when the electrode is implanted in the left, rather than the right, periaqueductal gray region. As there is no way to determine whether a patient will respond better with the electrode implanted in the left side or the right, and as bilateral implantation does not appear to produce greater morbidity, I routinely implant electrodes bilaterally to increase the chance of finding the optimal pair of contact points for stimulation that will produce the most effective analgesia.

After correct unilateral or bilateral X, Y, and Z coordinates, either unilaterally or bilaterally, for the prospective site(s) of implantation have been obtained, side bars are attached to the frame at the appropriate Y coordinate. The dura of the left burr hole is opened and the cortical surface is prepared as described earlier. The insertion tool is placed through the trajectory stage of the frame and is adjusted to ensure that the tip of the tool will hit the target point accurately. The arc is attached to the frame by clamping it to the side bar at the predetermined X and Z coordinates.

The scalp posterior to the burr holes is then infiltrated with a local anesthetic, and is penetrated with a 14-gauge needle with its stylet in place. The needle is inserted approximately 5 cm posterior to the burr holes and is passed subgaleally to each burr

hole. The stylet is then removed from the needle. The percutaneous extension of the electrode is passed through the needle shaft from the site of the burr hole to the hub of the needle; as the extension appears from the needle hub, the needle is carefully withdrawn from the scalp. The connector of the electrode to the percutaneous extension is taped (with steri-strips) to the self-retaining retractor on the burr hole incision.

The electrode is now inserted. The tip of the insertion tool is placed within the terminal loop of the electrode. The electrode always should be lateral to the insertion tool to avoid unnecessary damage to the posterior medial thalamus and hypothalamus by a leukotomy-type injury created by the angle between the insertion tool and the electrode. The surgeon holds the electrode close to the insertion tool using blunt forceps, and the assistant advances the insertion tool into the brain. It is very important to avoid excessive tension of the electrode against the insertion tool because this will uncoil the second contact point, which might alter the distance between the first contact or loop to the second contact or possibly break the loop.

When the insertion tool reaches the target point, the electrode is disengaged from the tool by very gentle clockwise and counterclockwise rotation of the tool around an approximately 45° angle. Excessive and vigorous rotation of the tool should be avoided because it will dislodge the electrode from the target. The insertion tool is withdrawn from the brain. The electrode is temporarily fixed to the edge of the burr hole by a small ball of bone wax, and the burr hole is covered with a wet cotton ball.

Test stimulation is delivered between the most distant pair of contact points, using the most inferior contact point as the cathode. The settings for test stimulation are pulse duration, 0.5 msec; frequency, 50 Hz; and amplitude starting at 1 V and gradually increasing. At about 6–8 V, the patient invariably reports oscillopsia or an inability to initiate ocular movement. I have found that the suppression of conjugate upward gaze during stimulation is the most reliable physiological determinant to assure correct placement of the electrode. Although pain relief is effected at a much lower amplitude, I do not demonstrate the analgesic efficacy of stimulation of the periaqueductal gray region in the operating room as a determinant of accurate electrode placement because, under the stress of being operated on under local anesthesia, the patient may perceive the pain to be alleviated when in fact it is not.

The same procedure is repeated to implant the electrode on the right side.

After both electrodes are implanted and after electrical stimulation induces a satisfactory ocular response, the cortex is covered with Gelfoam and the electrodes are fixed to the edge of the burr holes with cranioplastic material. A subgaleal pocket is developed and the extra length of electrode connector and percutaneous extension cable are inserted into it; the wounds are then closed in two layers. The final confirmation of electrode localization is usually made at this stage; however, if the surgeon is not certain that the electrode is situated optimally—for example, if the expected ocular response is not obtained—then confirmatory x-ray films (anteroposterior and lateral views) must be made before the electrode is fixed to the burr holes by cranioplasty. Correction of the electrode position can be made by removing the electrodes, re-examining the coordinates, and reinserting the electrodes. Multiple trials of electrode insertion are unquestionably inadvisable because, with each trial, the risk of ocular palsy or possible intracerebral or intraventricular hemorrhage is increased.

Sensory Thalamic Nuclei. For implantation of the somatosensory thalamic region, the target point is in the area where the medial lemniscus enters the sensory thalamus: For patients with facial pain, it is in the ventral posterior medialis, and for those with pain of the arm, leg, or trunk, it is in the ventral posterior lateralis. The basic coordinates for the sensory nuclei of the thalamus are obtained from the Schaltenbrand–Bailey stereotactic atlas.[21] The widest coronal dimension of the nuclei is approximately 10 mm posterior to the midpoint of the line joining the anterior and posterior commissures. The face area of the nucleus presents medially, starting 9–11 mm laterally at 2 mm below the level of the line joining the anterior and posterior commissures; the arm and leg area are located farther laterally, 2–3 mm apart. The dimensions and location of the sensory thalamic nuclei vary considerably among individuals according to the length of the line joining the anterior and posterior commissures and the width of the third ventricle.

Exploratory stimulation of the target area with a monopolar electrode, 0.8 mm in diameter with a 2–3 mm exposed tip, is advised. The exploratory stimulation begins 5 mm proximal to the target point, extending approximately 5–7 mm beyond the target point along the same trajectory.

The patient reports the area in which he or she experiences paresthesia in order to guide the surgeon in placing the stimulation electrode at the point where optimal induced paresthesia is obtained. In cases of deafferentation pain, the most crisp response of induced paresthesia in the desired area of the body is usually obtained at the boundary of the gray and white matter or where the medial lemniscus enters the sensory nuclei; therefore, impedance monitoring may also be useful.

If induced paresthesia is not experienced in the desired area of the body, the surgeon must withdraw the monopolar electrode and replace it either medially or laterally, and often 2–3 mm posteriorly—especially in cases of pain in the lower extremity. It is therefore not unusual for the final coordinates of the target point to deviate 2–3 mm in any direction (X, Y, or Z) from the target initially calculated on the basis of the ventriculogram and the stereotactic atlas.

The insertion of the electrode follows essentially the same procedure as that described for the target in the periaqueductal gray region, except that the surgeon has to move the trajectory of the insertion tool 1 mm medially to ensure that the most inferior contact point of the permanent electrode rests in the correct target area. Placement of the electrode is reaffirmed by stimulation of the most distant pair of contacts, using the most inferior contact as the cathode. The stimulation settings of 0.5 msec pulse duration, 50–100 Hz frequency, and 1–3 V should induce pleasant paresthesia in the region of the body involved with deafferentation pain. The electrodes are fixed to the burr holes by cranioplasty, and confirmatory x-ray films (anteroposterior and lateral) are obtained. The wound is closed in the same manner as described earlier.

Postimplantation Patient Care

After the operation to implant the electrode(s), patients often complain of headache, nausea, and occasionally, in cases of implantation in the periaqueductal gray region, diplopia; in addition, they feel their original pain. To control the pain at this

stage, administration of a short-acting opiate analgesic, such as meperidine (Demerol), given intramuscularly is preferred in order to avoid masking an altered level of consciousness that would signify possible intracerebral or intraventricular hemorrhage. Dexamethasone (Decadron) rarely is used unless the patient complains of significant diplopia. Compazine is give intramuscularly to control nausea and vomiting, if they occur.

On very rare occasions a patient may have a seizure 4–8 hr after the operation. This is thought to be a consequence of the circulation of potentially epileptogenic contrast medium (Conray) from the ventricular system out into the subarachnoid space over the convexities. Despite the relative infrequency of this complication (in about 2–3% of patients), it is wise to start the administration of Dilantin 24 hr before the implantation. To ensure rapid washout of contrast medium from the CSF, patients should be well hydrated. If the patient cannot maintain adequate oral fluid intake, intravenous fluid therapy is continued.

TRIAL STIMULATION PERIOD

A few days after the implantation, when scalp discomfort subsides, patients begin a period of trial self-stimulation during which various contact points for the electrode(s) are tested to determine the most effective pair of contact points for obtaining pain control. At this stage, the percutaneous leads from the patient's electrode are connected to an external direct-stimulation device that is regulated by the patient. After the optimal contact points are determined, the patient uses stimulation for a trial period of several days to a week to confirm that the selected points consistently provide the most effective pain control. Characteristically, stimulati parameters are 3 V, 30 Hz, 0.2-msec pulse duration for stimulation of the periaqueduc l gray, and 2–5 V, 50–75 Hz, 0.2-msec pulse duration for stimulation of the somatosensory area of the thalamus.

Stimulation of the periaqueductal gray region at the appropriate level of current produces no alteration in the patient's sensorium except for the gradual disappearance of pain over a period of a few minutes. Stimulation of this area with a much stronger current, however, produces oscillopsia, nystagmus, or, more often, inhibition of vertical gaze. In most cases, half of the amount of current required to produce such unpleasant visual and ocular symptoms is sufficient to induce alleviation of pain, and 15–20 min of stimulation of the periaqueductal gray area is generally followed by a pain-free period lasting 4–6 hr. Stimulation in the somatosensory area of the thalamus generally produces "pleasant" paresthesias covering the area of pain. The patient who has had a burning dysesthesia often reports that the pain is replaced immediately by a "cool," comfortable sensation induced by the electrical stimulation.

When the efficacy of the contact points is established, the patient undergoes a second operation during which the pair of contact points is connected to the bipolar cable that extends to a radiofrequency receiver. This receiver, which has a circuit breaker that prevents passage of excessive current to the brain, is designed to be highly insensitive to radiotransmission in order to obviate its being activated by radiofrequency noise from sources other than the system's transmitter. With the patient under

general anesthesia, the system is implanted subcutaneously. All wires and cables are implanted under the scalp and skin extending to the receiver, and the receiver is placed in a subcutaneous pocket developed on the patient's anterior chest wall. After the operation, patients are instructed in how to operate the self-stimulation device.

Self-Stimulation

To activate the stimulation system, the patient uses a transmitting antenna that must be placed directly over the implanted radiofrequency receiver. This transmitter (a small, independent, battery-powered unit that may be carried or worn on a belt) has two external control dials that are used by the patient, one dial to regulate voltage and the other to control the rate of stimulation (Hz). Additional controls for setting stimulation parameters are located within the transmitter and are accessible only to the physician; these control the pulse duration and mode of stimulation—either steady or ramp stimulation varying from 2–30 sec. Whereas the steady mode is used for stimulation of the periaqueductal gray region, ramp stimulation adjusted to 20–30 sec is more efficacious for stimulation of the somatosensory area of the thalamus.[5,12]

Patients who have an electrode in the periaqueductal gray region are instructed to initiate stimulation at a voltage level of half that which induces ocular symptoms (usually 2–4 V, 20–30 Hz, and 0.2–0.3-msec pulse duration) for 15–20 min, the period that should provide pain relief for 4–6 hr. Patients with an electrode in the somatosensory area of the thalamus are instructed to use the stimulator at the current level that induces pleasant paresthesias in the area of pain (2–6 V, 50–100 Hz, and 0.2–0.3-msec pulse duration). In contrast to syndromes that respond to stimulation of the periaqueductal gray, deafferentation pain generally recurs slowly after cessation of the thalamic stimulation, requiring the patient to activate stimulation every few hours for periods ranging from a few to several hours at a time.

The patients are discharged from the hospital when they have healed satisfactorily and are confident in the use of their stimulation device. They return for follow-up reviews at 2–3-month intervals for the first year after their operation, and twice yearly thereafter.

REVIEW OF A SERIES OF PATIENTS TREATED WITH SUBCORTICAL ELECTRICAL STIMULATION

Patients

Over a period of 12.5 years (1970–1982), 562 patients with chronic pain were evaluated at our institution. Of these, 122 patients, reported in detail elsewhere,[22] were selected to undergo the implantation of an electrical brain-stimulation system for the control of pain. The group consisted of 55 men and 67 women ranging from 27–71 years of age (mean age, 50 years).

Each of these patients had severe, chronic, intractable pain that was refractory to medication, including opiates in large doses (Tables 1 and 2); 103 (84%) of them had

Table 1
Results of Deep-Brain Stimulation in Patients with Deafferentation Pain[a]

	Total number of patients	Initial results		Internalized results	
		Success	Failure	Success	Failure
Thalamic pain	13	8	5	6	2
Anesthesia dolorosa	12	5 (1)	7	4	1[b]
Postherpetic neuralgia	5	3	2	2 (1)	1
Brachial plexus lesion	6	4	2	2 (1)	2
Paraplegia	8	3	5	2	1
Phantom-limb pain	2	1	1	1 (1)	0
Postcordotomy dysesthesia	9	8	1[c]	8 (3)	0
Lumbosacral radiculopathy	21	20	1	19	1[d]
TOTAL	76	52	24	44	8

[a]Numbers in parentheses indicate patients (total of seven) who had total or almost complete relief with less than 6 months of stimulation.
[b]Patient had a good result with stimulation of the somatosensory thalamic nucleus (ventral posterior medialis) for 11 months, until the electrode malfunctioned from a break in the insulation. A new electrode was inserted into the medial lemniscus; thereafter, stimulation controlled the patient's pain for only 3 months.
[c]Patient suffered a ventricular hemorrhage and the electrodes were removed.
[d]Patient's entire stimulation system was removed because of infection. (Reprinted with permission from Hosobuchi.[22])

previously been evaluated and/or treated at one or more multidisciplinary pain clinics without obtaining satisfactory pain control. The mean duration of the chronic pain state, from the onset of their particular condition to their operation for electrode implantation, was 6.5 years. As there is no means by which to quantitate level or duration of pain, the diagnosis of a chronic pain state was based on the patient's subjective experience and the presence of a physiological condition known to be associated with pain. The time of onset was established on the basis of the patient's estimation of when he or she first noticed persistent intractable pain, which usually coincided with the onset of their associated physiological disorder.

The largest group in the series consisted of 49 patients with chronic low-back and leg pain from herniated lumbar discs. These patients had undergone an average of 2.3 operations on the low back that had failed to control their pain. Twenty-one of these patients, 19 of whom had both leg and back pain, had unequivocal changes in their electromyographic examination and motor sensory findings that were consistent with lumbosacral radiculopathy; five had previously undergone rhizotomy without obtaining relief.

The patients with a thalamic syndrome constituted a heterogeneous group with dysesthesia resulting from a lesion in the brain or brainstem. Those who had anesthesia dolorosa experienced dysesthesia of the trigeminal distribution after being treated for trigeminal neuralgia either by sectioning of the trigeminal nerve or by radiofrequency coagulation of the Gasserian ganglion. In the patients with postherpetic neuralgia, herpetic eruption in the distribution in the ophthalmic division of the trigeminal nerve caused hyperesthesia and dysesthesia in the afflicted area. The patients with paraplegia

Table 2
Clinical Summary of Patients Using Stimulation of the Periaqueductal Gray Region[a]

Etiology of pain	Number of patients	Results	
		Success	Failure
Cancer	7	5	2
Chronic low-back pain	49[b]	39	7[c]
Peripheral neuropathy	1	1	0
Cauda equina syndrome	3	3	0
Nonmalignant abdominal pain	2	1	1
Nonmalignant perineal pain	1	0	1
Osteoporosis of the spine	1	0	1
Atypical facial pain	1	1	0
TOTAL	65	50	12

[a]Reprinted with permission from Hosobuchi.[22]
[b]Of these 49 patients, 19 had electrode(s) implanted simultaneously in the somatosensory thalamic area also.
[c]Three patients had their stimulation system removed 2 years after implantation, two because of ineffectiveness of the stimulation and one because of a delayed infection.

experienced a constant burning, crushing sensation of the lower trunk and limbs that had been rendered totally anesthetic from the injury of their thoracic spinal cord; many reported a sensation of their lower limbs being distorted. Two patients had classic symptoms of phantom-limb pain: a viselike, crushing pain in the amputated portion of the limb and a sensation that the amputated limb was partially telescoped into the stump, often in a distorted position. The nine patients who had undergone spinal cordotomy experienced dysesthesia in the area of their body rendered analgesic by the operation. The three patients with neurological signs characteristic of cauda equina involvement had dysesthesia of the lower extremities, which were partially paralyzed. In two of these patients, the problem was a sequela of intrathecal hypertonic saline lavage to control their chronic low-back pain. The remaining patients had pain from cancer, constant midabdominal pain caused by chronic pancreatitis, chronic pain in the perineal region that was of undetermined etiology but was not the result of malignancy, atypical facial pain, or injury to the brachial plexus including myelographically documented brachial plexus avulsion.

Selection Criteria

The screening tests used in the selection of these patients for implantation of a subcortical electrical stimulation system are described earlier in this chapter. Because of the nature of these patients' pain, the brain-stimulation technique was recommended in preference to an ablative surgical procedure. In addition to the high risk of neurological deficit associated with such operations, ablative procedures are likely to fail as therapy for these types of pain syndromes.[14,15]

During the initial years of this series, CT was not widely available; until 1976, it was not used in evaluating patients for the electrode-implantation procedure. Three of the patients with severe dysesthesia associated with thalamic syndrome underwent CT some time after their electrodes were implanted, when the thalamic stimulation failed to provide any relief. It was found that each had a large area of encephalomalacia in the lateral aspect of the thalamus and, therefore, had no anatomical substrate for the stimulation. On the basis of this finding, a CT scan is now required as an additional selection procedure for patients who have a thalamic syndrome.

Results

Information regarding the results in this series was obtained for all 122 patients in this series, either directly from the patients or from the family if the patient had died. The patients had had periodic follow-up evaluations for at least 2 years, and for as long as 14 years, after their operations. Patients who had earlier reported that they had stopped using their stimulation system because it failed to provide pain relief were asked whether at any time they had either resumed stimulation or had experienced a change in their condition.

In evaluating this series, brain stimulation was considered to be therapeutically successful only if the patient was able to control the pain for which the electrode was implanted by stimulation alone or together with adjuvant medication (L-tryptophan, L-dopa, mild sedatives, or in a few instances disulfiram) during the entire follow-up period. Stimulation was considered a failure if the patient needed a narcotic to obtain or enhance pain relief at any time during the follow-up period, or if a complication caused death or required removal of an electrode. The patient's functional state, such as a return to a prior level of physical activity or employment, was not a criterion in the evaluation of the analgesic effect of brain stimulation.

Of the 76 patients who had an electrode implanted in the thalamic somatosensory area for their deafferentation pain, 52 (68%) reported immediate, satisfactory relief of pain and chose to have their electrodes permanently implanted (Table 1); 24 patients (32%) did not obtain relief with stimulation from the externalized thalamic electrode and had their electrodes removed. Three of these patients had a thalamic-syndrome-like pain resulting from brainstem infarction, such as in the case of a lateral medullary syndrome. The lack of an anatomical substrate for stimulation because of a large area of encephalomalacia appeared to be the cause of therapeutic failure in two patients. Stimulation failed to induce paresthesia in the entire painful area in seven patients with anesthesia dolorosa, two with postherpetic neuralgia, and one with phantom-limb pain; in seven patients, five with paraplegia and two with brachial plexus lesion, thalamic stimulation simply did not supress the pain. Two other patients were considered acute therapeutic failures because of surgical complications; one had a ventricular hemorrhage and the other had an intracerebral hemorrhage causing death. Of the 52 patients who had the stimulation system internalized, 44 patients (57%) continued to be pain-free for longer than 2 years using only stimulation. These 44 patients were considered to have long-term therapeutic success. Seven of the 44 patients reported total or nearly total disappearance of their original dysesthesia within 6 months of continuous stimulation; the earliest resolution of pain occurred within 2 weeks. In these patients, either

the pain has never recurred or has not recurred to the original level of severity, and they no longer need to use brain stimulation. Although the basis for this effect is unknown, this result corresponds with the findings reported by Mazars.[23] Six patients who still use stimulation are considered therapeutic failures because they require either a narcotic or a major sedative, such as diazepam (Valium). Two patients had their devices removed because of infection (Tables 1 and 2).

Of all patients with a deafferentation syndrome, those with postcordotomy dysesthesia had the best long-term results with thalamic stimulation. Despite our initial impression that the patients with facial anesthesia dolorosa had long-term therapeutic success,[5] the results over an extended follow-up period have proved disappointing.

The eight patients in this series who had a lacunar infarct of the thalamus or cortical injury as a result of ischemia or trauma responded well to thalamic stimulation. Three other patients initially had sufficient relief with thalamic stimulation to undergo permanent implantation of the system, but the effectiveness ceased entirely several months to 2 years later and the electrodes were removed; CT scanning subsequently demonstrated a massive area of infarction in the substrate for stimulation.

Thirty-six patients in this series had an electrode implanted in the somatosensory area of the thalamus and in the periaqueductal gray region for simultaneous stimulation of both areas of the brain. Of these, the 19 with radiculopathy who had both leg and back pain found that their back pain was relieved by stimulation of the periaqueductal gray, whereas their dysesthesia leg pain was controlled more effectively by thalamic stimulation. In contrast, the 17 patients who had central deafferentation pain (seven with thalamic syndrome, five with postherpetic neuralgia, and five with paraplegia pain) reported that stimulation from their somatosensory electrode was therapeutic, but none experienced pain relief with stimulation of the periaqueductal gray region.

The patients with pain of peripheral origin and those with opiate-responsive pain responded well to stimulation of the periaqueductal gray region (Table 2). Of the 65 patients with electrodes in the periaqueductal gray region, all of whom had bilateral implantations, 64 had the electrodes placed subcutaneously. All but three patients reported that the electrode in the left periaqueductal gray provided better pain relief than did the electrode on the right. It is interesting to note that two of the patients who found the electrode in the right periaqueductal gray to be more effective were left-handed individuals. In the third such patient, stimulation from the left electrode, which was placed in the mesencephalic reticular formation, did not produce analgesia; however, stimulation with the right electrode, which had traversed the aqueduct to the left periaqueductal gray, produced a strong analgesic effect.

During the early years of this series, it was disturbing to find that after a variable period of time the stimulation of the periaqueductal gray region no longer provided pain relief for many of these patients. This tolerance to stimulation of the periaqueductal gray often was accompanied by tolerance to opiate analgesics; a period of abstinence from brain stimulation usually restored the analgesic efficacy of both the stimulation and opiates. Since the introduction of the adjuvant use of L-tryptophan to reverse tolerance to the analgesic effect of periaqueductal gray stimulation,[12,13] the results in these patients have improved progressively. Presently, the long-term success rate in this group is 77% (Table 2).

Twelve patients were considered therapeutic failures. One had to have the stim-

ulation system removed because of chronic subgaleal infection. In two patients, who initially responded well but later obtained no relief with stimulation, migration of the electrode was well documented on x-ray films. The nine other patients presented a very difficult problem when, 6–12 months postoperatively, their stimulation of the periaqueductal gray region began to fail to provide pain relief. The analgesic effect of stimulation was partially, although not adequately, restored after a course of L-tryptophan loading, but the opiate doses these patients required to supplement the stimulation were far in excess of those required before the implantation procedure. Over a period of several months, however, the patients found that a combination of periaqueductal gray stimulation and variable but moderate doses of opiates tended to control their pain satisfactorily most of the time.

Complications

The complications in this series of 122 patients are summarized in Table 3. In two cases, minor ventricular hemorrhage was detected almost immediately after the insertion of thalamic electrodes. In both cases, the ventricles were irrigated copiously with saline solution and the patient was kept in a semisitting position on the stereotactic operating table for 15 min. The bleeding stopped without further sequelae. The source of hemorrhage was thought to be the terminal vein or its branch lying at the dorsolateral border of the thalamus. In the third case, the hemorrhage had an arterial component requiring continuous ventricular drainage and irrigation. On CT scans, the hemorrhage appeared to be confined to the ventricular cavity. The bleeding ceased on the third day, although continuous ventricular drainage for several days and eventually a ventriculoperitoneal shunt were required. The patient suffered marked psychomotor retardation after this catastrophic event and died suddenly, 9 weeks later, from massive coronary occlusion. In two other cases, an intracerebral hematoma was detected within 6 hr postoperatively, when a CT scan was obtained to evaluate progressive hemiparesis; in both, the hematoma was evacuated immediately by craniotomy. The hemorrhage occurred on the trajectory of the electrodes in both instances: One patient recovered uneventfully and the other died from massive cerebral edema and recurrence of hematoma in the basal ganglia. The intraventricular or intracerebral hemorrhages

Table 3
Complications of Deep-Brain Stimulation in 122 Patients

Complication	Number of cases
Ventricular hemorrhage	3[a]
Intracerebral hemorrhage	2[a]
Ventriculitis (*Propionibacterium acnes*)	1
Subgaleal infection[b]	4
Subdural empyema (*Staphylococcus aureus*)	1
Eye-movement dysfunction	3

[a]One patient died.
[b]Two *Staph. epidermidis* and two *Staph. aureus*.

were thought to be caused by a leukotomy effect created by the insertion tool and electrode. The incidence of such an effect is low. A coaxial electrode system currently being developed will avoid the cutting effect created by the present electrode and insertion tool, as insertion of the coaxial electrode is established by a removable stylet inside the electrode.

The next most serious complication, which posed a problem that was both disappointing and challenging, was infection occurring several weeks or months after the electrodes were placed subcutaneously, when the patients were obtaining excellent pain relief with brain stimulation and were very reluctant to have the electrode system removed. Because all the patients who incurred infection asked that we try to retain the system, aggressive antibiotic therapy was tried before removal of the hardware was contemplated. This aggressive approach allowed us to save the system in the patient who had ventriculitis from *Propionibacterium acnes*. He was treated with antibiotic drugs parenterally for 6 weeks and orally with antibiotics for 6 months. More than 3 years after the infection, the patient seems to have suffered no ill effects. He continues to use stimulation of the periaqueductal gray region to control his chronic back pain, and he is actively employed. Four patients developed subgaleal infection. In three of these cases, two from *Staphylococcus epidermidis* and one from *Staph. aureus*, a similar antibiotic approach was successful and the patients were able to retain the implanted system. In the fourth patient with subgaleal infection (*Staph. aureus*) and in the patient with a subdural empyema (*Staph. aureus*), the system hardware had to be removed because of persistent infection.

Three patients who underwent implantation of an electrode in the periaqueductal gray region during the period between 1975 and 1979 had permanent dysconjugate vertical eye movements after their operation. Since that time, it has appeared certain that the tip of the electrode need be placed only at the iter of the aqueduct of Sylvius to produce satisfactory pain control; this complication can be avoided by not placing the electrode a few millimeters farther caudally.

Electrode migration from the target point, and consequently failure of stimulation, occurred in two patients who had been implanted with platinum and beryllium alloy electrodes. The electrodes made of this alloy are somewhat stiffer, but springier, than the pure platinum electrodes that are now used. In each case, the old electrodes were removed and new ones made of pure platinum were reimplanted and connected to the patient's original radiofrequency receiving unit. Since we have been using electrodes made of pure platinum, there has been no case of electrode migration.

In two patients, erosion of the scalp overlying the connector between the electrode and the radiofrequency coupling lead developed 1 and 1.5 years, respectively, after internalization of the electrode. Even though this connector is relatively small and thin, it may create a mass effect in the subgaleal plane in an individual who has a thin scalp. Both of these patients required plastic repair of the scalp.

The conclusions that can be drawn from the results in this series are, tentatively, the following. Stimulation of the periaqueductal gray region is not effective in patients with pain syndromes caused by damage to the central nervous system, and it is these syndromes that are the most difficult to treat (Table 1). Deafferentation pain may respond to stimulation in the region of the sensory thalamus, but the results are not

consistently successful. Conversely, intractable pain caused by lesions in the periphery responds well to stimulation of the periaqueductal gray region. Although the therapeutic efficacy of electrical brain stimulation is evident, the responsible mechanism has still not been defined satisfactorily, and issues regarding the optimal site of stimulation and the development of tolerance are not completely resolved.

ISSUES AND CONTROVERSIES

Validity of Morphine Infusion as a Screening Test

It was clinically apparent in this series that a preoperative response to morphine sulfate infusion correlates directly with the therapeutic success that is likely with stimulation of the periaqueductal gray region. In general, deafferentation pain does not respond to morphine sulfate or to stimulation of the periaqueductal gray region, as proved to be the case in this series. However, although cauda equina syndrome is considered a form of deafferentation pain, all three of the patients with this condition responded to morphine infusion. Based on this finding, their electrodes were implanted in the periaqueductal gray region. Stimulation of this region provided excellent pain relief for all of them, and all are still using it with continued success. I can offer no explanation for this result.

When patients respond incompletely to morphine infusion, interpretation of the test findings is complex. In some circumstances, the patient's condition may combine peripheral pain and deafferentation pain. Such patients do extremely well when a stimulation electrode is implanted in both the periaqueductal gray and the somatosensory area of the thalamus. If the incomplete response to morphine infusion represents tolerance to opiates and/or opiate dependence, however, the patient may not respond to periaqueductal gray stimulation as readily or as well as do patients who have a clearcut response, even after a period of L-tryptophan loading. No definite conclusions can be drawn regarding the optimal selection criteria for such patients because of the relatively small number of patients in this series who had an altered response to the test. In this particular group, it is possible that an opiate antagonist such as naloxone, rather than the opiate agonist morphine sulfate, may provide a medium for distinguishing opiate tolerance or dependence in a patient. The greater the opiate dependency or tolerance, the less is the amount of naloxone that will precipitate a withdrawal phenomenon. A test of the patient's response to naloxone, perhaps in conjunction with a test of the response to morphine infusion, might be a more useful screening measure.[24]

Somatosensory Thalamic Stimulation

The effect of stimulation of the subcortical somatosensory area of the thalamus in relieving deafferentation pain was discovered empirically in humans.[4,5] Although the neurophysiological basis of deafferentation pain has not been defined, it is thought to be, at least in part, the result of hyperactivity of deafferented secondary- or tertiary-order ascending neurons.[25] Benabid and colleagues[26] have demonstrated that stimulation of the somatosensory thalamic nucleus suppressed the response of medial thalamic

neurons to peripheral noxious stimuli, but did not inhibit the response of spinal cord dorsal horn units to the same stimuli. This suppressive effect was not reversed by the opiate antagonist naloxone.[26] It is tempting, but premature, to speculate that suppression of projected deafferentation hyperactivity in the medial thalamic structures may result from the stimulation of the sensory thalamus in humans. The poor response of deafferentation pain syndromes to an opiate analgesic correlates well with their poor response to stimulation of the periaqueductal gray region, as documented in this series.

An anecdotal observation in this group of patients supports the contention of Tsubokawa and colleagues that pain relief obtained by thalamic stimulation may be based on the dopaminergic system.[27] Until lately, we believed that patients using somatosensory stimulation were not likely to develop tolerance. A few of our patients who controlled their pain successfully for several years by thalamic stimulation, however, have since reported a considerable loss of efficacy. Based on the report of Tsubokawa's group,[27] we placed these patients on a regimen of L-dopa (1 g daily) given orally; the efficacy of the stimulation was restored within a few days. A few patients with deafferentation pain who were placed on Aldomet (methyldopa) to treat hypertension had a similarly diminished efficacy of thalamic stimulation. When they stopped taking Aldomet, this difficulty resolved within a week; the reversal was accelerated by L-dopa administration. Moreover, the patients who used this type of dopamine analog together with thalamic stimulation reported that they needed to activate their stimulator less frequently.

There is no histological verification of the precise sites of electrode implantation in patients with electrodes placed in the region of the somatosensory thalamic nucleus, as all such patients in our series are still alive. Despite the relative accuracy of radiographic localization of the electrode by postoperative ventriculograms, it is impossible to delineate with absolute certainty whether the pair of stimulating electrodes are placed in the sensory nucleus itself, in the medial lemniscus, or potentially, in patients with a wide third ventricle, even within the posterior limb of the internal capsule.[28] Because electrical stimulation at any point in this region will produce similar paresthesias in the body, localization of the precise anatomical site of the electrode cannot be discerned on the basis of the quality of paresthesias alone.[15] A few studies performed recently in both animals and humans have suggested that stimulation of the ventral area of the sensory thalamus, where maximum peripheral sensory evoked responses can be recorded, provides the most effective pain control.[29,30] We have not used somatosensory evoked response recordings routinely to delineate the target point for the implantation of the thalamic electrode because it is often difficult to elicit sensory evoked responses from the deafferented portion of the body. Such a neurophysiological delineation of the electrode implantation site may improve our success rate in the control of difficult deafferentation pain by thalamic stimulation.[30]

Stimulation of the Periaqueductal Gray Region

Significant relief from severe intractable pain of peripheral origin is obtained by electrical stimulation of the periaqueductal gray region, but the effectiveness of this stimulation is compromised by the development of tolerance. The analgesia is potenti-

ated by disulfiram, which inhibits the central norepinephrine system to prevent this problem.[31] Once tolerance develops, however, disulfiram is ineffective and the tolerance can be reversed only by abstinence from stimulation of the periaqueductal gray region—an unsatisfactory alternative in clinical therapy.

Experiments in animals have shown that analgesia induced by stimulation of the periaqueductal gray region is mediated by the descending pain inhibitory system that originates from the raphe nuclei of the brainstem and is, at least in part, serotonergic.[32] It is probable that, in humans, chronic stimulation of the periaqueductal gray induces a depressed rate of serotonin turnover in these serotonergic neurons.[12] In stimulation-tolerant patients, dietary supplementation with 4–6 g daily of L-tryptophan, a precursor of serotonin (5-HT), reverses the tolerance state.[13] As the rate of serotonin synthesis in the neurons is determined by the enzyme tryptophan-hydroxylase,[33] loading the system with this serotonin precursor presumably serves to enhance the rate of metabolic turnover of serotonin.[34] It is highly probable that what induces the tolerance to chronic stimulation is decreased turnover of serotonin in both the rostral and caudal serotonergic systems projected from the periaqueductal gray region.[12,35]

In contrast to the lack of histological verification of electrode placement in patients using thalamic stimulation, there are three cases in which autopsy findings on patients with electrodes implanted in the periaqueductal gray region are documented. Each of these patients in the series had been treated for the pain of cancer and eventually died of that disease. The results of the autopsy examination showed that, in all cases, the effective electrode tip was located in the ventrolateral periaqueductal gray region at the level of the posterior commissure, confirming that the target point producing the maximal analgesic effect of electrical brain stimulation in humans lies within the ventrolateral periaqueductal gray region. The tip of the electrode was found in the region of the periventricular bundle and its fibers connecting the periaqueductal gray region with the diencephalon: dorsal to the nucleus of the third nerve within the periaqueductal gray, medial to the mesencephalic reticular formation, and dorsal and rostral to the dorsal tegmental nucleus of Gudden.

The average power density that had been used for stimulation for all three patients was 6×10^{-6} W/cm^2, with a maximum power density of 2×10^{-5} W/cm^2; this is well within the maximum limit of safety for electrical stimulation of neural tissues (8×10^{-5} W/cm^2).[5] Detailed histological analysis of the brain parenchyma surrounding the electrode trajectories and tips uniformly revealed minimal gliosis or other parenchymal or neural reactions in all cases.[10] These findings, which correlate with those of other investigators,[36,37] confirm that the power density that provides satisfactory pain control affords safe brain stimulation. The likelihood that future results will support this conclusion is suggested by indirect evidence from the patients in this series who are still alive. Over the course of follow-up review, no patient who continues to obtain satisfactory pain relief from self-stimulation of either the thalamic or the periaqueductal gray region has found it necessary to increase the level of current used. This suggests that stimulation has caused minimal, if any, gliosis that would increase impedance at the tissue/electrode interface and minimal or no damage to the population of neurons being stimulated.

The mechanism through which analgesia is produced by electrical stimulation of

the periaqueductal gray region is only partially understood. Many observations in studies of both humans and animals support the concept that the analgesia so produced is a specific effect and is not the result of a generalized sensory, motivational, emotional, attentional, or motor response.[38] Studies in humans have excluded the possible influence of a placebo effect: Among patients who were given dead batteries for their stimulators in a double-blind study, none who attempted stimulation experienced analgesia;[10] and the mere insertion of the electrode, without induced stimulation, rarely reduces pain in humans. Nor is the theory that stimulation produces an electrical blockade of adjacent neural structures defensible: Whereas the somatotopic localization of the spinothalamic tract is such that the face and upper extremities are closest to the electrode tip, the pain relief obtained with stimulation is bilateral and is often greater in the lower extremities.

Although it has been thought that stimulation may act directly to inhibit some component in a pain-transmission pathway, much evidence has indicated that the analgesic effect of stimulation of the periaqueductal gray region in humans, which can be totally reversed by the administration of the opiate antagonist naloxone,[10,39] is accompanied by the release of endorphins into ventricular CSF.[40–43] A recent study disputes this observation, suggesting rather that the rise of endorphin levels in ventricular CSF is an artifact induced by the iodinated contrast agent used for ventriculography.[44,45] Despite the uncertainty about the involvement of endorphins in the mechanism of pain relief induced by stimulation of the periaqueductal gray region, the long duration of pain relief obtained following a brief period of stimulation suggests the involvement of some modulatory substance. Mayer and Hayes[46] have observed cross-tolerance of exogenous opiate analgesics and stimulation of the periaqueductal gray area in rats, and 12 of the patients in this series developed tolerance to periaqueductal gray stimulation and cross-tolerance to opiates, lending further support for a mechanism of response to stimulation of this region that involves a descending pain-inhibitory pathway that mediates opiate analgesia.

CONCLUSIONS

The criterion for success of the electrical brain-stimulation technique is the patient's ability to resume a normal, pain-free life. Retrospectively, in our series, those patients whose pain is controlled satisfactorily without the aid of opiates appear to be more active and productively employed than are those who require opiate medication. To determine the validity of this subjective impression, we are now engaged in a prospective study designed to document changes in the functional status of patients who undergo brain electrode implantation relative to their use of stimulation, medical management, or a combination of these modalities.

The empirical evidence supports the efficacy of deep-brain stimulation in the management of chronic pain. Although the implantation of electrodes and chronic stimulation of the subcortical area in humans are not entirely without risk or complications, the technique provides satisfactory control of pain for patients who have severe and intractable pain that is difficult or impossible to manage by medical means. In

comparison with ablative neurosurgical therapy of these pain syndromes, deep-brain stimulation appears to produce successful, long-term pain control without the high risk of additional neurological complications that attends those procedures.[11,14]

DISCUSSION

THE USE OF MAGNETIC RESONANCE IMAGING FOR ELECTRODE PLACEMENT

Apuzzo raises the possibility of using MRI for electrode placement. We had considered studying the electrode positions, utilizing the standard stereotactic apparatus, as to their localization with MRI. We are satisfied with the documentation of placement by MRI for the sensory thalamus. On the other hand, periaqueductal gray placement is much more time-consuming and expensive to do with MRI because of the difficulty in obtaining a true lateral image of the iter.

Apuzzo indicates that with a 1.5-Tesla MR machine the time involved in obtaining the lateral image of the iter would not be that excessive. It was our intention to try the MRI, but if all else fails we can continue to do ventriculography.

THE TECHNIQUE OF ELECTRODE PLACEMENT

Apuzzo asks if a cannula is used to pass the electrode to the target site, or is the electrode passed directly through the brain tissue?

We first use the standard monopolar electrode to explore the area in order to obtain the proper response, e.g., the physiological response or an evoked response if one is recording, and after that the "push-in" type of electrode is passed into the target.

PHARMACOLOGICAL ASPECTS OF STIMULATION-INDUCED ANALGESIA

Abrams inquires as to whether ACTH elevations paralleling the rise in β-endorphins that occurred with periaqueductal gray stimulation could have any effect in producing analgesia? In a similar vein, since the periaqueductal gray region contains a number of peptides, many of which have been shown to have analgesic properties, he asks if there is any other evidence of specificity other than naloxone reversibility, or is it naloxone reversibility that defines the β-endorphin analgesic effect?

There are many other peptides at which we have been looking, including cholecystokinin (CCK). If one studies the 16-K fragment or the bigger portion of pro-opioaminocortin, one sees that it also rises. I believe the entire molecule is brought out by stimulation. Interestingly, substance P also rises with stimulation of the periaqueductal gray. Whether this is an epiphenomena or an integral part of the analgesia induced is not known. The function of substance P can vary tremendously, as can its location in the nervous system, and it need not be involved with pain transmission.

L-TRYPTOPHAN

Patterson notes that it has been shown that L-tryptophan has helped some patients. How many of these patients had been taking L-tryptophan, or is L-tryptophan part of the postoperative management?

My patients are encouraged to take L-tryptophan. L-tryptophan was used along with stim-

ulation of the periaqueductal gray for a little over half a year. After 6–7 months the need to stimulate drops and this raises the other aspect of pain management. Long has shown (Chapter 5, this volume) that many people do not need additional medications if they are kept on strict opiate control. He may also suggest that certain surgical procedures for the control of pain may not be required, and that may be correct.

Patterson states that L-tryptophan acts to facilitate the analgesic effect. He cites King, who presents patients with rhizotomy and cordotomy in whom the area of analgesia shrunk over time, but in whom the analgesic area re-expanded when he gave them 2 g of L-tryptophan. Are these events related?

They are indeed related because the descending inhibitory system, which modifies the C fibers, is related to the serotonergic system, which in turn is enhanced by L-tryptophan. When L-tryptophan is given the system doesn't make more serotonin, but it makes the serotonin more rapidly, whereas L-tryptophan has no effect in thalamic stimulation.

ANATOMICAL AND FUNCTIONAL DIFFERENCES IN THE PAIN SYSTEMS OF DIFFERENT SPECIES

Holtzman asks if Asanuma knows why the nucleus of the median raphe is different in animals as compared to man, to which Asanuma replies that she does not.

Long emphasizes that the anatomy of the pain system is very different from species to species and as a result, conclusions derived from animal studies may not be applicable to man. Bill Mailer has taught us that very well.

TOLERANCE TO STIMULATION

Tew asks if there is generally a time beyond which one finds tolerance becoming unreasonably high, and does it change if one stops stimulating for a while?

There are situations in which permanent tolerance occurs, and we have had a number of such patients. We still have them in follow-up and ask them to turn the stimulator on and off. Occasionally they do obtain some analgesic effect, but none sufficient to rely upon. We don't know why this occurs. We do know that the thalamus must be stimulated with certain stimulation parameters. When one stimulates with a steady current one loses efficacy and that loss could be permanent. Yet there are no lesions of any kind, including alterations, to evoke responses. The reason for the development of such tolerance is not fully understood.

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III

Surgical Experience in the Diencephalon

7

SUPERIOR SURGICAL APPROACHES TO THE DIENCEPHALON

The Diencephalic and Paradiencephalic Regions

Michael L. J. Apuzzo

INTRODUCTION

A broad spectrum of pathological lesions affects the diencephalic and paradiencephalic regions.[1] From the surgical perspective each presents both a strategic and a surgical challenge.[2,3] This paper will direct attention to the definition of major presenting groups of structural substrates, which may then serve as a directive toward the selection of either certain open surgical corridors or indirect surgical methodologies. It will focus upon technical maneuvers attendant to the superior operative approaches and upon surgical options at the foramen of Monro for gaining exposure of the third ventricular chamber. It will discuss the utilization of imaging-directed stereotaxy in the evaluation and management of disease processes in this region. Finally, comments will be made that are related to the current management of colloid cysts, the prototype of "classical" tumors of the third ventricular chamber.

STRUCTURAL PRESENTATIONS AND CLASSIFICATIONS

In considering structure, it is of value to initially identify three major groups (Fig. 1) by CT and MRI.[4–6] These groups may be termed (1) extraaxial intraventricular, (2) intraaxial with ventricular component, and (3) basal.

Extraaxial intraventricular lesions are histologically benign masses with minimal areas of origin and adherence to the elements of the ventricular wall. The colloid cyst is the primary example of this group; however, a variety of developmental, neoplastic, vascular, and infectious processes may account for this structural presentation.[7,8]

Intraaxial lesions may directly expand into the third ventricular chamber, metas-

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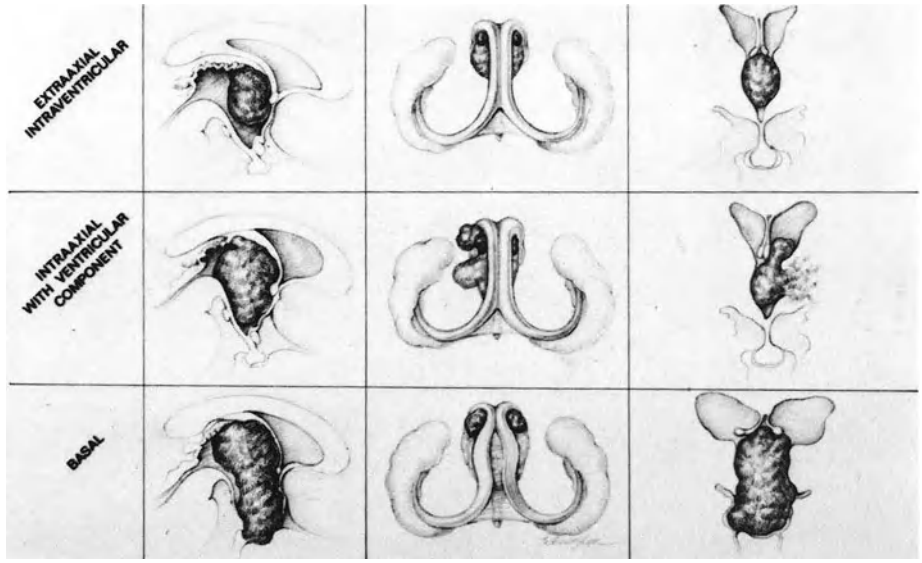

Figure 1. Schematic representation of the major types of structural presentation of anterior and mid third ventricular masses.

tasize, or secondarily deform the wall. Intrinsic tumors of the glial spectrum are the most common imitators of such a structural presentation.

Basal masses may have developmental, neoplastic, vascular, or infectious etiologies. However, they share a common region of origin in the sella, skull, or brain base, subsequently expanding rostrally to involve the third ventricular cavity. Craniopharyngioma is the most commonly encountered lesion of this group. Occasionally in the expansion of basal masses the hypothalamic floor will be disrupted and the lesion will present at the foramen of Monro.

OPERATIVE OBJECTIVES AND APPROACHES IN RELATION TO STRUCTURE

With recognition and imaging disclosure of any of these structural processes the surgeon must direct his efforts toward achieving four major goals[9,10]:

1. Definition of the nature of the process
2. Maximum feasible excision of the lesion
3. Relief of alteration in cerebrospinal fluid dynamics
4. Relief of focal signs and symptoms attendant to the regional mass.

For purposes of describing operative corridors, two major groups may be considered.[4] These are the *basal,* which includes all extraaxial approaches to the brain base

(i.e., transphenoidal, subfrontal, frontotemporal, pterional, or subtemporal), and the *superior,* which includes the intraaxial transfrontal and transcallosal routes.

In consideration of the structural substrate, tumors with basal origin are generally best approached by a basal corridor.[4,5,11–18] The particular angle of access and desired exposure are dictated by the location and extent of basal origin and direction of mass extention. Occasionally, a basal exposure combined with a superior corridor should be considered in either a single or a staged procedure.[19]

For purposes of this discussion, focus will be directed toward superior approaches, as they provide the major capability for entry to and visualization of the third ventricular chamber.[9]

Superior Operative Approaches

These corridors afford exposure of the foramen of Monro and diencephalic roof via entry through the middle frontal gyrus or trunk of the corpus callosum.[8,9] The exposures provide an initiation for excision of intraventricular lesions or intraventricular components of lesions that are not optimally accessible by basal exposures. They are applied to extraaxial intraventricular lesions and may be considered for intraventricular components of the axial processes in the event that[9]

1. The histological nature as defined by imaging-directed biopsy is not manageable by indirect methods, e.g., radiotherapy, chemotherapy, and antibiotics.
2. The lesion is not highly malignant.
3. The intraventricular component is the major component of mass presentation.
4. Signs and symptoms related to the mass presence (exclusive of hydrocephalus) exist.

Certain basal masses with superior extension may be managed entirely by this corridor[9,20]: These are cylindrical lesions, no greater than 2.5 cm in width, with a base in the midline and associated disruption of the diencephalic floor and presentation at the foramen of Monro.

The *transcortical* approach is undertaken through the right middle frontal gyrus in the presence of ventriculomegaly. It offers excellent visualization of the foramen of Monro, with satisfactory visual alignment for lesions of the mid and anterior component of the third ventricular chamber. It provides optimum angulation for employment of the subchoroidal transvelum interpositum exposure,[21–24] but offers less satisfactory visual alignment for the interforniceal exposure or appreciation of the contralateral foramen. Its limitations for flexibility of intraoperative options and sacrifice of cortical tissue make it a less desirable corridor.

The *transcallosal* corridor, fashioned by interhemispheric exposure of the body of the corpus callosum in the pericoronal region via a 2-cm incision of the trunk, offers the major advantages of constant anatomy, shorter transit to the diencephalic roof, and ability to easily develop exposure of the entire third ventricular cavity.[9,20,25,26] There is no disruption of the hemispheric tissue, and ventricular size is irrelevant. For these

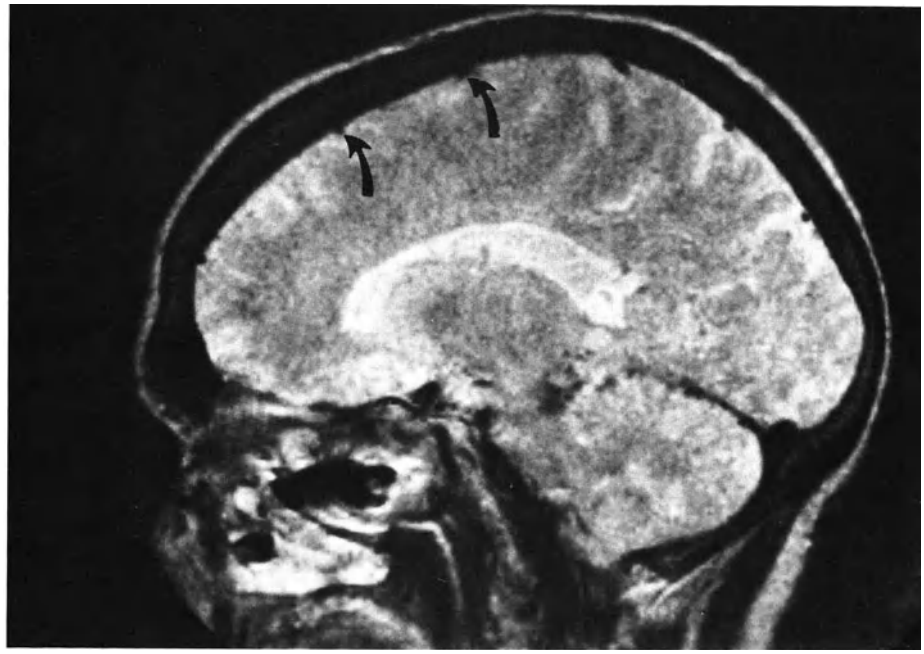

Figure 2. Sagittal MRI (T_2-weighted image), which may be employed in planning bone flap and entry corridor, demonstrating parasagittal venous entry.

reasons, this approach has been used nearly exclusively for our cases requiring exposure of the third ventricular region.

The approach is facilitated, and its safety enhanced, by attention to cortical venous anatomy during the preoperative evaluation of the patient.[20] We have recommended evaluation of the venous phase of cerebral angiography in planning of bone-flap placement and more recently have used MR images to provide elements of detail in parasagittal venous anatomy in the pericoronal region (Fig. 2). Attention to this detail, preservation of regional venous structures,[27] and minimization of retraction assure minimum occurrence of postoperative cortical deficits. The deformation of the midline should not exceed 5 cm and retraction of the medial hemisphere from the falx should not exceed 2 cm at the surface of the corridor.[25]

Midcallosal section is accomplished with apparently minimal physiological cost, as presently assessable.[20,28,29] However, certain possible exceptions to this generalization include (1) mutism, (2) auditory effects, and (3) tactile transfer deficits.[28] Transient mutism may be observed after either bilateral cingulage retraction or thalamic injury in association with midcallosal section. If dichotically tested, auditory suppression may be detected in one ear in the occasional patient. Depending on the difficulty of the task, deficits in somesthetic transfer may be observed in some patients; however, our experience with test batteries designed to elicit such deficits failed to disclose any. Detailed further evaluation of individuals undergoing trunk section is

indicated and is required to afford an absolute statement regarding these issues; however, the observed costs of transcallosal entry would appear to be minimal, well within acceptable limits, generally requiring specialized testing to elicit.

Chamber Entry

Following exposure of the lateral ventricle in the region of the foramen of Monro a number of options (Fig. 3) are available for third ventricular entry. These include[7,30]

1. Transforamenal entry (unilateral or bilateral)
2. Transforamenal entry expanded by ipsilateral forniceal column section
3. Subchoroidal entry
4. Interforniceal entry.

These maneuvers afford options to the surgeon as he attempts to maximize excision with a balance of minimal trauma to adjacent neural tissues. The amount of exposure required will vary with the type of disease process and the experience of the operator. Requirements for exposure are variable, but familiarity with each method of

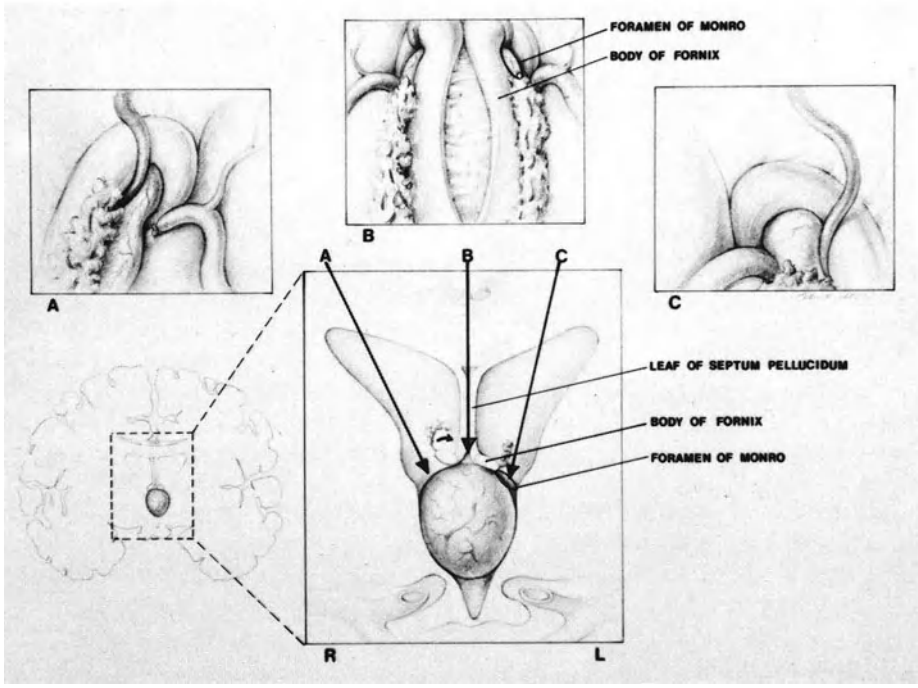

Figure 3. Major options for chamber entry following lateral ventricular access. (A) subchoroidal exposure via velum interpositum, viewed at the right foramen, with sacrifice of the thalamostriate vein to expand the entry area over the tumor; (B) interforniceal exposure; (C) transforaminal exposure, viewed at the left foramen.

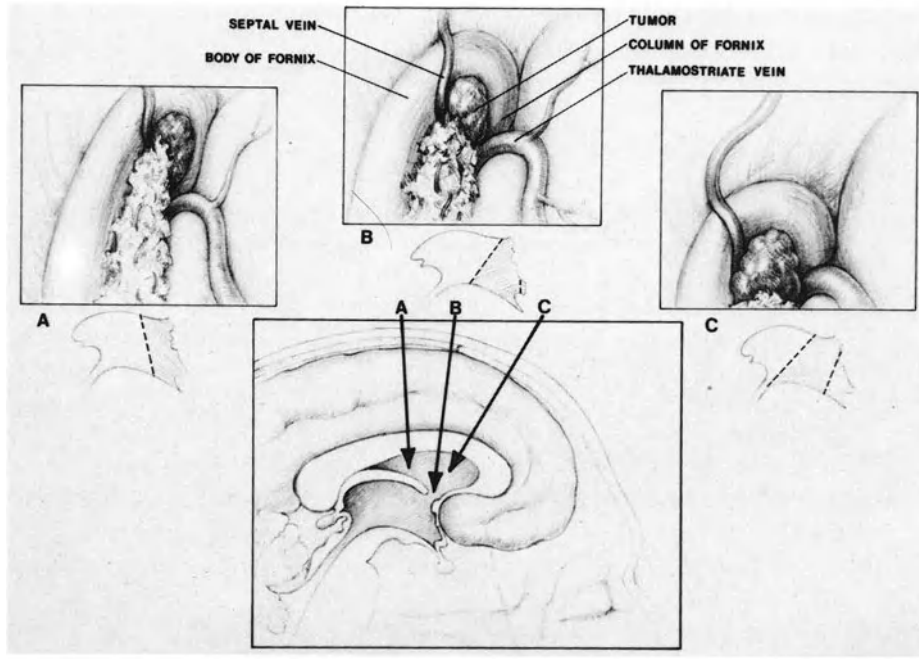

Figure 4. Relation of surgical corridor entry angles in pericoronal region to the view of the foramen of Monro and transforaminal exposure of chamber. Posterior (A), coronal (B), and anterior (C) view within the chamber will vary additionally in relation to the size of the foramen.

exposure increases the options and hence the potential for positive accomplishment in each operative procedure.

Transforamenal entry is facilitated by the presence of a large lesion that distends the foramen. This is not a dependable feature of third ventricular masses. In addition, the angle of exposure and access to the foramen is critical, as the surgeon's ability to satisfactorily deal with a mass within the chamber through the limitation of foramenal exposure may be compounded by the visual angle of the surgical corridor (Fig. 4). The consistency of the lesion and its resistance to methods of microexcision are another important factor in both achievement of lesion excision and avoidance of a neural injury. *Forniceal column section* is not recommended, as other maneuvers permit the realization of adequate exposure without sacrifice of neural elements.

Subchoroidal exposure exploits a natural plane at the lateral margin of the choroid plexus, which allows mobilization of the choroid and forniceal complex away from the side of dissection.[21–24,31] The method provides access to the central portion of the chamber via the velum interpositum. The exposure may be further enlarged by sacrifice of the thalamostriate vein at the foramen. This method appears to be safe and would appear to confirm the ability of collateral connections to shunt blood from deep medullary to subependymal venous systems.[22,24,32] Lines of visualization are optimized by the transcortical approach. In the presence of a small lesion retraction of the thalamus may be required to achieve adequate visualization.[24]

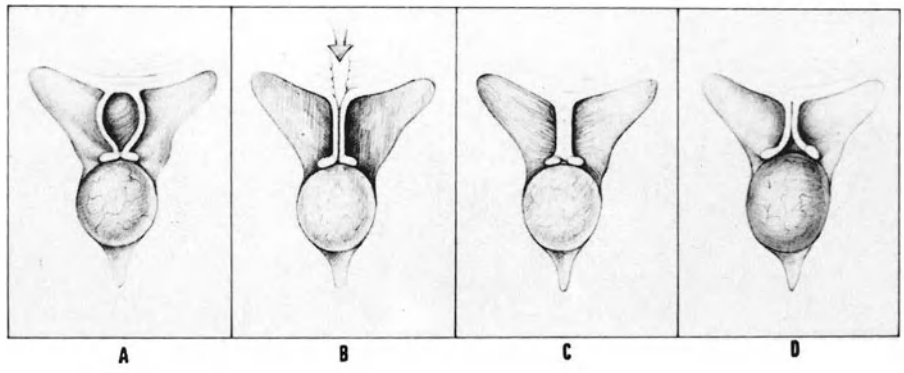

Figure 5. Anatomical variations encountered in the region of the septum pellucidum in relation to surgical development of the forniceal raphe. (A) cavum septum pellucidum; (B) separate leafs of septum pellucidum; (C) fusion of leafs; (D) raphe opened by mass presence.

With *interforniceal exposure*[20,25] a natural division (forniceal raphe) is developed between the columns and body of the fornix that opens through the diencephalic roof (Fig. 5). This division is easily appreciated with the presence of the cavum septum or may be developed by separating the septum leaves. Occasionally, it is partially initiated by distension of the dorsal forniceal complex by a mass. The line of septal attachment to the fornix defines its origin. *This exposure, combined with the transcallosal corridor, affords complete access to the third ventricular chamber and basal midline structures.* Mass presence generally negates the requirement for active retraction in the region. The internal cerebral veins are displaced laterally by the mass and are easily moved from the active operative field.

This exposure may be used with biforamenal visualization and simultaneous mass manipulation in the event that it is required. Development of the raphe should be initiated at the foramen of Monro and not exceed 2 cm in extent to preserve the hippocampal commissure (Fig. 6). It should be stressed that although this has been our primary method of attaining extensive midline exposure, *it is undertaken only if transforamenal exposure is inadequate or manipulation seems excessive.* The technique may be employed safely without natural corridors enhanced by ventriculomegaly or regional mass.

Our recent experience with 32 cases, operated via a transcallosal interforniceal corridor, is presented in Table 1. Exposure proved to be adequate for total excision of 24 of 26 (92%) lesions which were potentially excisable (i.e., extraaxial intraventricular or components of basal masses). There were no mortalities and major morbidity included only transient short-term memory loss, which occurred in 10 of 32 (30%) patients. This problem resolved in one week in 70% of cases, and no patient exhibited alteration in retention at 3 months postoperatively.

In consideration of this complication, it is apparent that soft, easily decompressed lesions carried the least risk of complication (i.e., cysticercosis cysts—16%), while firm lesions, which required more extensive regional trauma for excision, carried a much higher risk (i.e., craniopharyngioma—57%) (Figs. 7, 8). This data would imply

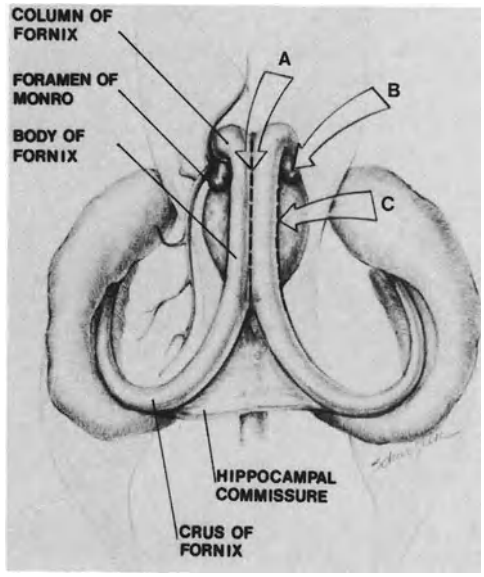

Figure 6. Schematic representation of the anatomy of the fornix (dorsal view), with extent of raphe development for the interforniceal corridor. (A) Hippocampal commissure to be preserved; (B) transforamenal entry region; (C) subchoroidal entry region.

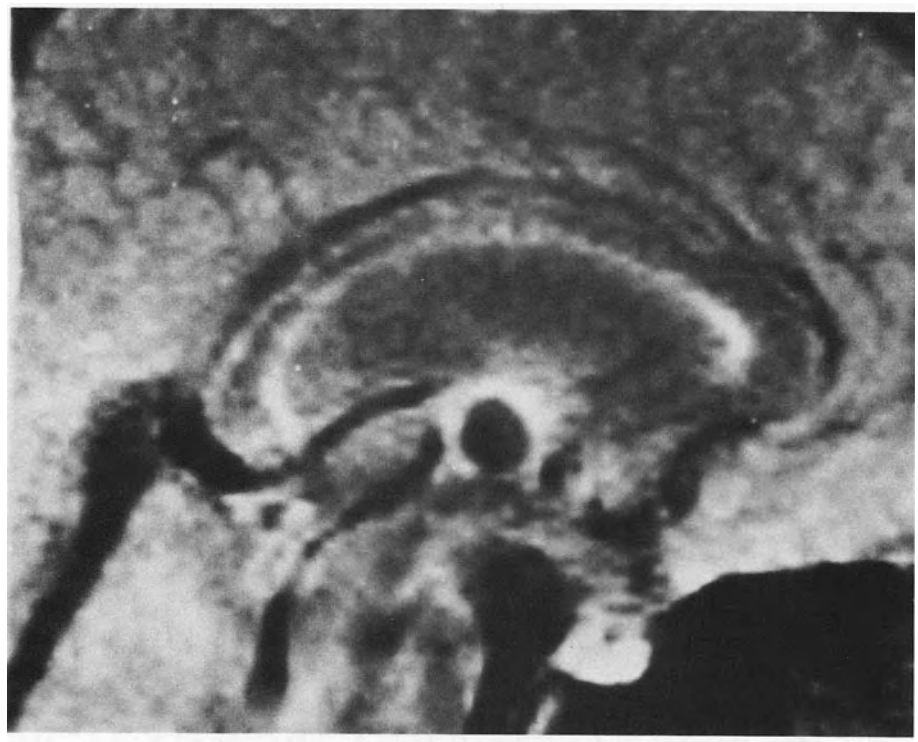

Figure 7. Sagittal MR image showing an extraaxial intraventricular mass (craniopharyngioma), which is managed by transcallosal interfornical excision.

Table 1
Interforniceal Exposure of the Third Ventricular Chamber[a]

Case number	Location of lesion	Pathology of lesion	Notes[b]
1	Anterior third ventricle	Colloid cyst (1.5 cm)	V,M,T
2	Anterior third ventricle	Colloid cyst (2 cm)	V,T
3	Anterior third ventricle	Colloid cyst (1 cm)	T
4	Anterior third ventricle	Colloid cyst (1.5 cm)	T
5	Third ventricle	Colloid cyst (2.5 cm)	V,M,T
6	Anterior third ventricle	Colloid cyst (1.5 cm)	V,T
7	Third ventricle	Colloid cyst (2.5 cm)	V,T
8	Third ventricle	Craniopharyngioma (3 cm)	V
9	Third ventricle	Craniopharyngioma (2.5 cm)	V,T
10	Third ventricle	Craniopharyngioma (2.0 cm)	V,M,T
11	Third ventricle	Craniopharyngioma (2.5 cm)	V,T
12	Third ventricle	Craniopharyngioma (4 cm)	V,M
13	Third ventricle	Craniopharyngioma (3.0 cm)	V,M,T
14	Third ventricle	Craniopharyngioma (2.5 cm)	V,M
15	Mid and posterior third ventricle	Cysticercosis (2 cm)	V,T
16	Foramen of Monro, anterior third ventricle	Cysticercosis (1.8 cm)	V,T
17	Foramen of Monro, anterior third ventricle	Cysticercosis (1.7 cm)	V,T
18	Foramen of Monro, anterior third ventricle	Cysticercosis (2 cm)	V,T
19	Foramen of Monro, anterior third ventricle	Cysticercosis (2 cm)	V,T
20	Foramen of Monro, anterior third ventricle	Cysticercosis (2 cm)	V,T
21	Anterior third ventricle	Cysticercosis (2 cm)	V,M,T
22	Third ventricle	Cysticercosis (2.5 cm)	V,T
23	Third ventricle	Cysticercosis (2 cm)	V,T
24	Posterior third ventricle	Cysticercosis (1.5 cm)	M,T
25	Third ventricle	Cysticercosis (1.8 cm)	V,T
26	Third ventricle	Glioma	V,M
27	Third ventricle	Glioma	V
28	Third ventricle	Glioma	V
29	Third ventricle	Glioma	V
30	Third ventricle	Glioma	V
31	Foramen of Monro, third ventricle	AVM[c]	M,T
32	Posterior third ventricle	Bullet (.022 caliber)	

[a]Based on 32 consecutive cases of transcallosal interforniceal exposure of the third ventricular chamber. Note range of size, consistency, and texture of lesions in relation to transient postoperative disturbances in mentation.
[b]V, associated ventriculomegaly; M, associated transient memory loss; T, total excision achieved, assisted by CT.
[c]Arteriovenous malformation.

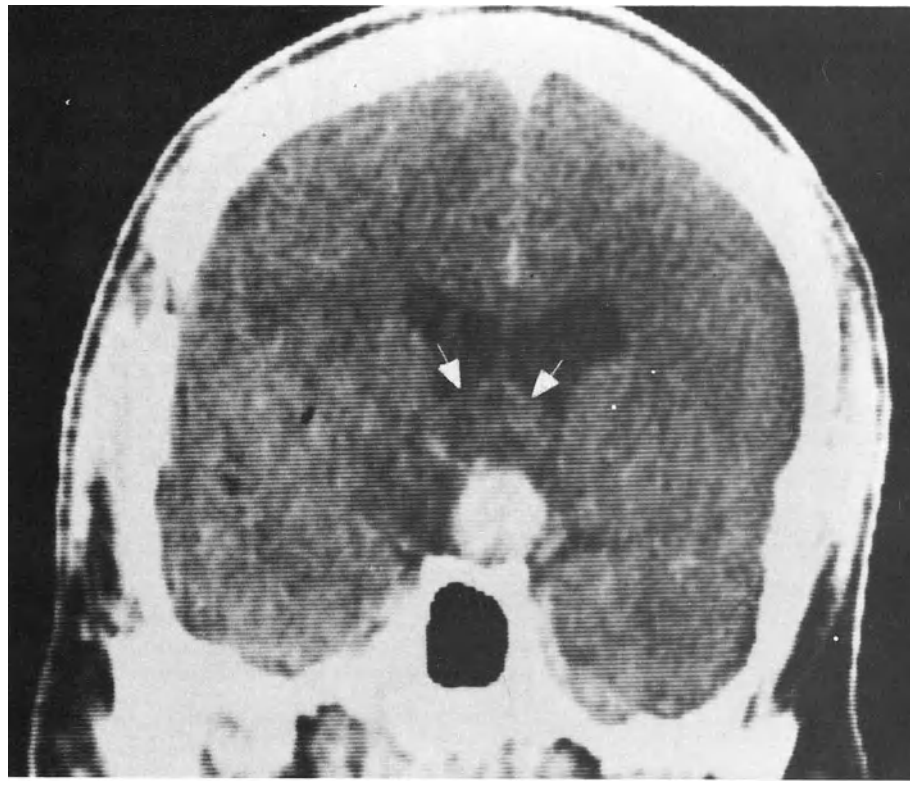

Figure 8. Solid and cystic (arrows) basal lesions (craniopharyngioma), seen in a contrast-enhanced coronal CT slice. Note narrow (< 2.5 cm) solid and superior cystic component. Lesion had disrupted the hypothalamic floor and presented at the foramen of Monro. Total excision was by the transcallosal interforniceal approach.

that this corridor is relatively safe but that there is difficulty inherent in microexcision of firm lesions in this region without some temporary cost of neurological impairment.

MEMORY

As noted, although a number of complications have developed in the hands of experienced microsurgeons,[20,33–37] the most frequent postoperative problem associated with manipulation of the midline basal cerebral structures is a *transient amnesic syndrome*. The alteration in mentation is observed in the immediate postoperative period and usually resolves within a period of days to several weeks.[20]

The fornix by "tradition" rather than fact has received primary focus as the isolated structure of injury in such cases. The literature fails to provide substantive evidence that integrity of the fornix is required for normal memory.[9,20,38] *Although this structure represents one major limbic pathway, significant comparable fiber bun-*

dles remain intact following isolated forniceal injury. Almost all hippocampal connections with the associated cortices are preserved.

It is becoming apparent that diffuse, multifocal midline injury is required for additive and collective impact on regions concerned with the memory process.[30,38,39] These regions include: (1) basal forebrain nuclei, (2) thalamic nuclei, and (3) inferior thalamic peduncle.

The *basal nucleus of Meynert* lies in the substantia innominata, adjacent to the midline and millimeters from the third ventricle. Major cortical cholinergic input is derived from this region. Forniceal injury could alter cholinergic input to the hippocampal formation, which could compound basal nuclei injury and alter all cortical cholinergic innervation.

The *nuclei reuniens* and *paraventricular nuclei of the thalamus* are situated between the anterior reticular and the dorsal medial thalamic nucleus. They provide major input to the entorhinal cortex. The nucleus reuniens projects to the hippocampus. In the event of forniceal injury, associated injury to these nuclear groups would alter hippocampal afferent and efferent activities.

The *inferior thalamic peduncle* carries a major component of amygdaloid output and provides a major connection with the dorsal medial thalamic nucleus, both of which are considered primary structural components of the memory process. Its proximity to the third ventricle places this vital component of memory structure at risk.

IMAGING-DIRECTED STEREOTAXY

The combination of principles of stereotaxy, radiographic imaging techniques, and microinstrumentation has added a new and vital dimension to the management of intracranial mass lesions.[6,40–45] The deep midline structures of the diencephalic region are particularly accessible by this approach, with a precision and inherent safety that has not been available in the past.[25,41,46–49,51,52]

A number of stereotactic devices that provide capability for translation of imaging data to the operating room in a rapid and useful fashion are currently commercially available. Our experience with the Brown–Roberts–Wells (BRW) system at the University of Southern California Medical Center Hospitals in over 1000 cases attests to the value, safety, and flexibility of such a system, with appropriate support, as a resource in major medical centers (Figs. 9–11).

Access to the target point is achieved readily, rapidly, and safely with local anesthesia and an anesthesiologist standing by in all but selected pediatric patients, in whom general anesthesia is required.[48,49] Access to the target point is usually attained within 60 min from the time of initiation of the procedure, with all trajectory settings and target locales verified extracranially on a phantom simulator.[49]

Multiple microinstrumentation capabilities at the target point allows for

1. Histological and microbiological assay
2. Cyst and abscess aspiration
3. Installation of permanent or temporary drainage conduits

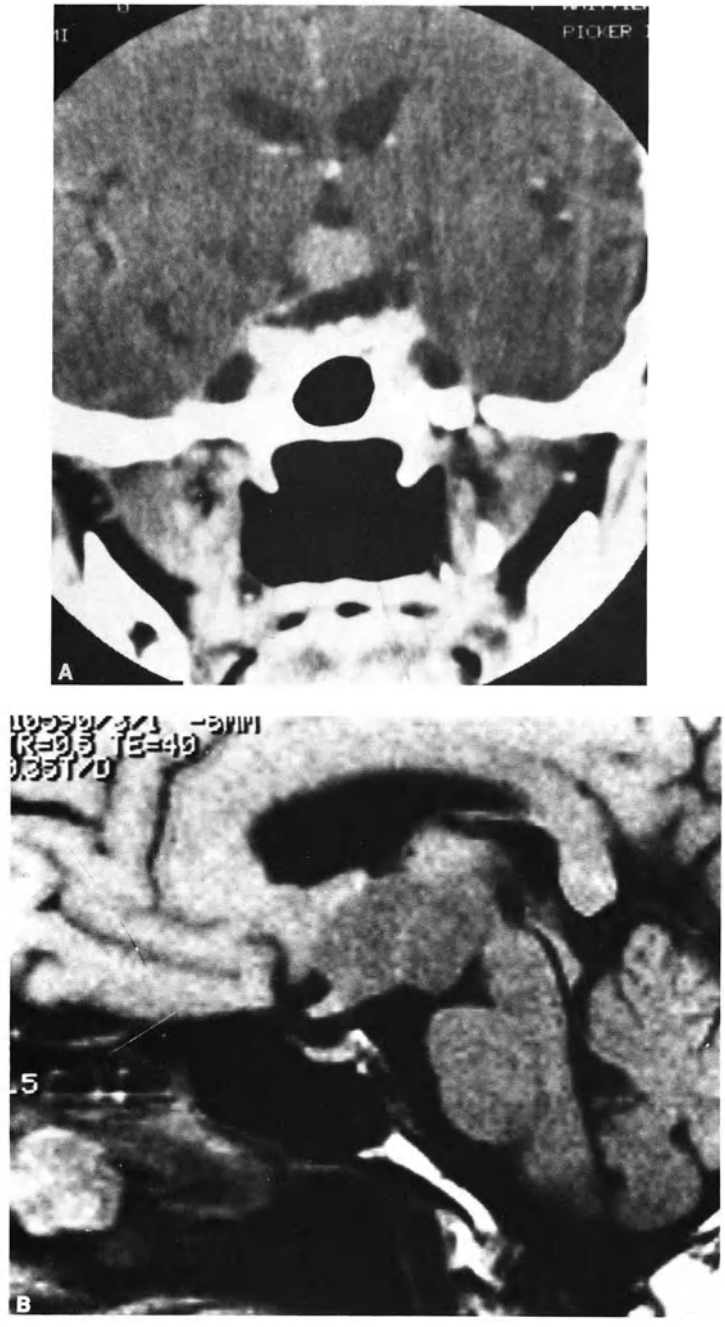

Figure 9. (A) Contrast-enhanced coronal CT slice of a hypothalamic tumor (1° lymphoma) in a 70-year-old male. No immunosuppression was evident. (B) Sagittal MR image 1 week later. Tumor was evaluated by stereotactic biopsy, and rapid resolution was achieved with radioteletherapy.

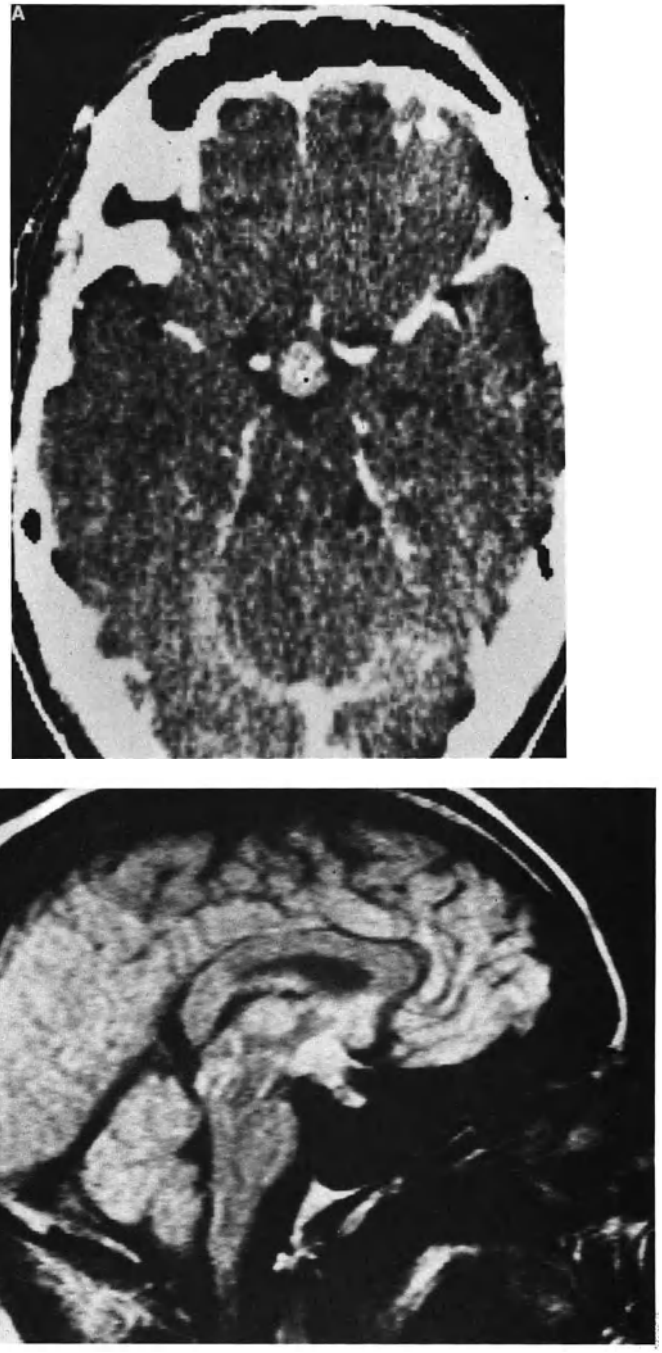

Figure 10. Intraaxial lesion with ventricular component (metastatic germinoma). (A) Axial contrast-enhanced CT slice in a 20-year-old male; (B) sagittal MR image of the lesion which was managed by CT-guided stereotactic biopsy with 2° radiotherapy. Markers are negative.

4. Point-source or colloid-based brachytherapy
5. Intralesional immuno- or chemotherapy
6. Cerebroscopy and ventriculoscopy with biopsy, aspiration, or excision
7. Placement of biological grafts
8. Ablative procedures
9. Neuroaugmentation procedures.

Ventriculoscopy[46,49] is performed with local anesthesia and standby (Fig. 12). A target is selected at the right foramen of Monro for cystic lesions presenting in the anterior component of the chamber. An entry point is centered at or slightly anterior to the coronal suture in the pupillary line. An 18-mm burr hole is prepared and, after cruciate opening of the dura, a 1-cm cortical window is designed at the point of entry of the ventriculoscope sheath. We have employed a 6.2-mm endoscope sheath with a blunt obturator that is introduced to the target. With removal of the obturator an angled ventriculoscope is introduced allowing for visualization, irrigation (Ringers lactate solution), aspiration, and introduction of either instrumentation for biopsy, cyst perforation, and aspiration, or quartz fiber for conduction of argon laser energy. The

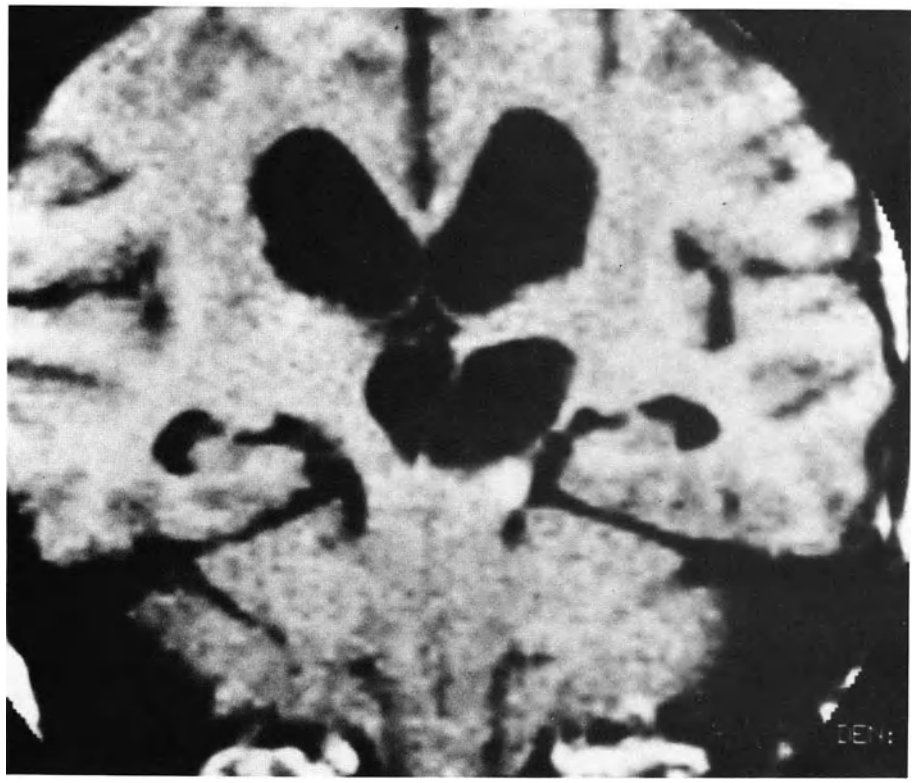

Figure 11. Intraaxial lesion with ventricular component (cystic ganglioglioma). Axial contrast-enhanced CT.

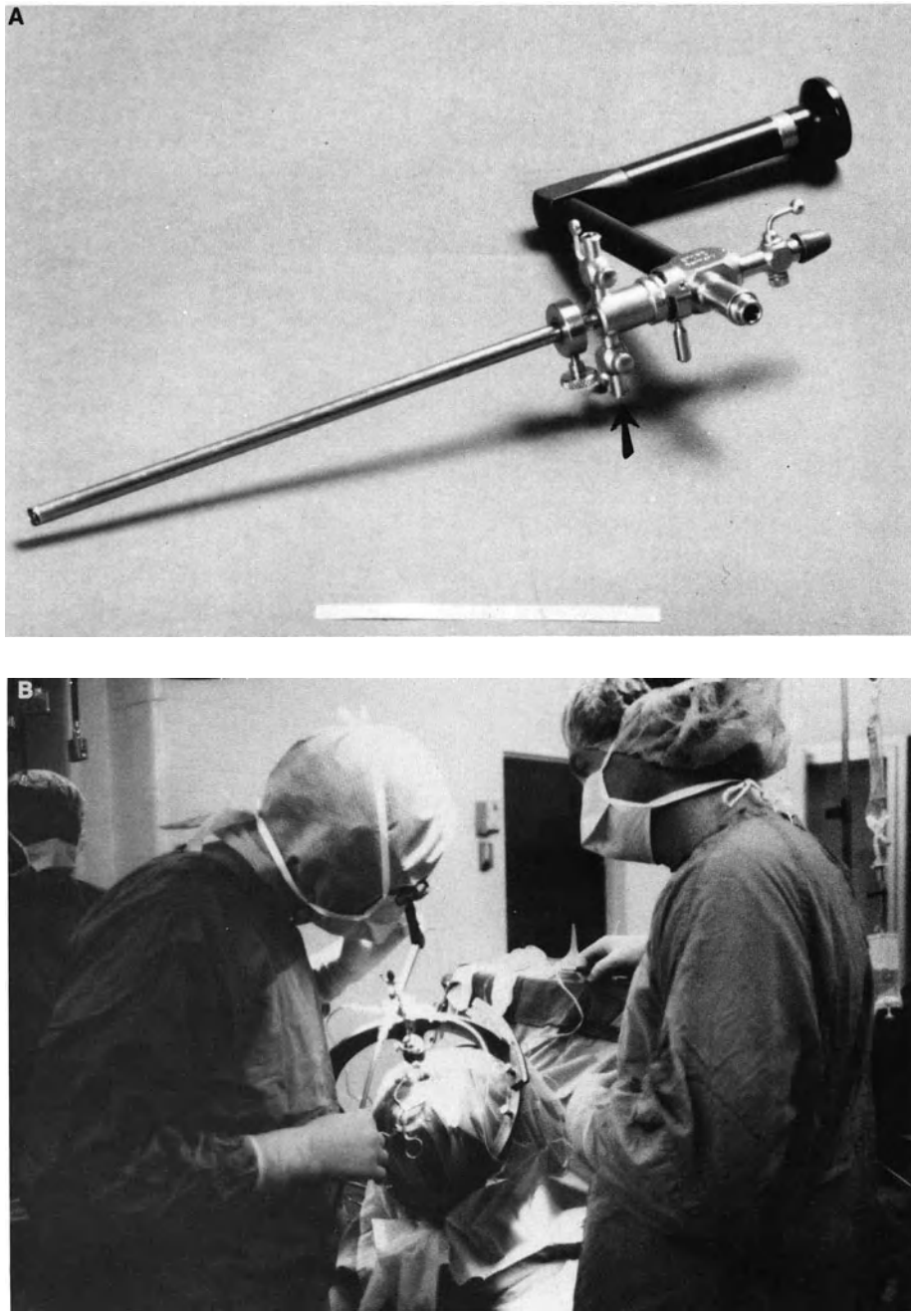

Figure 12. (A) Angled endoscope with sideports (arrow) for local irrigation and evacuation, with capability for instrument introduction through the main shaft. (B) Ventriculoscopy in progress, with stereotactic placement (using local anesthesia).

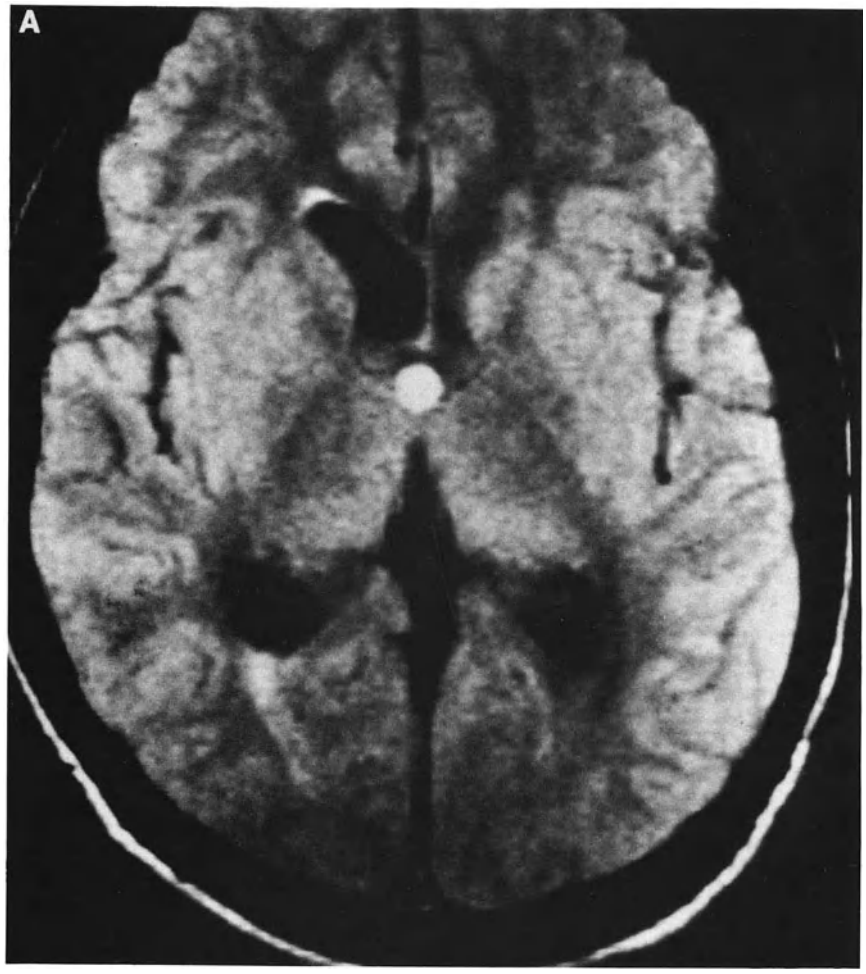

Figure 13. Extraaxial intraventricular mass (cysticercosis cyst). Axial (A) and sagittal (B) MRI views of the same lesion, managed by CT-guided ventriculoscopic excision. (C) CT water-soluble contrast ventriculogram, demonstrating the mass and unilateral ventriculomegaly.

sheath is introduced through a rigid bushing directed by the arc guidance component of the BRW system, with precise placement to the foramen. Minor adjustments and changes in angulation may be made by adjustment of four angulation settings on the arc, which allow infinite degrees of motion (Fig. 13).

Targeting for 150 lesions of the third ventricular region at the University of Southern California Medical Center Hospitals is presented in Figure 14. Histological verification of a process was attained in 95% of cases, and realization of the objectives of a procedure was achieved in 97%. These objectives included biopsy, biopsy with culture, biopsy with aspiration, biopsy with installation of Rickham drainage systems,

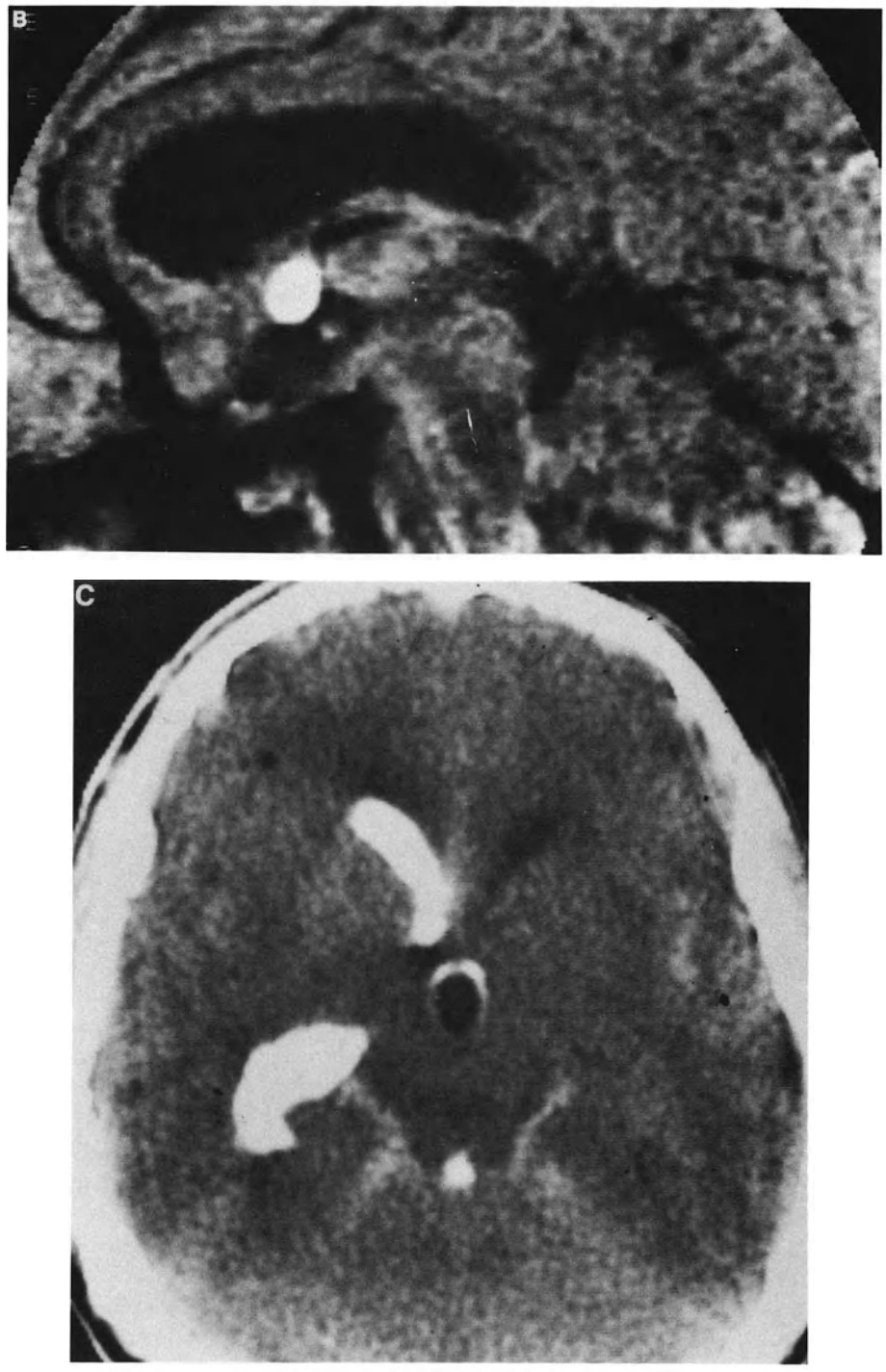

Figure 13. (*Continued*)

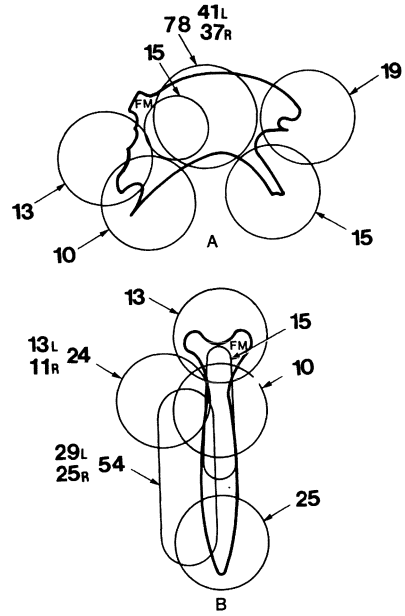

Figure 14. Breakdown of targeting for 150 lesions in the third ventricular region by CT-guided stereotactic techniques. Lateral (A) and superior (B) third ventricular silhouettes, with circles indicating lesion location. Numbers indicate number of cases. FM, foramen of Monro.

point-source or colloid brachytherapy, endoscopic visualization with biopsy, and endoscopic excision. Operative morbidity was less than 1%, while only one death occurred in this series. Craniotomy was indicated or ultimately required in less than 20% of those undergoing the initial stereotactic procedure.

These methods are particularly valuable in the assessment, management, and logical development of treatment plans in individuals with lesions affecting the third ventricular chamber. They should be considered part of the management armamentarium for the following reasons:

1. The histological nature of intraaxial lesions may be rapidly and safely assessed, often circumventing the need for craniotomy.
2. Cystic lesions of basal or intraaxial origin may be drained with precise control, with permanent conduits placed for later treatment with colloid brachytherapy or other intralesional methods.
3. Intraventricular cystic lesions may be aspirated under endoscopic visualization (colloid cyst) or totally excised (cysticercosis cyst).
4. Basal lesions with superior extension, to or above the foramen of Monro, may be evaluated by ventriculoscopy to assess disruption of the hypothalamic floor prior to developing a primary surgical strategy.
5. Third ventriculostomy may be performed in cases of aqueductal or fourth ventricular outlet, atresia, or stenosis.

COLLOID (NEUROEPITHELIAL) CYSTS

Colloid cysts represent the classical prototype of the benign tumor of the third ventricular chamber.[53] Most commonly, these lesions arise in the anterior part of the third ventricle immediately posterior to the foramen of Monro.[1] They usually project inferiorly into the third ventricle and vary in extent superiorly and rostrally. Attachments of various dimensions are present with the tela choroidea of the third ventricular roof. Occasionally, the forniceal columns superior to the anterior commissure will be separated by the mass presence and involve the septum pellucidum.[54] The cysts are well circumscribed, smooth, and spherical with dimensions that have been reported to vary from 0.3–9 cc. They are filled with homogeneous material of varying viscosity containing cellular debris. This variability is related to multiple factors, including desquamated epithelial cells, leukocytes, red cells, gitter cells, and cholesterol pigment.

These lesions may occur posterior to the foramen of Monro and be attended by various degrees of aqueductal stenosis.[55] Presentation may be in the form of

1. Acute and intermittent increases in intracranial pressure
2. Chronically increased intracranial pressure
3. Local pressure effects
4. Truly "incidental" findings on imaging studies.

Computed tomography demonstrates an anterior third ventricular mass, usually with attendant ventriculomegaly. The lesion is commonly slightly hyperdense with enhancement upon contrast. Isodense, nonenhancing lesions or ring enhancement may be encountered.[56] "Incidental" lesions generally present as small (less than 1 cm) masses posterior to the foramen of Monro without ventriculomegaly.

Because of their location and mechanical propensities, these lesions represent a menace to life[57] (personal communication with E.-O. Backlund, April 1986). Although the absolute risk of demise in the individual patient has not been accurately determined, the location of the lesion and repeated documentation of rapid and fatal neurological deterioration dictate a need to initiate definitive management to either reduce cyst mass and/or maintain normal CSF dynamics.

Arguments exist for the following management options: (1) biventricular shunting, (2) stereotactic aspiration, and (3) direct excision. Options 2 and 3 do not necessarily obviate the need for some form of CSF diversion, as approximately 30% of these lesions are associated with aqueductal stenosis or atresia.[55]

Stereotactic aspiration is best accomplished under direct vision. We have employed a 6.2-mm angled endoscope in association with a 13-gauge cannula with blunt and sharp (for capsule penetration) stylette for this purpose. Our modest experience (8 cases), communications[57] (personal communication with E.-O. Backlund, April 1986), and review of available literature would indicate that satisfactory cyst aspiration is possible in 50–60% of cases by current techniques. It is our experience that difficulty is usually encountered with lesions of less than 1 cm in diameter. Although a large body of data is not available, it would appear that at least in certain cases this

method will offer feasible therapy and should be pursued to ultimate refinement, including laser reduction of the cyst capsule.

Our current method of managing these lesions is to attempt endoscopic aspiration in all cases in which the cyst is greater than 1 cm in diameter[46] (personal communication with T. Rahn, June 1986). If this is unsuccessful, primary excision is offered to individuals who are less than 50 years old and biventricular CSF diversion is offered to those who decline direct surgical excision or are greater than 50 years old. Craniotomy is undertaken with a transcallosal corridor with foraminal exposure or foraminal exposure augmented by the interforniceal approach.

CONCLUSION AND SUMMARY

Surgery of lesions affecting the diencephalic and paradiencephalic regions is a technical and intellectual challenge. It requires lucid comprehension of normal[10,58,59] and pathological alterations of anatomy on the part of the managing surgeon. Multiple options are available and familiarity with these, as well as thoughtful experience in the management of problems involving the region, will enhance the opportunity for satisfactory results and minimize complications.

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8

SUPERIOR SURGICAL APPROACHES TO THE DIENCEPHALON

Surgery Around the Hypothalamus

Russel H. Patterson, Jr.

This chapter outlines our experience with a number of techniques that can be useful for surgery around the hypothalamus.

PETROSAL SINUS CATHETERIZATION

Cushing's disease is defined as hypocortisolism due to a pituitary adenoma secreting excess adrenocorticotropic hormone. The condition can be difficult to diagnose since conventional imaging techniques may not identify the small pituitary tumor that is usually present. Following the lead of Zovickian et al.,[1] we have had some experience with sampling petrosal venous blood in order to establish the source of excess ACTH as the pituitary.

In 10 of our patients, venous catheterization of both inferior petrosal sinuses was accomplished through a femoral approach (Table 1). A catheter was placed in each petrosal sinus via the jugular vein, the proper placement of the catheter being determined by an injection of contrast agent. Blood was then drawn simultaneously from both catheters, as well as a peripheral vein, for measurement of ACTH concentration.

In nine of these 10 patients, petrosal vein sampling showed some gradient between pituitary ACTH and the ACTH in the peripheral veins. This verified that the pituitary was the source of the elevated levels of ACTH. The patient in whom the test was negative had received cyproheptadine prior to petrosal vein sampling. Some evidence suggests that this antiserotonergic agent can suppress pituitary adenomas from secreting functioning ACTH.

Of the 9 patients who had a gradient between petrosal and peripheral venous blood, 1 patient had only one petrosal sinus catheterized and had a large gradient. Of the eight other cases, a tumor was found on the side of the gradient in six cases. In a

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Table 1
Results of Petrosal Sinus Catheterization in 10 Cases

Patient	Petrosal sampling	Localization	Pathology[a]	Postoperative cortisol
1. C.M.	Right 175 pg/ml Left 34 pg/ml Peripheral 20 pg/ml	Right	Pituitary adenoma found on right side of gland	4.2 μg/dl 10.4 μg/dl
2. M.J.	Right 152 pg/ml Left 45 pg/ml Peripheral 19 pg/ml	Right	No tumor found; right half of gland removed	28.5 μg/dl 40.5 μg/dl
3. J.R.	Right 31 pg/ml Left 53 pg/ml Peripheral 20 pg/ml	Nonlocalizable	Small tumor seen at surgery in midline. NL gland on path	1.0 μg/dl 1.0 μg/dl
4. L.H.	Right 10 pg/ml Left 45 pg/ml Peripheral 10 pg/ml	Left	Pituitary adenoma found on left. Further w/u revealed left adrenal tumor, which was removed with resultant cure	23.5 μg/dl 19.8 μg/dl 31.6 μg/dl 1.0 μg/dl (postresection adrenal tumor)
5. S.J.	Right 50 pg/ml Left 48 pg/ml Peripheral 53 pg/ml	Nonlocalizable	Reddish tumor seen at surgery in midline. Pathology revealed NL gland	1 μg/dl
6. K.M.	Right 91 pg/ml Left 10 pg/ml Peripheral 20 pg/ml	Right	Adenoma found on right side of gland	1.9 μg/dl
7. A.P.	Right 2883 pg/ml Left unable to catheterize Peripheral 31 pg/ml	Unable to localize	Adenoma found bilaterally, more predominant on right side	2 μg/dl
8. P.B.	Right 194 pg/ml Left 1370 pg/ml Peripheral 54 pg/ml	Left	Adenoma found on left side of gland	1.3 μg/dl
9. J.D.	Right 1341 pg/ml Left 81 pg/ml Peripheral 117 pg/ml	Right	Adenoma found on right side of gland	2.2 μg/dl
10. M.Z.	Right 236 pg/ml Left 31 pg/ml Peripheral 46 pg/ml	Right	Adenoma found on right side of gland	1 μg/dl

[a]NL, normal; w/u, workup.

seventh, no tumor was identified at surgery, and one half of the pituitary gland was resected. No tumor was seen in the specimen, and the patient was not cured of her Cushing's disease (see Table 1). In two patients, the ACTH levels were not localized as to side and in both patients the tumor was found in the midline. Surgery cured these cases.

In the patient in whom half the gland was resected without achieving a cure, further treatment with heavy-particle radiation was administered. This has not resulted in a cure either. Another patient who had a small microadenoma removed without cure of the Cushing's disease was subsequently found to have an additional adenoma in the adrenal gland, which was removed with cure.

In summary, we find petrosal sinus catheterization to be a valuable diagnostic tool in patients in whom imaging studies reveal no tumor. It may point to the side of the gland producing the ACTH, which can then be treated by partial removal of the gland.[2]

MAGNETIC RESONANCE IMAGING AND THE CONSISTENCY OF PITUITARY ADENOMAS

One disadvantage of the transsphenoidal surgical approach is that in the case of large tumors with substantial suprasellar extension, a fibrous tumor does not collapse into the sella at surgery. Consequently, it would be advantageous to identify tumors that are firm or even fibrous. Such a finding might point to craniotomy as a better operation.

We reviewed the MRI of 15 patients with large pituitary adenomas studied with a 0.5 Tesla Technicare Superconducting Scanner. Of these tumors, three were firm, and each one was isointense at both T_1 and T_2 relaxation times. The scans were sagittal spin echoes with echo times of 30 and 90 msec and repetition times of 50 and 1500 msec (Fig. 1).

Pathological examination of the specimen in the three cases designated as firm showed marked perivascular fibrosis in one, dense fibrous tissue with dilated capillaries in the second, and dense collagen-containing pituitary cells in the third. In contrast, six of the 11 patients with soft tumors showed a diffuse pattern without fibrosis on microscopic examination. In three others, only mild perivascular fibrosis was identified. Two soft tumors seemed to have marked perivascular fibrosis or dense collagen tissue.

In summary, this differentiation between hard and soft tumors seems to be relatively reliable and should be taken into consideration when deciding on the appropriate surgical approach.[3]

THE SUBFRONTAL APPROACH TO CRANIOPHARYNGIOMA

For an intracranial approach to the region of the pituitary, we favor a right frontal craniotomy with exposure of the chiasm from an oblique angle over the roof of the orbit. Needless to say, the sawcut must be flush with the roof of the orbit, even if it means opening large frontal sinuses. Suzuki and co-workers[4] have advocated a bifron-

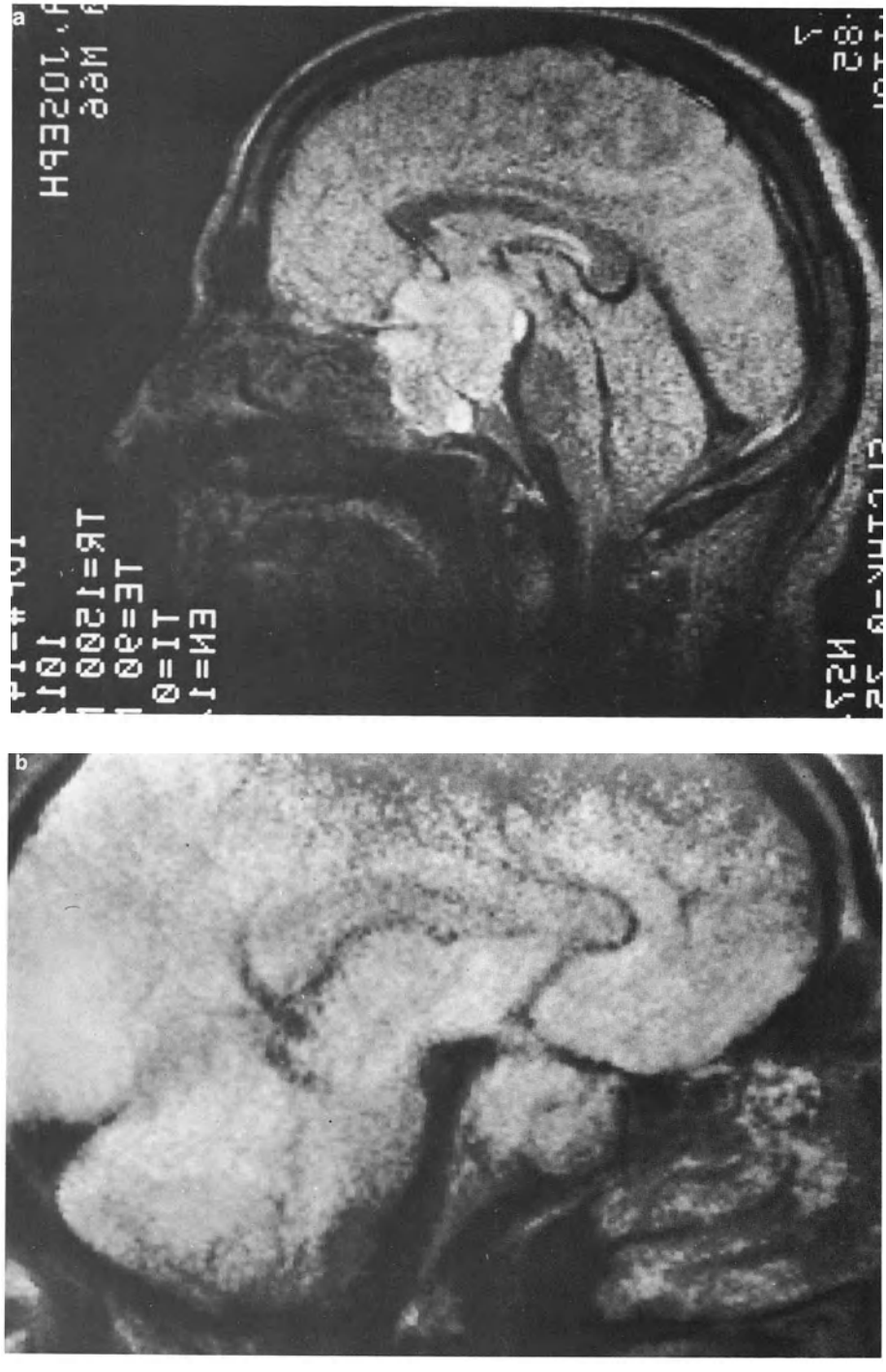

Figure 1. (a) An adenoma hyperintense on T_2; it proved to be soft. (b) An adenoma isointense on T_2; it was of firm consistency.

tal approach, dissecting out the olfactory tracts to expose the chiasm. We have tried this, and it is certainly possible to expose the area, preserving the olfactory tracts and guarding the sense of smell. However, it does mean retracting both frontal lobes, and I believe that the postoperative course is not as smooth in these patients as it is in those with just a right frontal craniotomy. A pterional craniotomy is favored by many since the distance to the chiasm is shorter. However, the surgeon must work around the optic nerves and carotid artery. Dolenc[5] has suggested exposing the carotid artery in the cavernous sinus by removing the entire sphenoid ridge and clinoid process. This, coupled with removal of the posterior clinoid process, gives a view up into the region of the hypothalamus. I have no experience with this approach, but it seems likely that it has the disadvantages of the more usual pterional approach, i.e., the optic nerve and carotid artery block access.

The disadvantage of the frontal approach is that in many cases the optic nerves are short, which would appear to impede exposure. However, if the tuberculum sellae is removed, a step which can easily be accomplished, then the space between the optic nerves is quite large. Approaching the tumor through the lamina terminalis and sphenoid sinus allows the removal of a craniopharyngioma without difficulty and without the problems associated with the pterional approach. The tumor can be pushed down into the sphenoid sinus and extracted without disturbing the optic nerves.

In craniopharyngiomas, as well as in other tumors in the third ventricle, we have had substantial experience with enlarging the foramen of Monro by dividing the large veins at the posterior rim of the foramen. The exposure is obtained either through the corpus callosum or more obliquely by opening a frontal sulcus to gain exposure to the frontal horn of the lateral ventricle. The choroid plexus is elevated and, at the posterior edge of the foramen of Munro, the thalamostriate and septal veins can be seen. Often a direct lateral vein is present farther down the length of the ventricle. This vein drains blood from the basal ganglia into the internal cerebral vein.

Dividing the thalamostriate vein allows elevation of the internal cerebral vein, which provides a wide route of access into the third ventricle. If the septal vein is divided, the internal cerebral vein can be depressed, which also gives a big exposure. Which vein to divide would depend on the exact location of the tumor and can be determined at the time of surgery. In a number of cases we have divided both veins when the direct lateral vein was present. We have seen no difficulty associated with this (Fig. 2). We used this approach to remove a craniopharyngioma from the cavity of the third ventricle. The floor of the third ventricle came out with the tumor, and we were able to see the basilar bifurcation and other prepontine structures through the frontal craniotomy. Interestingly, the patient had no endocrine deficits, including no diabetes insipidus.[6]

In considering craniopharyngiomas, the question arises as to whether all of them can be totally removed. Clearly, they cannot. Sometimes the tumor has a papillary configuration with processes that enter into the hypothalamus. It is questionable whether the tumor can be extracted without breaking off some of the papillary projections, thereby leaving some tumor behind in the hypothalamus to grow again with time.

The cystic craniopharyngioma poses an equally difficult problem, since some cyst wall may be left upon removal of the tumor. We have observed a higher recurrence rate

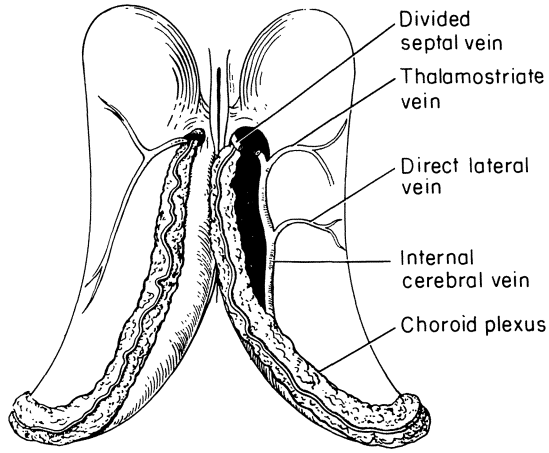

Figure 2. Exposure of the third ventricle.

in patients with cystic craniopharyngiomas than in those patients with solid tumors. Perhaps the best way of treating cystic tumors is with the installation of colloidal yttrium into the cyst. With time, the cyst seems to shrink away, according to Backlund.[7]

THE USE OF DEEP HYPOTHERMIA DURING SURGERY

Occasionally, for complex basilar aneurysms, we have resorted to deep hypothermia with cardiopulmonary bypass (Fig. 3). One case in which this was particularly useful was that of a young woman who had a large aneurysm at the basilar tip. At surgery, when a clip was applied to the neck, a massive hemorrhage ensued. Fortunately, it was possible to stop the hemorrhage with a second clip. However, a postoperative angiogram revealed persistent filling of the aneurysm. The problem was how to repair the aneurysm with two large clips precariously placed.

The patient was reoperated on 1 week later under deep hypothermia. The body temperature was lowered to an esophageal temperature of 20°C and a rectal temperature of 10°C. Prior experience indicated that the brain temperature was about halfway between that of the esophagus and the rectum. At this temperature the heart had stopped, and the patient was exsanguinated into the extracorporeal system. Removal of the clips showed that the first clip had perforated the aneurysm near the neck. The second clip had occluded the hole in the aneurysm but allowed persistent filling of the sac. We were able to apply a clip that occluded the aneurysm as well as the hole. The patient had an uncomplicated recovery from the surgery, and a repeat angiogram showed no filling of the aneurysm.

Many have experienced trouble using deep hypothermia—mostly from persistent bleeding at the end of the surgery, resulting in postoperative hematomas. We have not

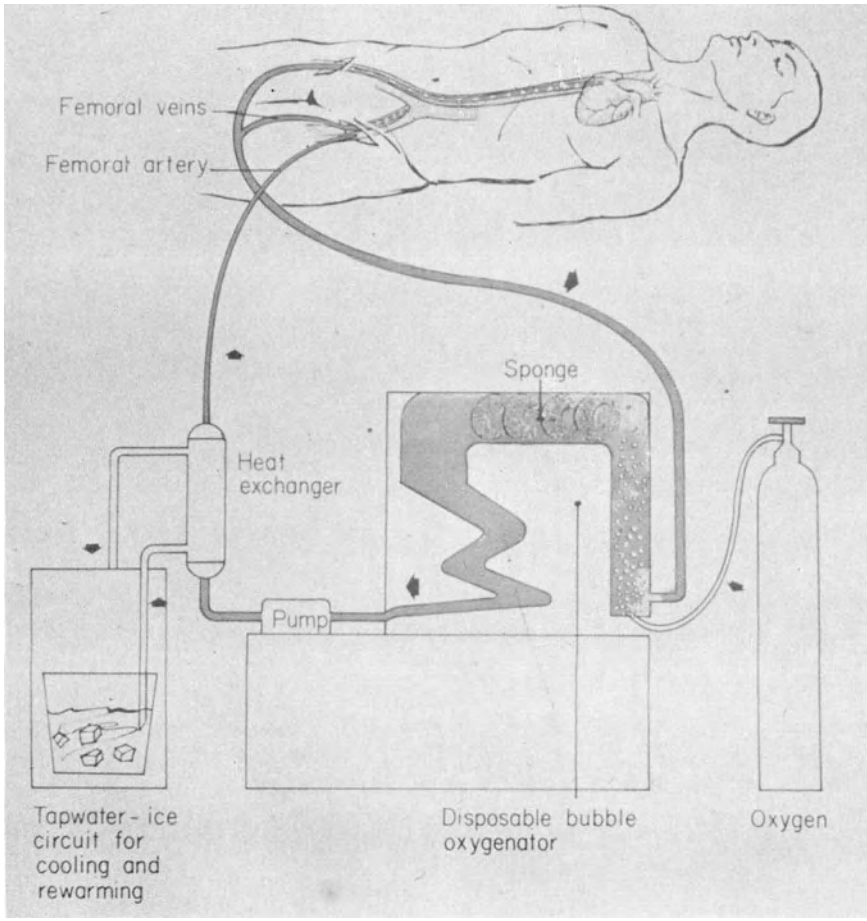

Figure 3. The extracorporeal circuit for deep hypothermia.

had any problem with this since we started using Epsilon aminocaproic acid (Amicar) during and after the procedure. We put 5 mg of this in the pump oxygenator and, following surgery, maintain a drip of 1 g/hr of the drug for 24 hr. With this regimen, we have seen no abnormal bleeding.

Deep hypothermia is not a technique that needs to be used frequently, but at times it can allow a kind of surgery that is not possible otherwise.

DISCUSSION

THE SUBCHOROIDAL APPROACH VIA TRANSCALLOSAL INCISION

Tew asks if we have experienced any difficulty with the subchoroidal approach via a transcallosal incision. We have not. Lavyne prefers the transcortical approach, splitting gyri

apart, because of the angle to the lesion. Certainly a consideration for favoring a transcortical approach over a transcallosal approach would be the anatomy of the parasagittal venous drainage in the region of the coronal suture.

ASPECTS OF PITUITARY TUMORS

Post indicates that with the 1.5 Tesla MRI unit one could delineate microadenomas of 2-mm size, but not smaller ones. He adds that, on the basis of a recently finished study of his using gadolinium with the MRI, the gadolinium is picked up by the normal pituitary gland and the tumor leaves a small hole in the gadolinium picture.

Petrosal Sinus Collections

Post points out that in place of petrosal sinus collections, one may use CRF stimulation, to distinguish ectopic sources of ACTH: Cushing's disease or basophilic tumors will stimulate while ectopic secreting tumors will not.

Unique Examples of Cerebral Metastases from Basophilic Adenomas

Patterson cites two patients with Cushing's disease who were operated upon 23 years ago. One was an 8-year-old boy with a third nerve palsy and the other a teenage girl. Postoperatively, the boy received radiation therapy and the girl did not. They both had an 18-year interval, during which they were asymptomatic. They both were reevaluated and found to have multiple cerebral metastases, which on biopsy proved to be histologically the same as their pituitary tumors of 18 years previously. They were both treated with whole-brain radiotherapy, with disappearance of all metastasies during the past 5 years. He also cites a third patient who has undergone surgery for her pituitary adenoma with skull, brain, and liver metastases.

Fukushima states that among the 600 to 700 cases at the University of Tokyo, he has never seen a metastasis from a treated adenoma.

Post indicates that Dr. Al Fleischer from New York University wrote about diffuse metastases, which looked like pituitary carcinoma on microscopic examination.

Pituitary Hyperplasia in Hypothyroidism

It should be emphasized that hypothyroidism may cause pituitary hyperplasia. Operation upon patients with enlarged pituitary glands in this case would result in finding normal tissue.

Complications with the Bypass Procedure during Hypothermia

Tew asks how benign the bypass procedure is. To answer, in the 50 cases we've performed, there were 2 deaths. One was a subintimal dissection in the groin that dissected upward and resulted in coronary artery occlusion. The second was due to rewarming in the sitting position, and there was resultant cerebral hypoperfusion.

The main problem during the rewarming has been bleeding. We have solved this by giving patients Amicar: five grams in the pump, and postoperatively at 1 g/hr for 24 hr. The Amicar completely controls bleeding.

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9

Chiasmatic–Hypothalamic Tumors in Children

Luis A. Rodriguez and Michael S. B. Edwards

INTRODUCTION

Gliomas of the optic pathway are usually reported as a single entity. Martin and Cushing[1] found 0.84% of 823 tumors in all age groups to be gliomas of the optic pathways. They noted difficulty in determining the site of origin of these tumors, since they often extend from the retro-orbital optic nerve and chiasm into the hypothalamus and vice versa. In children and adolescents the incidence (3% of 700 brain tumors)[2] of optic pathway gliomas is higher than in adults.

Approximately 75% of optic pathway tumors occur in patients less than 12 years of age[2,3] and 60% of these involve the chiasm and hypothalamus.[4,5] Posteriorly placed optic pathway tumors have a poorer prognosis than do those confined to a single optic nerve.[6] In this chapter, we review our experience with chiasmatic–hypothalamic tumors in children treated by the Department of Neurological Surgery of the University of California at San Francisco.

CLINICAL PRESENTATION

Chiasmatic–hypothalamic tumors occur primarily in children. An analysis of 33 cases treated at our institution demonstrated that the median age at presentation was 7 years, with a range of 5 months to 17 years.

Tables 1 and 2 summarize the presenting signs and symptoms. The most common symptom was decreased vision (29%), followed by headache (23%) and failure to thrive (20%). The last was seen only in infants less than 2 years of age and was invariably associated with the diencephalic syndrome of Russell.

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Table 1
Symptoms of Chiasmatic–Hypothalamic Tumors at Presentation

Symptom[a]	Number of patients	Percent of patients
Decreased vision	10	29
Headache	8	23
Failure to thrive	7	20
Nausea and vomiting	5	14
Abnormal eye movement[b]	5	14
Symptoms related to endocrine dysfunction	5	14

[a]Seven patients had more than one symptom.
[b]Initial complaint noticed by relatives.

The most common sign on initial examination was decreased visual acuity in one or both eyes and/or a visual field defect. Other findings included abnormal eye movement, loss of subcutaneous fat and low weight, ataxia, and signs of endocrine dysfunction (e.g., abnormal pubic hair or stature). In most patients, there were two or more associated signs and symptoms.

Small children, usually under 3 years of age, can present with diencephalic syndrome[7] (Russell's syndrome). This is characterized by marked emaciation and loss of subcutaneous fat—in spite of normal or increased appetite, alert appearance, increased vigor, and euphoria—pallor without anemia, and nystagmoid movements of the eyes. Sufferers have a normal height for their age. There might be elevation of growth hormone. This syndrome is usually not associated with neurofibromatosis.

Table 2
Signs of Chiasmatic–Hypothalamic Tumors at Presentation

Sign[a]	Number of patients	Percent of patients
Decreased visual acuity	11	33
Visual field defect	11	33
Optic atrophy	7	21
Abnormal eye movement[b]	7	21
Diencephalic syndrome	7	21
Signs of endocrine abnormalities	7	21
Ataxia	4	12
Papilledema	3	9

[a]Most patients had two or more clinical signs.
[b]Findings by examining physician.

Table 3
Endocrine Abnormalities Associated with Chiasmatic–Hypothalamic Tumors[a]

Type of endocrine dysfunction	Number of patients	Percent of patients
Precocious puberty	5	15
Growth hormone deficiency	5	15
Delayed puberty	3	9
Diabetes insipidus	3	9
Hypothyroidism	2	6
Panhypopituitarism	2	6
Hyperprolactinemia	1	3

[a]Seven patients had more than one type of endocrine dysfunction.

Endocrine abnormalities associated with chiasmatic–hypothalamic tumors are tabulated in Table 3. Fourteen patients (42%) had evidence of endocrine dysfunction, the most common of which were precocious puberty (15%) and growth hormone deficiency (15%). Other endocrine abnormalities included diabetes insipidus, delayed puberty, panhypopituitarism, and hypothyroidism. The majority of endocrine abnormalities were present at the time of diagnosis. Four patients developed endocrine dysfunction after their initial treatment: Two developed GH deficiency several years after treatment, the third developed diabetes insipidus immediately after surgery, and the fourth developed panhypopituitarism several years after treatment. Seven patients (50%) had more than one type of endocrine dysfunction.

HISTOLOGY

In 24 verified histological cases, we did not find any glioblastoma multiforme and only one patient had a highly anaplastic astrocytoma (Table 4). The two most common

Table 4
Histological Types of Chiasmatic–Hypothalamic Tumors

Histology	Number of patients
Juvenile pilocytic astrocytoma	9
Moderately anaplastic astrocytoma (MOAA)	11
Highly anaplastic astrocytoma (HAA)	2
Astrocytoma (not otherwise specified)	1
Ganglioglioma	1

histological types are juvenile pilocytic astrocytomas (nine patients) and low-grade anaplastic astrocytomas (11 patients). The moderately anaplastic tumors showed mild cellularity, minimal nuclear or cytoplasmic pleomorphism, very few mitotic figures, and on occasion abundant Rosenthal fibers.

DIAGNOSIS

The clinical presentation of visual and endocrine abnormalities in conjunction with failure to thrive is nearly pathognomonic of the diagnosis of a chiasmatic–hypothalamic mass. If there was associated hydrocephalus, which occurred in 60% of our patients, the presentation was that of increased intracranial pressure with headaches, nausea, and vomiting.

The diagnostic tests of choice are CT scan or MRI. In the last few years we have been utilizing MRI more frequently, because it provides better anatomical details of the location and extension of the tumor.

Complete ophthalmological and endocrine evaluation are performed in all patients at the time of diagnosis. This determines the need for hormonal replacement and helps in the assessment of response to therapy.

TREATMENT

Surgery

The different types of surgical procedures, at presentation and after initial treatment, performed in our 33 patients are summarized in Table 5. Most of the biopsies and partial resections were done through a frontal craniotomy. On two occasions a transcallosal approach was utilized, due to significant tumor extension into the third ventricle.

Among the 20 patients with hydrocephalus, 17 required shunts. Two patients did not require shunts after their hydrocephalus improved following partial resection of the tumor. One patient had mild hydrocephalus, which did not worsen on subsequent CT scans.

Biopsies and partial resections were performed after initial treatment failure, to reduce tumor mass, or when a previous histological diagnosis had not been made. Shunts were placed either at presentation or after initial treatment, depending on changes in the ventricular size and/or if the patient's intracranial hypertension persisted. Because of the critical location of these tumors, total excision is impossible without major morbidity. Symptomatic improvement can be offered to patients after partial resection. Due to the small number of our patients treated with partial resection, as opposed to biopsy or only a shunt procedure, it is impossible to assess whether surgery on the tumor mass has any impact on tumor progression or survival. Previous reports in the literature have failed to show any benefit from surgery.[6,8] We have had no mortality and minimal morbidity associated with surgery. There has been no loss of

Table 5
Surgical Treatment
of Chiasmatic–Hypothalamic Tumors

Type of surgery[a]	When performed	
	At presentation	After initial treatment
Partial resection	7	4
Shunt	2	5
Biopsy	5	1
Biopsy and shunt	2	1
Partial resection and shunt	4	3

[a]Six patients had surgery at presentation and at tumor prognosis.

vision related to surgical exploration and, except for postoperative diabetes insipidus and one intraventricular hemorrhage, there were no other significant deficits.

Lymphomas, germinomas, pituitary tumors, teratomas, and craniopharyngiomas, among others, can occur in the suprasellar–hypothalamic region and can be erroneously mistaken for gliomas. The need for histological diagnosis, the potential benefit of reducing tumor burden, and the low morbidity and mortality associated with current neurosurgical techniques justify surgical exploration for biopsy and/or partial resection. Symptomatic unresolved hydrocephalus is clearly an indication for a shunting procedure.

Radiation

Twenty patients in our study received radiation therapy as part of their initial treatment, and in four patients radiation therapy was administered at recurrence. Patients received local radiation administered with a median dose of 54 Gy (range: 43–60 Gy). Radiation was withheld in five of nine infants under 2 years of age and in five of seven patients with neurofibromatosis.

The median time to tumor progression (TTP) for patients who received radiation therapy as their initial treatment was 70 months, compared to 30 months for those patients who did not receive radiation as part of their initial treatment. This difference was statistically significant ($p < 0.05$) (Fig. 1). Since most of the patients are still alive, statistical conclusions regarding the effects of radiation on survival are not possible at this time.

Clinical and/or radiographic improvement was seen in 11 of the 24 (45%) instances in which radiation was utilized. Disease stabilization was achieved on another 11 occasions, and only two patients continued to have progression of their tumor immediately after irradiation. Improvement or disease stabilization was therefore achieved in 22 of 24 (91%) cases after radiation therapy.

The use of radiation therapy for hypothalamic–chiasmatic gliomas has been the

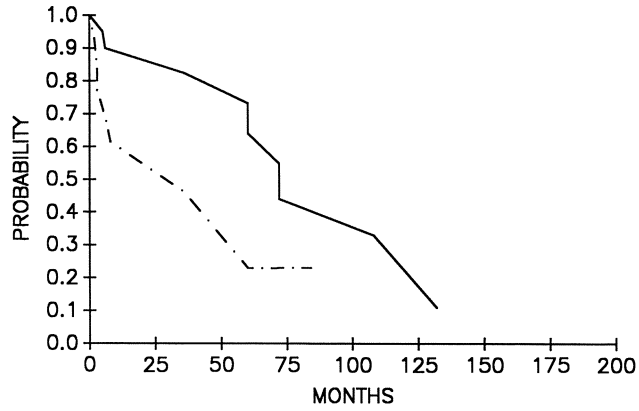

Figure 1. Kaplan–Meier representation of time to tumor progression in patients treated with (solid line) and without (dashed line) radiation therapy.

subject of great controversy. Some reports indicate significant improvement after radiotherapy,[9–11] while others have not observed any benefit.[12,13] In our series were several patients with objective improvement in their visual acuity and visual fields, and complete resolution of diencephalic syndrome occurred in some of the infants following radiotherapy. Even though there is significant evidence in the literature that radiation improves symptoms and decreases the chances of tumor progression, evidence is lacking in terms of its benefits on survival. After a mean follow-up of 20 years in 28 patients, Imes and Hoyt[14] were unable to demonstrate improved survival due to irradiation. In a series of 38 patients, Wong et al.[6] found that radiation significantly improved the recurrence rate from 86% in the nonirradiated group to 45% in the irradiated group. However, there were no differences in survival. Currently, we are not able to document improved survival as a result of radiation. Large numbers of patients, followed for prolonged periods of time, will be necessary to resolve this question.

Chemotherapy

Five patients in our study received chemotherapy as an initial treatment. Chemotherapy was given at recurrence in 11 cases. One patient received three different types of chemotherapeutic regimens because of progression of his disease.

Chemotherapy induced clinical and/or radiographic improvement on five occasions and stabilization on five occasions. Six patients continued to progress in spite of chemotherapy. Improvement or disease stabilization was therefore achieved in 10 of 16 (62.5%) cases after chemotherapy.

The use of chemotherapy for the management of chiasmatic–hypothalamic tumors is a relatively novel approach. Rosenstock et al.[15] treated 16 patients with actinomycin D and vincristine. Four patients were treated at recurrence and 12 patients were newly diagnosed and did not receive radiation therapy. Rosenstock and his

colleagues were able to stabilize or improve the disease in 12 of the 16 patients. Most of our patients received combination chemotherapy based on nitrosoureas, since we have used these drugs against other childhood gliomas with significant responses. The results of our treatment with chemotherapy is encouraging. Three of our patients received chemotherapy at presentation without irradiation. One recurred after 3 months, but the other two had clinical and radiographic improvement and are doing well 1 and 2 years after diagnosis. Two patients treated at recurrence, who had stabilized, have not progressed even after 4 and 6 years of follow-up. Currently, chemotherapy is not justified as adjuvant treatment for these tumors, but it may play a significant role when there is progression after radiation therapy. It should also be considered as an alternative to radiation therapy in young children, for whom radiation entails considerable risk.

PROGNOSIS

In spite of reports in the literature categorizing chiasmatic–hypothalamic tumors as slow-growing indolent lesions,[16] they do cause death and significant neurological deficit. Packer et al.[17] reported the outcome in 21 children with chiasmatic gliomas. These authors found a 48% recurrence rate at a median time of 6 years after diagnosis, with a 5- and 10-year actuarial survival of 89% and 60%, respectively.

Our 5- and 10-year survival probability for hypothalamic tumors in children are 93.5% and 74%, respectively. Two of the deaths occurred in patients with neurofibromatosis. The recurrence rate seen at our institution is 54% with a median TTP of 60 months.

There was no mortality and only minimal morbidity related to surgery, radiation, or chemotherapy. Twenty-nine out of 33 patients remain alive, and 24 are functional, with Karnofsky scores $\geq$ 70%. Some of these patients are clinically normal, while a few have mild endocrine abnormalities, mild-to-moderate visual impairment, mild mental retardation, nystagmus, or low weight. There are five patients at a nonfunctional level, mostly due to severe mental retardation or severe visual impairment.

Of great importance is the fact that these tumors can recur even after many years of stabilization, subsequently leading to death. This occurred in one of our cases, and has been reported by Imes and Hoyt.[14]

Some reports suggest that patients with neurofibromatosis may have tumors that behave in a more benign fashion,[13,18,19] although others have found contradictory evidence.[8] Imes and Hoyt[14] reported that patients with neurofibromatosis and chiasmatic tumors had the same mortality as did patients without neurofibromatosis; however, most of the deaths in neurofibromatosis patients were related to other central nervous system malignancies and not to their chiasmatic tumors. Among our seven patients with neurofibromatosis, two died—one from multiple gliomas of the cerebrum while his chiasmatic tumor remained stable, and the other from his chiasmatic tumor. There were five patients who did not receive any treatment. They are all alive after several years of follow-up, and four of them have not progressed.

Our experience suggests that these tumors indeed appear to behave in a more benign fashion in patients with neurofibromatosis, and conservative management in these patients may be justified.

SUMMARY AND CONCLUSIONS

Children with chiasmatic–hypothalamic gliomas have a better prognosis than do children with gliomas in other locations, but death and severe neurological deficits can and do occur. Radiation therapy is of significant benefit in tumor management and can decrease the time to tumor recurrence, although the impact on survival is still unclear. Chemotherapy can effectively decrease or stabilize tumor size: It should be considered as an alternative treatment to radiation therapy in infants and children, for whom radiation entails considerable risk, and is also of benefit in patients that have progressed after radiation therapy.

Patients with neurofibromatosis have a benign course, and conservative management is justified in most of these cases.

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10

THE THIRD VENTRICULAR REGION

Some Aspects of Third Ventricular Tumor Surgery

A. N. Konovalov

INTRODUCTION

The topic of this volume—diencephalic lesions—is a very serious and difficult one. The surgery of lesions located in different parts of the diencephalon, especially of third ventricular tumors, is a subject of special interest at present. In the past few decades some important results have been achieved in this field.

I was very much impressed by the splendid book *Surgery of the Third Ventricle,* compiled and written by Dr. Michael L. J. Apuzzo,[1] and I am honored to have been a participant in this work, which comprises the most important information concerning third ventricular surgery and thoroughly describes practically all the new surgical approaches. Nevertheless, some aspects of this very difficult problem need further elaboration.

Surgery of third ventricular tumors is one of the major topics of scientific interest at the Moscow Institute of Neurosurgery. Quite a large number of different tumors located in the diencephalic region have been operated upon, particularly in the last few decades. These include craniopharyngiomas, gliomas, giant pituitary adenomas penetrating into the third ventricle, basal meningiomas, and some others.

I would like to present the results of my personal experience with the surgical treatment of third ventricular tumors and discuss some of the problems associated with their removal. I will deal only with tumors of the anterior third ventricle, some of which are represented in Table 1. The most common type of tumor found in our study was the craniopharyngioma. I would like to stress that anterior third ventricular craniopharyngiomas represent only one third of all craniopharyngiomas, which are divided into three groups: endosuprasellar, suprasellar–extraventricular, and third ventricular. The last is further divided into two subgroups: 1) craniopharyngiomas located predominantly in the cavity of the third ventricle and 2) tumors that grow both in the cavity of the third ventricle and extraventricularly.

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Table 1
Microsurgery of Third Ventricular Tumors[a]

Age group and histology	Approach			Total cases
	Transcallosal	Transcortical	Subfrontal	
Children				130
Craniopharyngiomas	40	5	55	100
Gliomas	19	2	6	27
Others	1	2	–	3
Adults				87
Craniopharyngiomas	10	6	32	48
Gliomas	9	12	4	25
Others	11	3	–	14
Total cases	90	30	97	217

[a]Sampling of cases over the years 1974–1986.

The second large group is made up of glial tumors, which can be subdivided into 1) those predominantly located in the third ventricle and 2) tumors of both the chiasm and the third ventricle. Tumors located in both extraventricular and intraventricular compartments compel the surgeon to use various approaches.

APPROACHES AND SURGICAL TECHNIQUES

There are different approaches to tumors of the anterior third ventricle, all of which are thoroughly described in Apuzzo's book.[1] The general rule seems to be that the best approach is any approach a surgeon is accustomed to using.

For this reason we attempted to determine the relative efficacy of the different approaches we utilize in our practice. These are the subfrontal (trans-lamina terminalis), the transcallosal, and the transcortical approaches (see Table 1).

At the beginning of our study, practically all patients were operated on by the subfrontal/trans-lamina terminalis route, accompanied, if necessary, by a subchiasmal and trans-opticocarotid triangle access. This approach was performed in 97 cases (mostly in patients with craniopharyngiomas).

Nearly the same number of patients (90) were operated on by the transcallosal route.

Less often, we operated on patients with third ventricular tumors through the anterior horn of the lateral ventricle. This method has the disadvantage of an oblique angle, which makes it difficult to visualize the entire cavity of the third ventricle. For this reason, this approach will not be discussed.

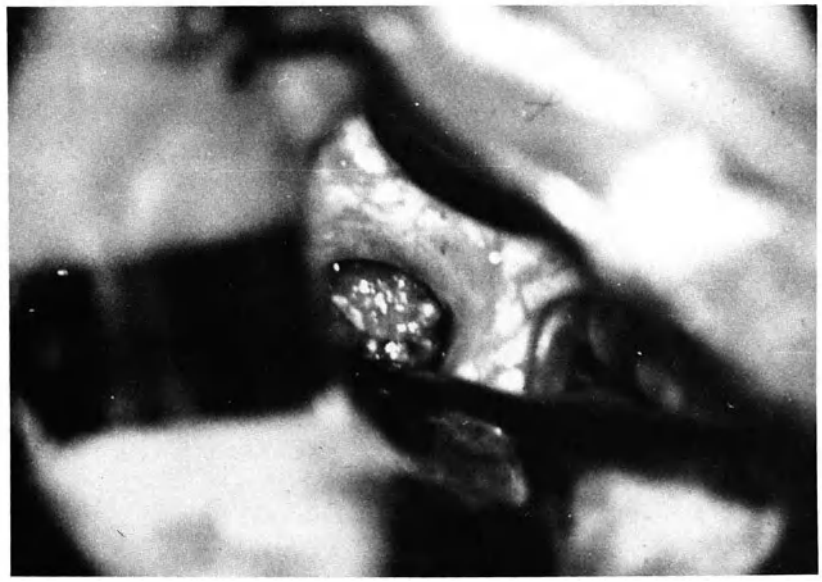

Figure 1. Removal of a suprasellar craniopharyngioma via the lamina terminalis.

Subfrontal (Trans-Lamina Terminalis) Approach

With the subfrontal (trans-lamina terminalis) approach, usually only small anteriorly located tumors can be radically removed. This route does not permit visualization of the upper and posterior portions of the third ventricle. One important stage of craniopharyngioma ablation is the removal of suprasellar calcification (Fig. 1). It is necessary to accomplish this in the early stages of the operation, because only after that can the solid part of a tumor and its capsule be mobilized, separated from the ventricular walls, and removed.

Transcallosal Approach

After section of the corpus callosum, a tumor can be removed through one or both foramina of Monro (Fig. 2), or through the fornix by splitting the columns of the fornix strictly in the midline (Fig. 3). Our experience shows that the transforniceal approach usually does not produce a pronounced or long-lasting memory disturbance.

The transcallosal route makes it possible to visualize all parts of the third ventricle. This approach permits radical removal of tumors located in the cavity of the third ventricle, and beneath its floor, in the overwhelming majority of cases (Fig. 4). Following the removal of such a tumor the basilar artery, its branches, and the sella turcica are usually exposed (Fig. 5).

Some portions of extraventricularly located tumors lying anteriorly or in a para-

Figure 2. View of the upper pole of a tumor through the foramen Monro.

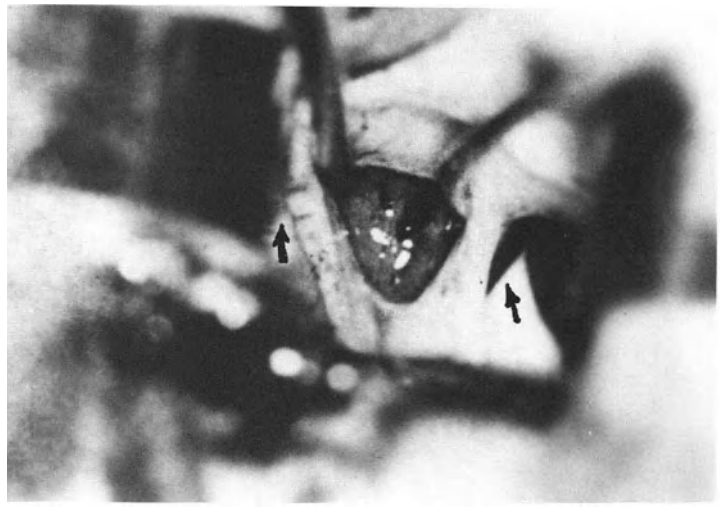

Figure 3. Approach to a tumor of the third ventricle via the splitting of the fornix columns. Foramina of Monro are indicated by arrows.

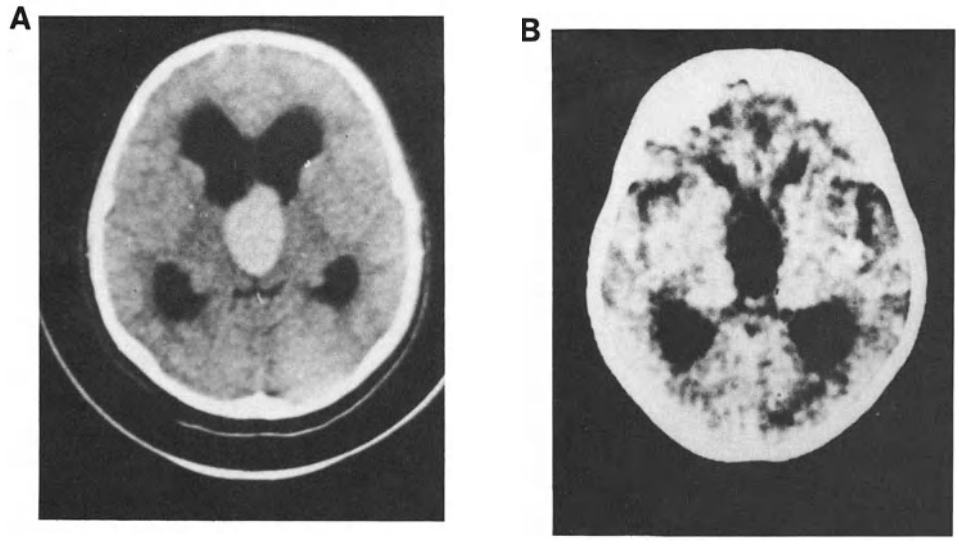

Figure 4. CAT scan of a patient before (A) and after (B) total removal of craniopharyngiomas through the corpus callosum.

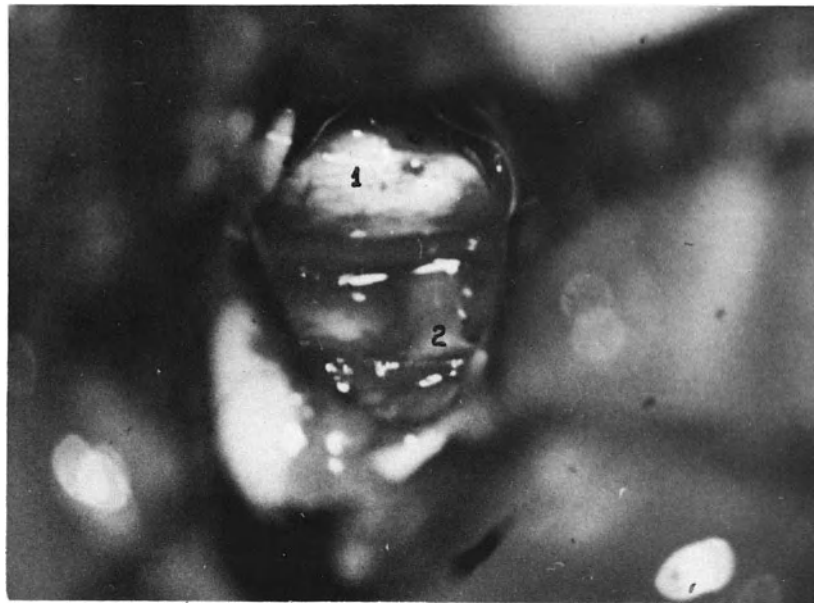

Figure 5. View of the operation field after removal of the extraventricular part of a tumor by the transcallosal approach. The dorsum of the sella turcica and the basilar artery, with its branches, are seen.

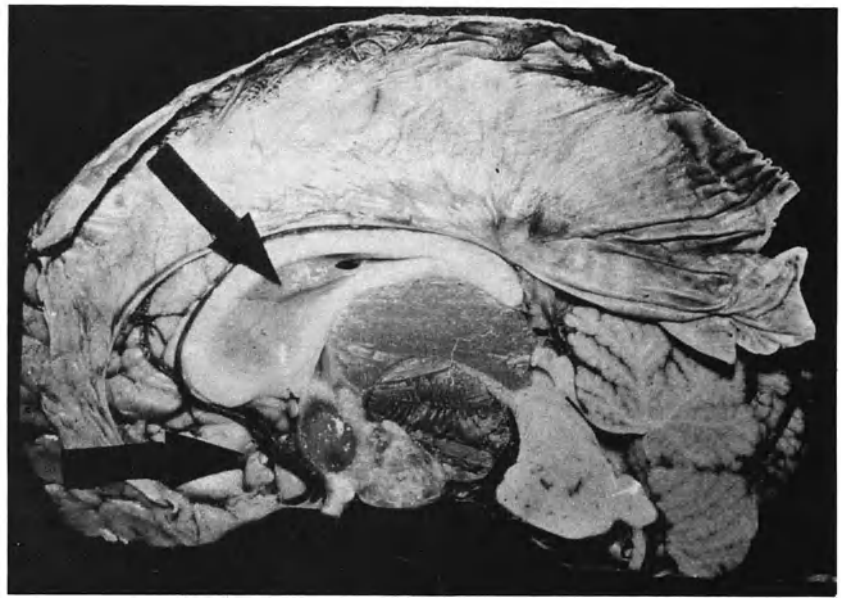

Figure 6. The direction of transcallosal (upper arrow) and subfrontal (lower arrow) approaches. (The patient, who had a large intraventricular craniopharyngioma, died before surgery.)

sellar position can't be reached solely by means of the transcallosal approach. In these cases, we use the combined transcallosal and subfrontal approach, which permits radical tumor removal (Fig. 6). In such cases we make either one large or two small bone flaps (Fig. 7). CT and MRI imaging usually enables us to decide, before surgery, in which case combined access for radical tumor removal may be necessary.

CRANIOPHARYNGIOMA SURGERY: EFFECTIVENESS OF DIFFERENT APPROACHES

To compare the effectiveness of the transcallosal and subfrontal (trans-lamina terminalis) approaches, consider two practically identical groups of patients: (1) 40 children with craniopharyngiomas whose tumors were removed via a lamina terminalis approach, and (2) 40 children whose craniopharyngiomas were removed through the corpus callosum. A comparison of results using these two approaches, and the transcortical approach, appears in Table 2.

We differentiate three degrees of radical tumor removal: (1) total, where the tumor is removed completely as visualized under the microscope; (2) subtotal, where small parts of tumor capsule remain adherent to the walls of the ventricle or to important blood vessels and are not removed; and (3) partial removal, where the substantial solid part of the tumor, its capsule, or suprasellar calcification are not removed.

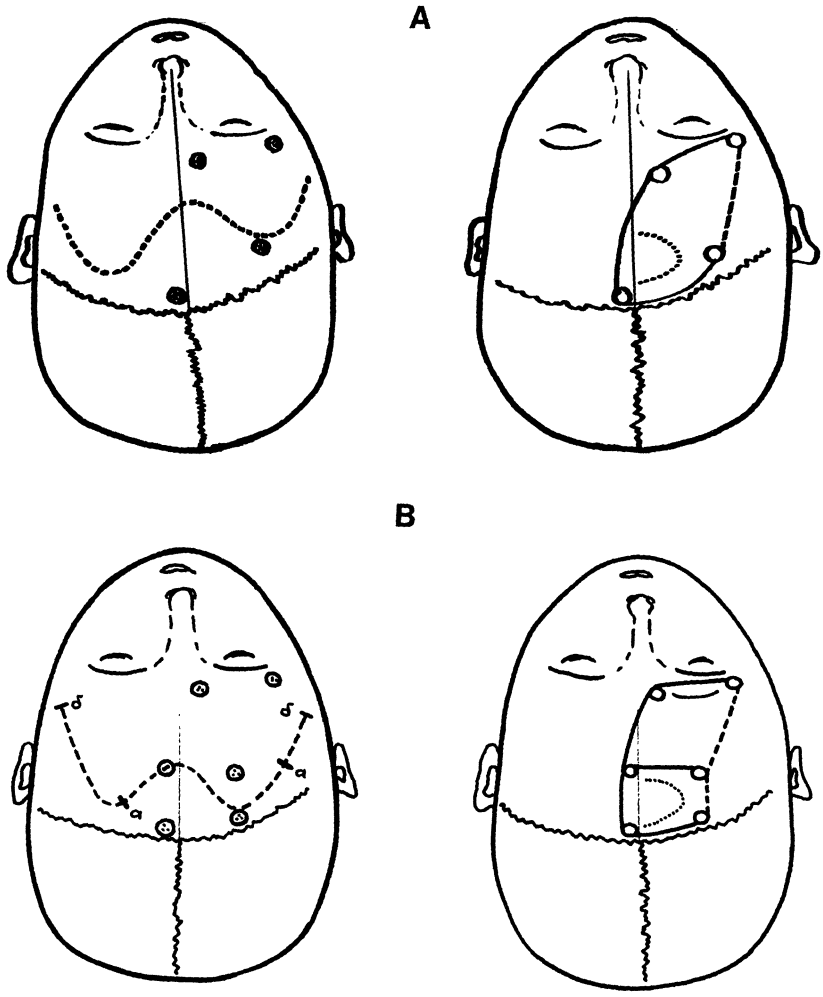

Figure 7. Scheme of skin incisions (A) and bone flaps (B) used for combined transcallosal approach.

An evaluation of the radicality of tumor removal during surgery is not easy in all cases. At any rate, this judgment does not differ very much from the results of postoperative CT controls.

From Table 2, one can see that the degree of radical tumor removal was much higher when transcallosal or combined approaches were used, as compared with the subfrontal approach alone. In addition, tumor recurrence was more frequent when the subfrontal approach was used exclusively. During an equivalent period of time—about 3 years—the tumor recurrence rates were 55% and 14%, respectively, for subfrontal and transcallosal approaches. The mortality rate, which is very high overall (about 20%), is practically the same in each group of patients. These results seem to show the advantages of the transcallosal approach in craniopharyngioma surgery.

Table 2
Microsurgery of Third Ventricular Craniopharyngiomas in Children[a]

Surgical approach	Number of operations	Type of removal			Rate of recurrence	Cases of postoperative mortality
		Total	Subtotal	Partial		
Transcallosal (combined[b])	40 (20)	28	11	1	14%	6
Transcortical (combined[b])	5 (5)	–	1	4	100%[c]	3
Subfrontal	40	7	15	18	55%	8
Total cases	85 (25)	35	27	23	–	17 (20%)

[a]Sampling of cases over the years 1979–1986.
[b]Combined with subfrontal approach.
[c]In both of two cases observed.

THIRD VENTRICAL GLIOMA SURGERY

Glial tumors of the third ventricle can also be removed using a transcallosal or combined approach in cases where tumors infiltrate the optic chiasm as well.

A quite substantial group of tumors are the giant gliomas of the optic chiasm, which often penetrate into the cavity of the third ventricle (Fig. 8). There can be

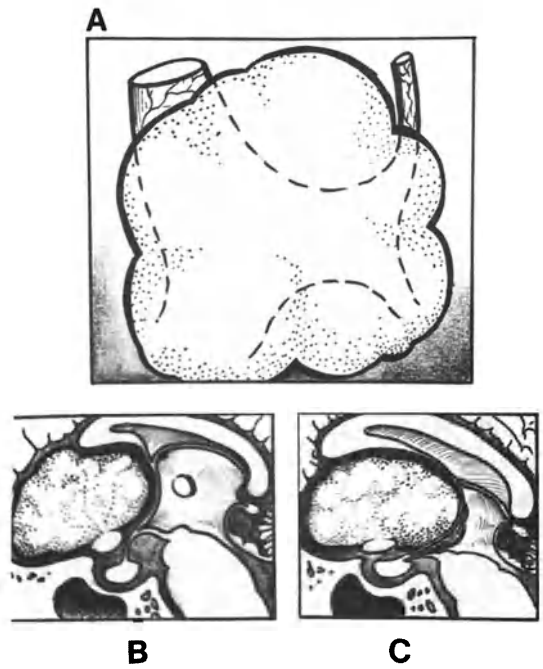

Figure 8. Types of growth of giant gliomas of the optic chiasma. (A) tumor as viewed from above; (B) tumor displaces the third ventricle; (C), tumor penetrates into the third ventricle.

variations in the tumor's growth pattern. Some of the tumors are exophytic and well circumscribed; others have infiltrative growth and spread along the visual pathways.

Our experience shows that giant gliomas of the optic chiasm can be quite radically removed with partial preservation of the visual pathways (Fig. 9). Table 3 shows the results of surgical removal of 16 giant optic chiasm tumors.

One should note that after tumor removal in some cases, vision is not worsened and may even be improved. After resection of the anterior part of the tumor, the part that penetrates the third ventricle can be mobilized and removed as well. In these cases, there is usually no necessity for the additional use of the transcallosal approach. The most difficult part of these operations is the separation and preservation of important cerebral arteries (e.g., the internal carotid artery and anterior cerebral artery), which may be embedded in the tumor tissue.

Indications for surgery in our cases included increased intracranial pressure, rapid deterioration of visual acuity, and, in some cases, deterioration of the patient's general health. We consider the problem of criteria of contraindications to be a very difficult problem in the management of giant tumors.

COMPLICATIONS

A major problem associated with third ventricular surgery is that of the complications of surgery. In spite of marked improvements in surgical technique, which include microsurgery, ultrasonic aspiration (Cavitron), and preoperative judgments regarding the best surgical approach, the results of radical third ventricular tumor removal are still far from satisfactory; for intraventricular craniopharyngiomas in particular, the mortality rate is a bit less than 20%—that is markedly higher than in other groups of craniopharyngiomas. We are very interested in this problem and are trying to discover the explanation for such a high mortality rate.

The problem of complications in the postoperative period is very complex. Therefore I will pay attention to only those facets which seem to us to be of great importance.

Cerebral Vessel Changes

Pathomorphological studies of the brains of operated and even unoperated patients with craniopharyngiomas reveal widespread and extremely profound changes in the cerebral vessels, especially in the arteries of the circle of Willis. These include

1. Chronic destructive changes, such as subendothelial fibrosis (Fig. 10) and deformation of the internal elastic membrane (Fig. 11), which are accompanied by stenosis of the arteries and partial thrombosis. These changes develop as a sequela of the illness itself.
2. Acute changes appearing during surgery or in the postoperative period, developing on the substrate of the chronic changes mentioned above. We have found morphological signs of long-lasting spasm (Fig. 12), acute dissecting

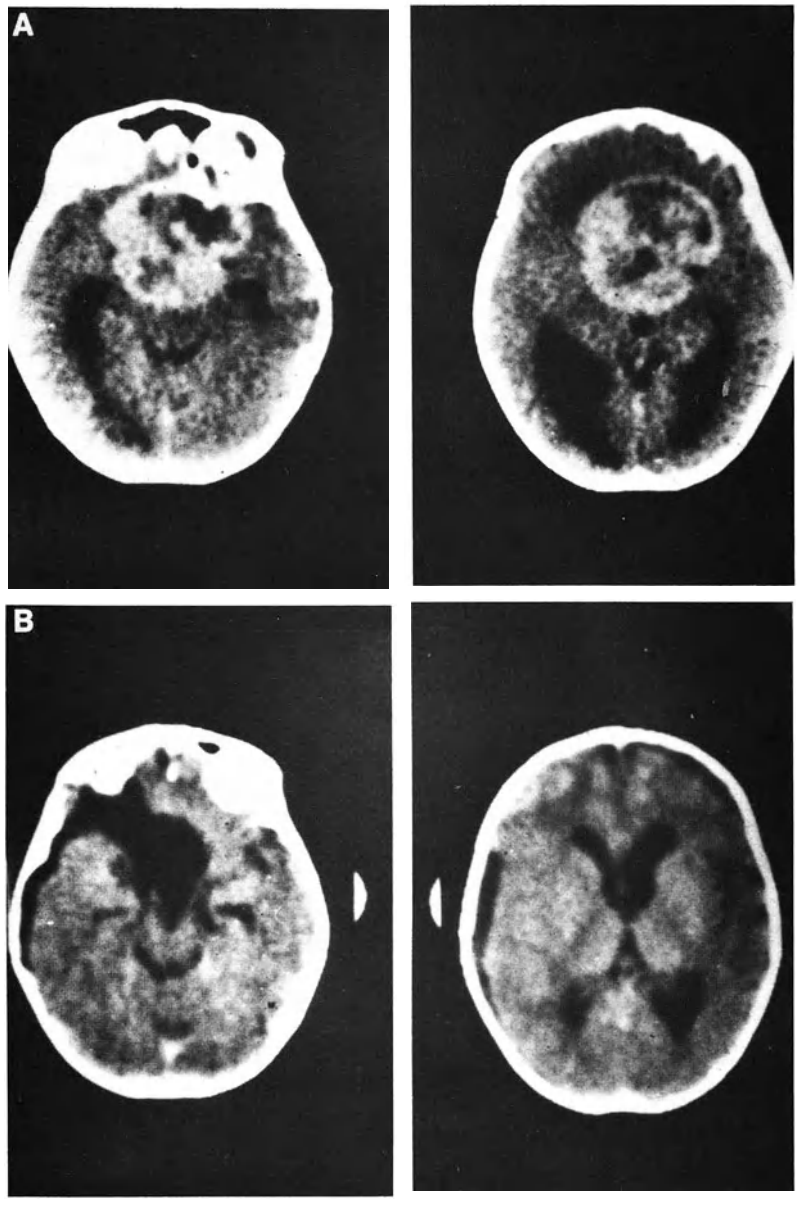

Figure 9. CAT scans of a patient with a giant glioma of the chiasma penetrating into the third ventricle before (A) and after (B) total removal of the tumor.

Table 3
Results of Surgery in 16 Cases of Optic Chiasm Tumors

Result of surgery		Number of cases
Death		1
Vision	Worsening	4
	Without change	8
	Improved	3

aneurysms with partial or total occlusion of the parent artery (Fig. 13), and acute arterial thrombosis (Fig. 14).

Chronic changes in the walls of the arteries lead to insufficient blood supply and increasing hypoxia of the brain tissue. In addition, chronic changes create preconditions for the development of acute disturbances, which in turn cause multifocal ischemic lesions of the brain (Fig. 15).

We have tried to find an explanation for this vascular pathology, as we consider it to be the most common cause of death.

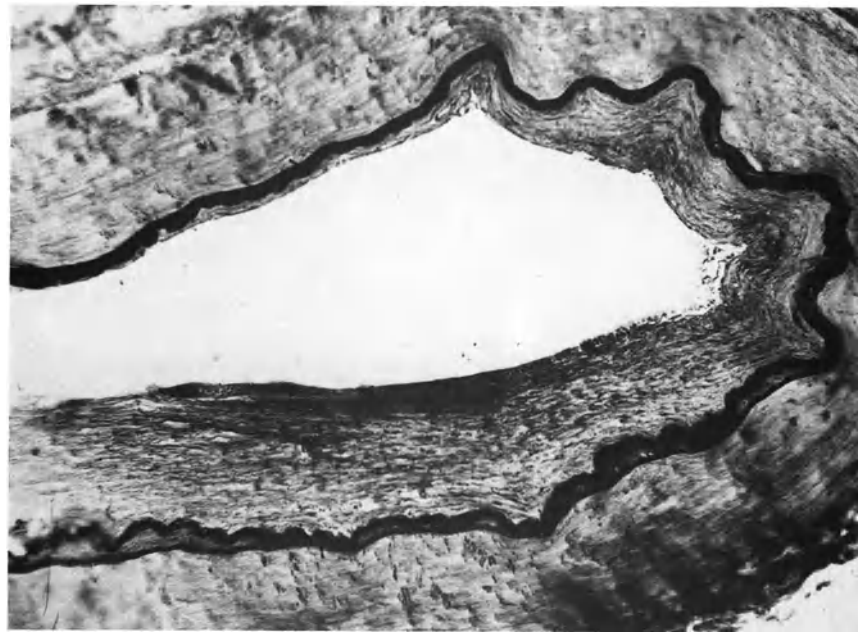

Figure 10. Marked subendothelial fibrosis of the basilar artery, shown using hematoxylin–eosin staining. (×200.)

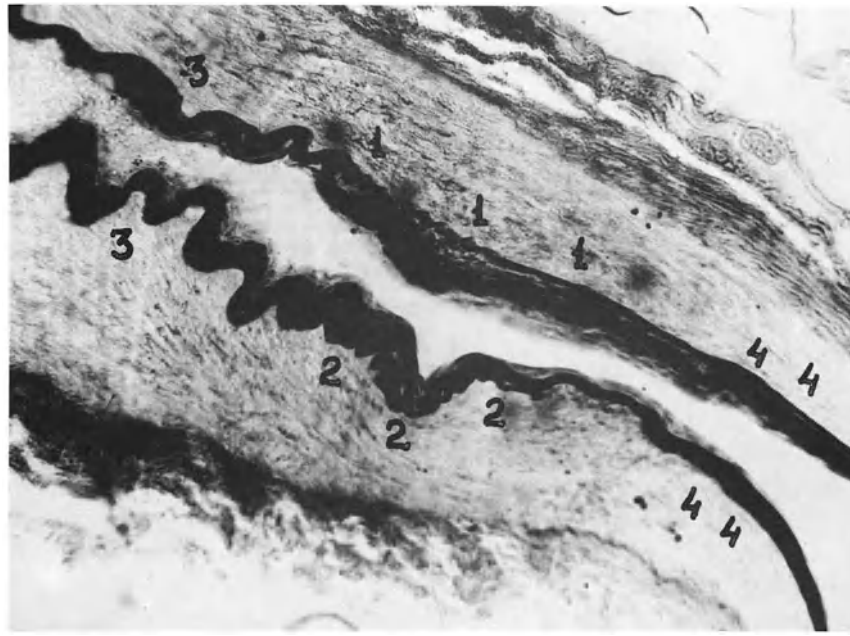

Figure 11. Chronic changes of the internal elastic membrane of the internal carotid artery: thickening (1), exfoliation (2), disturbances of rhythmic arrangement of folds (3), and disappearance of folds (4). Shown using resorcin–fuchsin staining. (×200.)

In some fatal cases we have found a circumscribed hemorrhage or clot in the bottom of the third ventricle, in places where main arterial branches supplying the tumor are localized.

It is possible that in these cases a clot, closely related to the perforating branches—or sometimes to the main trunk—of the basilar and posterior communicating arteries, produces long-lasting arterial spasm (as in cases of ruptured arterial aneurysms), which may explain the cerebral ischemic lesions. Taking these facts into consideration, we are now very careful to control even the slightest bleeding at the end of the surgical procedure.

We also try, whenever possible, not to damage the arachnoid membrane—Liliquist's membrane—which serves to separate the operative field from the basilar artery. Whether or not this is helpful has not yet been resolved.

To determine basal arterial reactions during tumor removal from the third ventricle, we have begun to evaluate the state of the arteries by means of a transcranial Doppler. Our experience is limited at present, but in some cases transcranial Doppler measurements have revealed changes typical of arterial spasm. These changes corresponded to the clinical deterioration of the patients.

It is interesting that in some patients who were examined before surgery we were also able to find signs of arterial spasm.

The second most important cause of hemodynamic disturbances is the water–

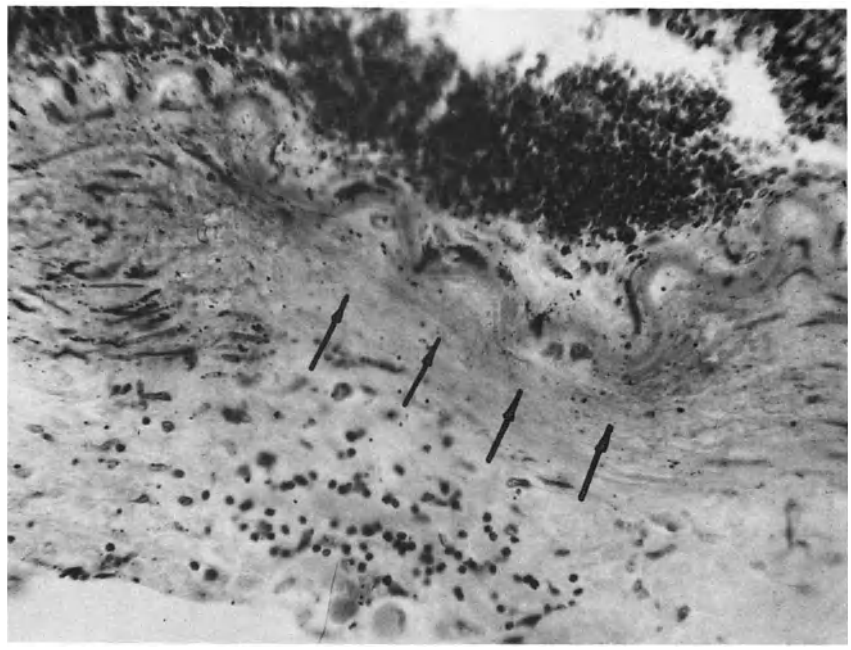

Figure 12. Morphological signs of long-lasting spasm in the walls of the anterior cerebral artery: foci of necrosis in the middle layer (arrows). Shown using hematoxylin–eosin staining. (×300.)

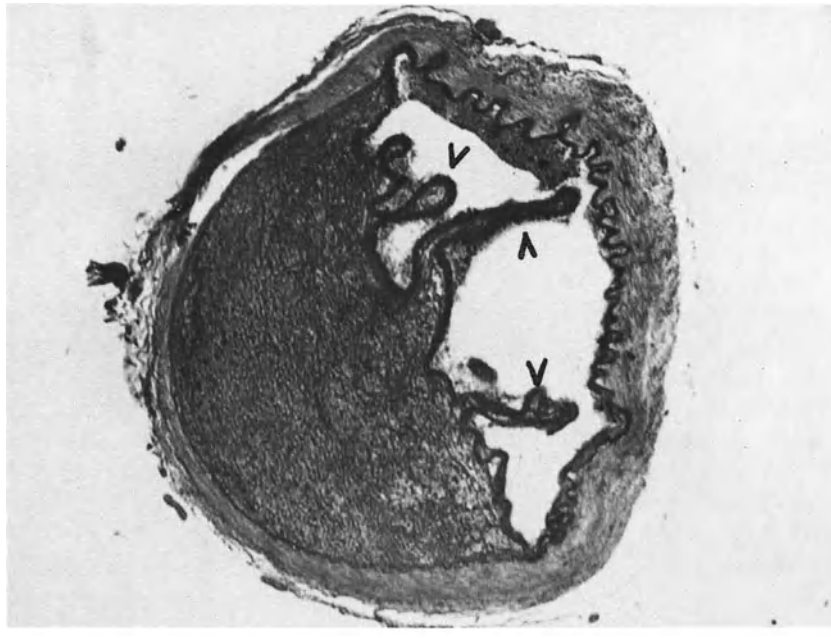

Figure 13. Acute dissecting aneurysm of the internal carotid artery with subtotal occlusion of the artery. Arrows indicate splitting of the internal elastic membrane. (×40.)

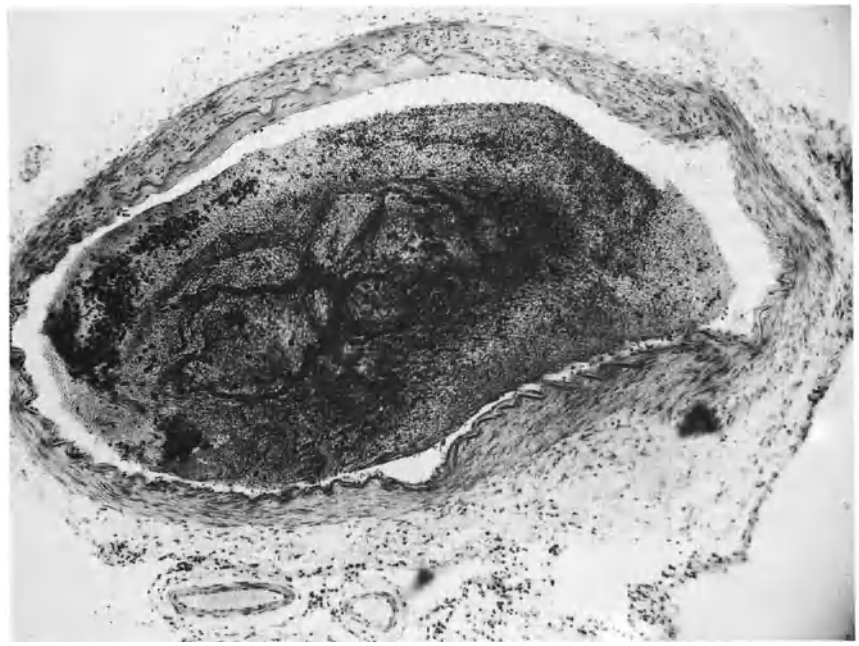

Figure 14. Acute thrombosis of the middle cerebral artery, shown using hematoxylin–eosin staining. (×100.)

electrolyte imbalance produced by hypothalamic lesions, particularly by lesions of the pituitary stalk, which result in signs of diabetes insipidus.

These changes, as mentioned above, are typical of craniopharyngiomas. After radical third ventricular craniopharyngioma removal, there usually was aggravation of water–electrolyte imbalance; the more pronounced clinical signs were found in patients presenting with severe water–electrolyte imbalance.

The hyperosmolar–hypernatremic syndrome is a direct consequence of anterior hypothalamic damage. The absence of thirst is a typical symptom in the postoperative period, and is caused by the failure of the so-called "neural circle" of thirst to function. The absence of thirst significantly increases the severity of dehydration and osmolarity disturbances.

In contrast, after removal of giant chiasmatic gliomas we observed signs of antidiuretic hormone (ADH) hypersecretion—the syndrome of inappropriate secretion of ADH, or SIADH—accompanied by a drop in blood osmolarity, low sodium levels, and the appearance of cerebral edema, which resulted in coma. We found this phenomenon in more than 25% of our cases.

Thorough investigation of metabolic disorders following tumor surgery of the third ventricle, and their adequate correction, is one of the most important ways of improving surgical results.

In conclusion, I would like to mention another of our observations—a rare case of

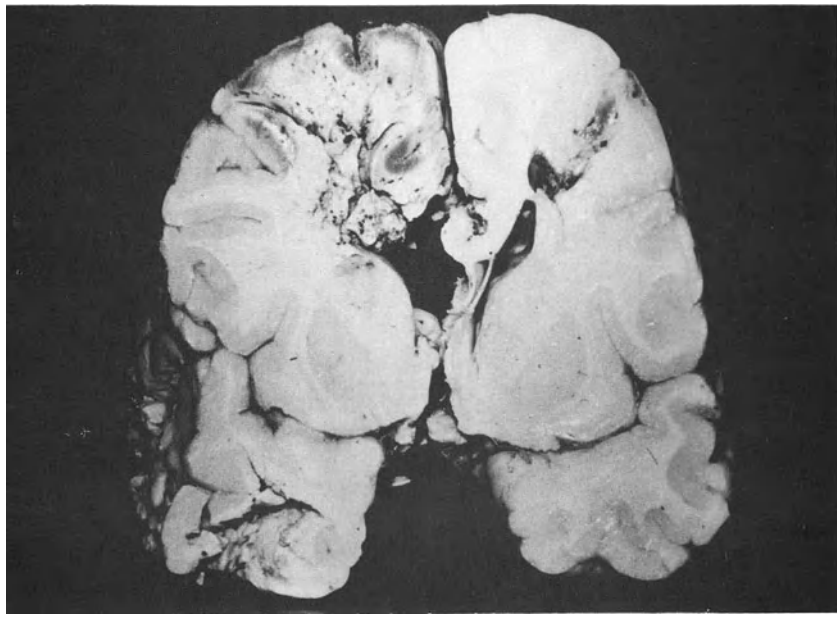

Figure 15. Multifocal infarctions in the parietal and temporal lobes, developed as a sequela (see Fig. 13) of the insufficiency of blood circulation.

cavernous angioma of the third ventricle that penetrated the adjacent structures of both the thalamus and midbrain.

Before surgery the patient was very drowsy, despite placement of a ventricular shunt, and was practically bedridden. After tumor removal her state worsened and for several days she remained stuporous. Investigations revealed the virtual absence of catecholamines, which may help to explain the patient's very low level of activity. This observation underlines the importance of the thorough control of bioamines in patients with third ventricular tumors.

We have taken only the first steps in the surgery of third ventricular tumors. There is much more to be done to achieve better results.

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11

THE THIRD VENTRICULAR REGION

Lesions of the Third Ventricle and the Surrounding Structures

Vinko V. Dolenc

INTRODUCTION

In the period from 1983 through 1987 a series of 95 patients were treated at our Neurosurgery Department for lesions in and/or around the third ventricle. In the majority of patients, disturbances or even a complete blockage of the passage of CSF accounted for the first typical symptoms and signs of hydrocephalus.

In a smaller number of patients, symptoms and signs were due to irritation, compression, or destruction of the cerebral tissue itself. This symptomatology was caused predominantly by lesions of the chiasm hypothalamus and/or lamina quadrigemina.

At this department, no patient had a shunting procedure performed either immediately before or after the main operation.

The lesion was amenable to complete removal in 70 cases. In 25 cases it was removable to such an extent that the CSF circulation was re-established via normal pathways.

All the patients included in the study were operated on at this department. The lesion was benign in 65 cases and malignant in 30 cases.

Of the 95 patients operated, three died, 23 showed increased neurological and/or endocrinological deficits, and 69 were improved.

PATIENTS AND METHODS

Our series included 45 females and 50 males, aged 3–45 years. Extracerebral lesions were found in 30 patients, of whom three harbored giant carotid–ophthalmic

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aneurysms, two had arteriovenous malformations (AVMs), and 25 had craniopharyngiomas. Twenty-eight patients had tumors of the cerebral tissue surrounding the third ventricle; tumors were situated in the hypothalamus in five patients, in the thalamus in four, and in the pineal region in 19 patients. Lesions involving only the third ventricle were found in 37 patients. In 52 patients the lesion was correctly located prior to their referral to this department. Forty-three patients were admitted because of markedly expressed signs of increased intracranial pressure (ICP), and the lesion was found only after admission. In all patients, the final diagnosis was confirmed by computed tomography or magnetic resonance imaging.

Thirty-six patients in our series had one or more previous surgical interventions performed at other institutions, consisting of a shunt operation and/or partial resection of the tumor. Patients with hypothalamic disorders underwent routine preoperative hormone testing and ophthalmological examination, including checking of the fundi and investigation of visual field defects as well as determination of visual acuity. In 31 patients, visual evoked potentials were monitored prior to and after surgery. EEG was routinely performed in all cases, while carotid and/or vertebral angiography was carried out only occasionally.

Candidates for the interhemispheric–transcallosal approach to the third ventricle whose condition allowed the procedure had psychological testing prior to and after surgery. In extracerebral lesions, craniopharyngiomas (Fig. 1), carotid–ophthalmic aneurysms, AVMs, and tumors of the chiasm, either a pterional approach[1,2] or a modified pterional approach[3,4] was used. Four patients presenting with a craniopharyngioma situated in the third ventricle or its wall, with its solid part located in the suprasellar and retrosellar region (Fig. 2), were treated by a combined interhemispheric–transcallosal and pterional operative approach, accomplished in one or two sessions.

In lesions confined to the third ventricle (Fig. 3), in tumors of the foramen of Monro (Fig. 4), and in tumors expanding from the third ventricle through the foramen of Monro to the lateral ventricle, the interhemispheric–transcallosal approach was used in all cases.

The interhemispheric–transcallosal approach was also used in patients with a hypothalamic tumor causing serious impairment of vision and almost complete destruction of the hypothalamus (Fig. 5), in order to preserve the residual visual function.

A suboccipital subtentorial approach in the midline[5] was considered to be the most suitable technique in the majority of lesions of the pineal region (Fig. 6). A small number of pineal tumors, as well as all lesions of the posterior thalamus (Fig. 7) and of the posterior lateral wall on either side of the third ventricle that extended toward the lateral ventricle, were treated by the occipital supratentorial approach along the line joining the falx and the tentorium.[6] This approach to the lesion included a routine incision of the frontal part of the tentorium.

RESULTS

Of the 30 patients with extracerebral lesions, two patients died—one 3 months after complete excision of a giant carotid–ophthalmic aneurysm, and one 2 days

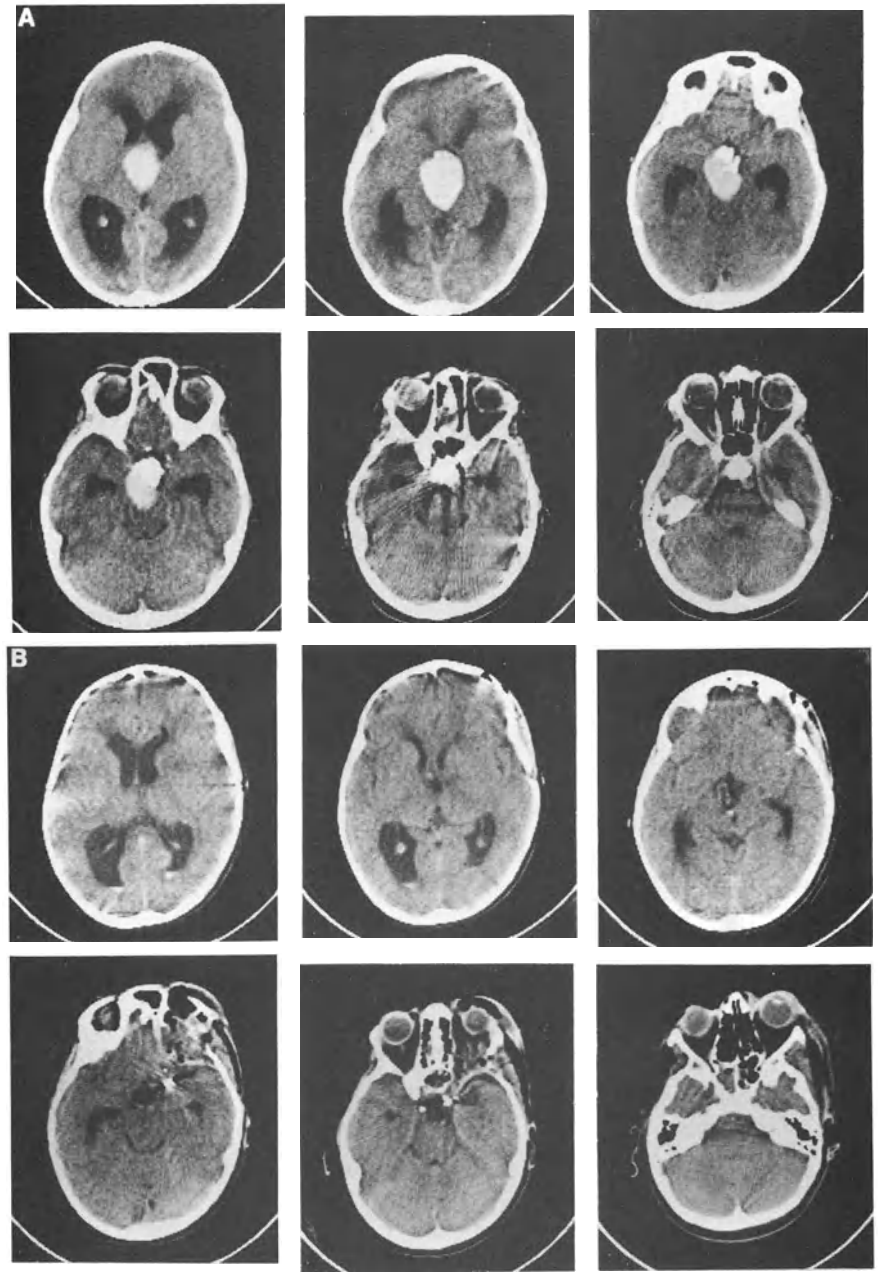

Figure 1. (A) CT scans of an 8-year-old girl, demonstrating a large, partially calcified craniopharyngioma and hydrocephalus. (B) CT scans of the same patient on the first postoperative day, showing no tumor and no significant reduction in the size of the ventricles.

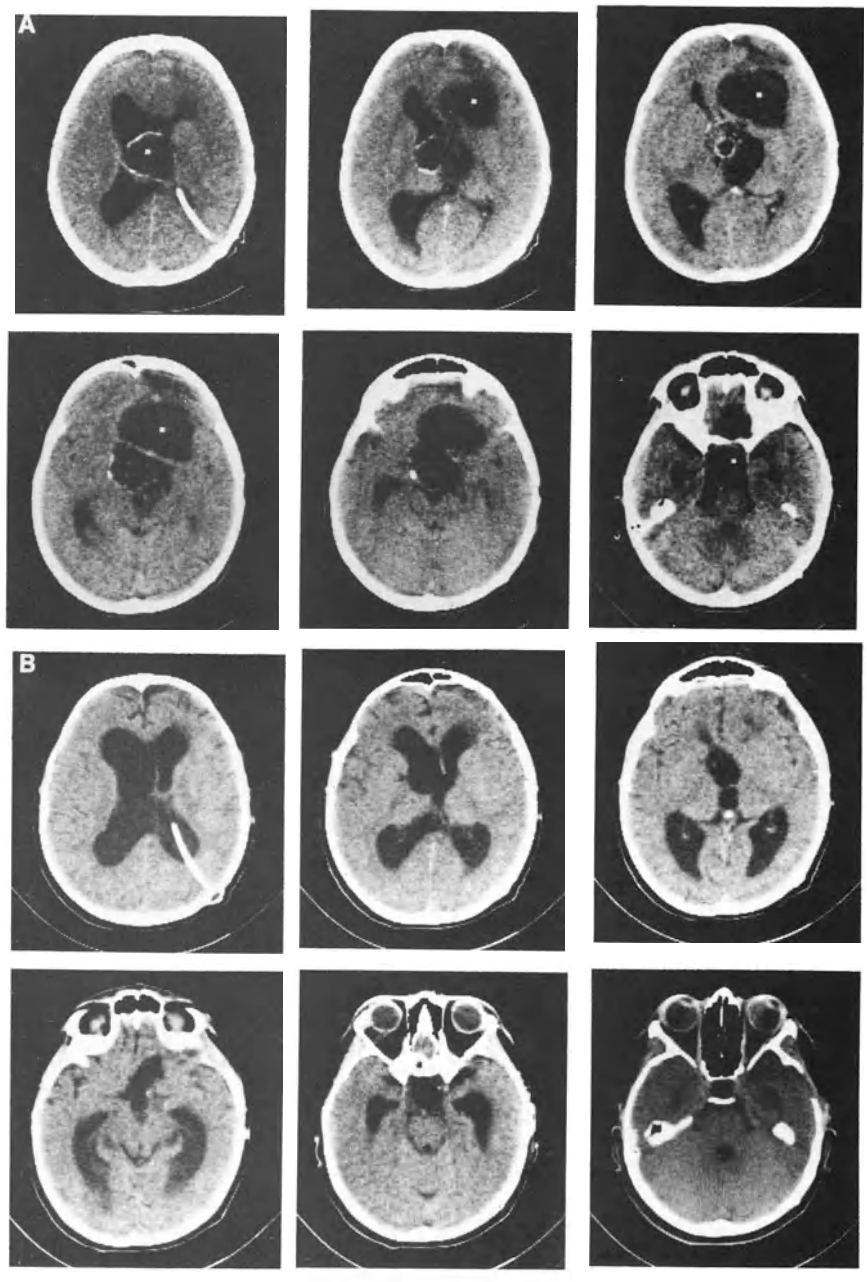

Figure 2. (A) CT scans of a 13-year-old boy, demonstrating a cystic craniopharyngioma following a shunt operation and biopsy. (B) CT scans of the same patient 2 months following a combined surgical procedure (interhemispheric–transcallosal and pterional approach), demonstrating no residual tumor.

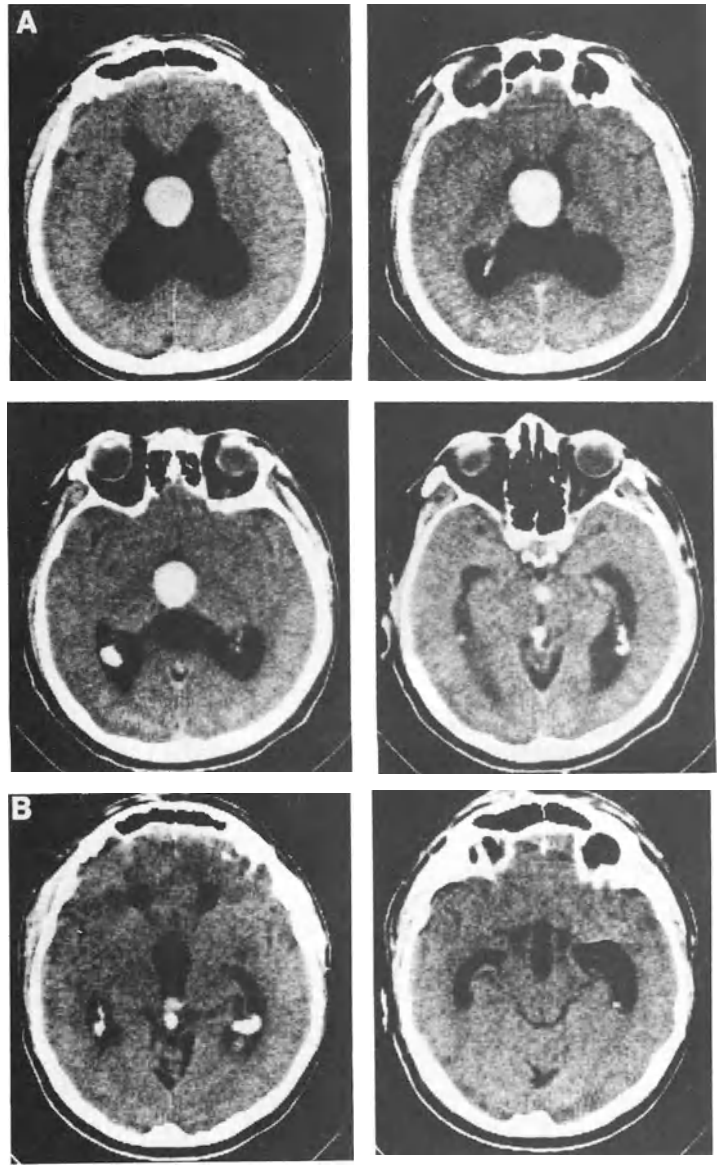

Figure 3. (A) CT scans of a 61-year-old man, demonstrating hydrocephalus and a round-shaped lesion in the third ventricle, characteristic of a colloid cyst. (B) CT scans of the same patient 2 days following surgery, showing no lesion in the third ventricle.

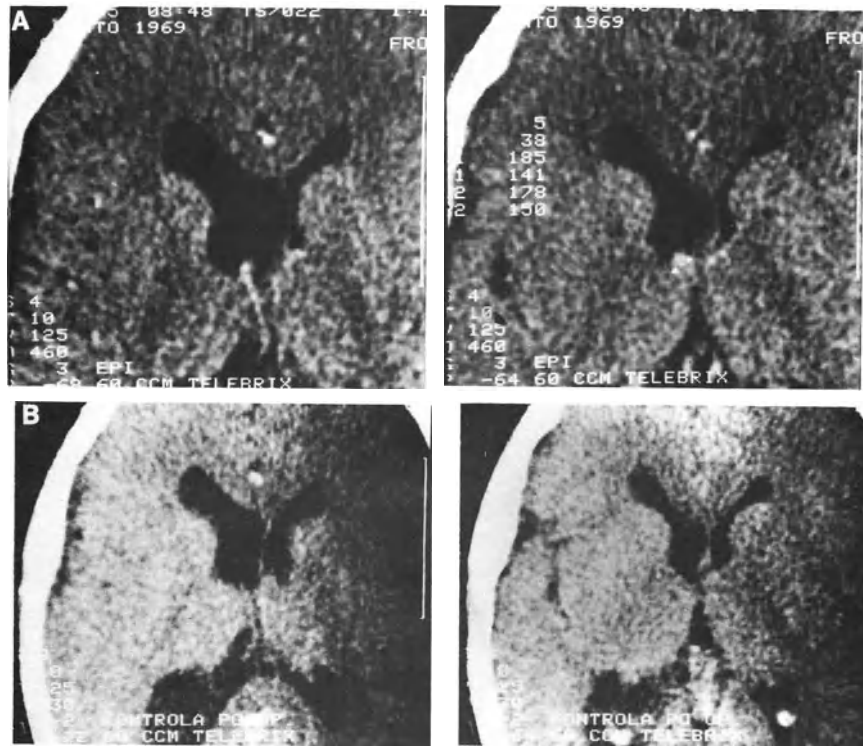

Figure 4. (A) Contrast-enhanced CT scans of a 16-year-old boy, demonstrating dilatation of the left lateral ventricle and a small lesion in the left foramen of Monro. (B) Postoperative CT scans of the same patient, demonstrating a notable reduction in the size of the left ventricle and absence of tumor at the left foramen of Monro.

following complete excision of a craniopharyngioma (Fig. 1). In all cases of giant carotid–ophthalmic aneurysms, AVMs, and craniopharyngiomas, complete excision of the lesion was carried out.

Twenty out of the 30 patients who underwent excision of an extracerebral lesion markedly compressing the hypothalamus had transient (15 patients), or permanent (5 patients) endocrinological disorders, which always included diabetes insipidus.

In all five cases of cerebral hypothalamic lesions (low-grade astrocytomas), the only safe surgical procedure was subtotal excision. Postoperatively, the endocrinological disorders remained unchanged, or were even more pronounced than prior to surgery. However, the postoperative course was good in all patients receiving substitution therapy. Lesions confined to the third ventricle were amenable to complete excision in all cases of colloid cysts (Fig. 3) and choroid plexus tumors (Fig. 4).

Tumorous lesions originating in the wall of the third ventricle were excised down to the site of origin, but were not completely removed. In five of these cases reoperation was necessary. Similar operative results were obtained in tumors arising from the thalamus, lateral ventricle, or corpus callosum and growing into the third ventricle,

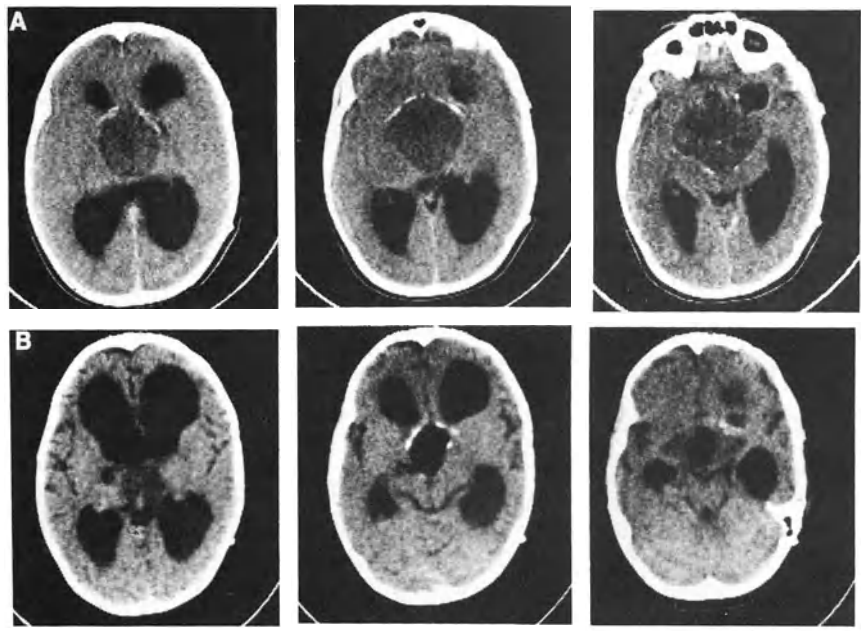

Figure 5. (A) CT scans of a 6-year-old boy, demonstrating a large hypothalamic tumor after surgical treatment including two partial excisions of the lesion and a shunt procedure. (B) CT scans of the same patient 1 month after subtotal resection of the tumor, demonstrating a postoperative cyst and a residual calcified capsule.

which could be treated safely only by subtotal excision. AVMs were amenable to complete excision. Three of the 37 patients treated by interhemispheric–transcallosal surgical resection developed sequelae due to an operative trauma to the fornix, while 34 patients of this group made an excellent recovery and showed no postoperative neurological deficits.

Four patients with infiltrative tumorous lesions of the pineal region could be safely treated only by partial surgical excision, while in 15 cases the lesion was completely removed. One patient, who had a benign tumor of the pineal region completely excised, died 2 months after the operation due to infection. Three patients presented with a few-month history of neurological deficits following complete extirpation of a tumor of the lamina quadrigemina. Their leading signs included loss, or at least impairment, of consciousness, speech problems, impaired motor coordination, and Parinaud's syndrome. Fourteen out of the 19 patients operated on for a tumor of the pineal region made a rapid and complete recovery.

CONCLUSION

Clinical features of lesions situated in the third ventricle and the surrounding structures are too numerous to be discussed in more detail in this report.[7] Owing to the

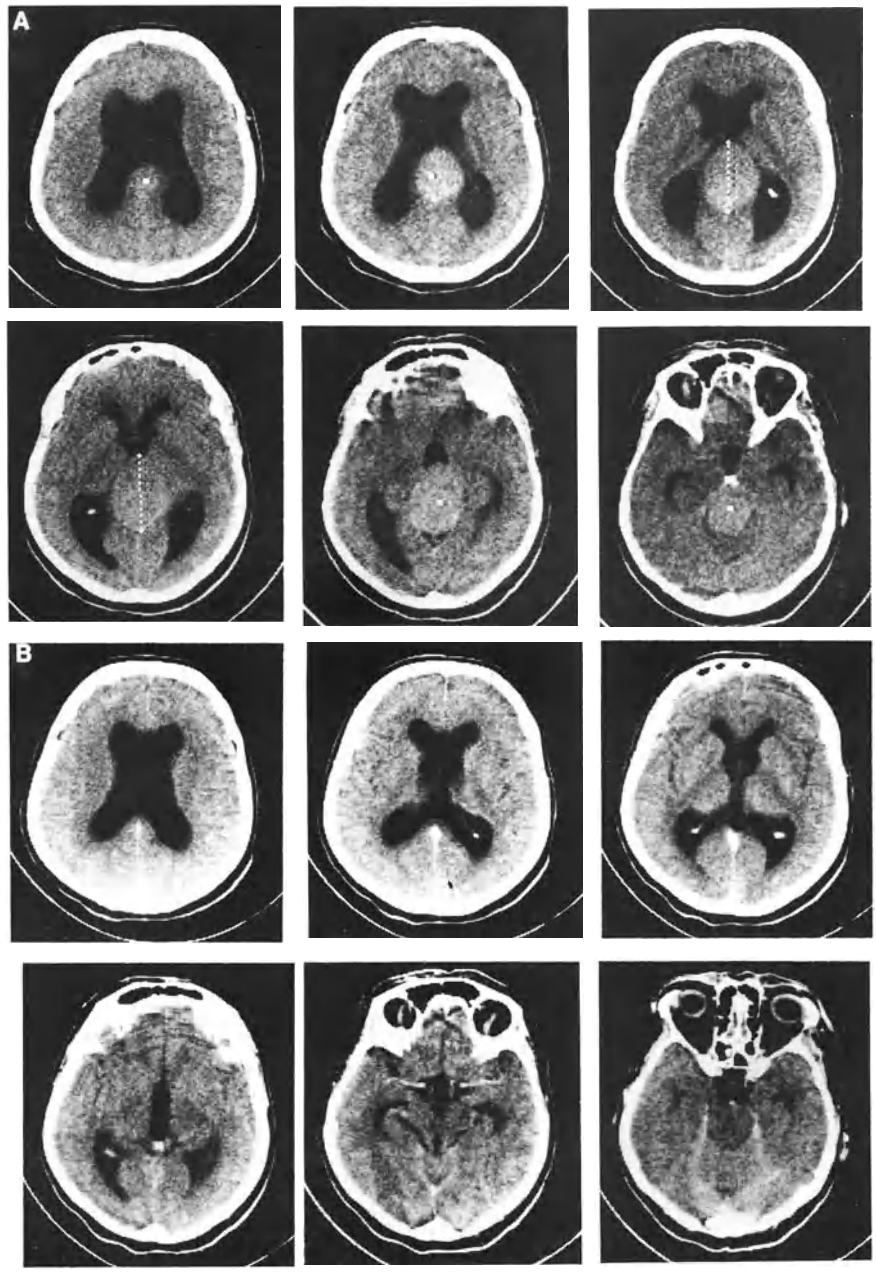

Figure 6. (A) CT scans of a 44-year-old woman, demonstrating meningioma of the pineal region and hydrocephalus. (B) Postoperative contrast-enhanced CT scans of the same patient, showing no residual tumor and no hydrocephalus.

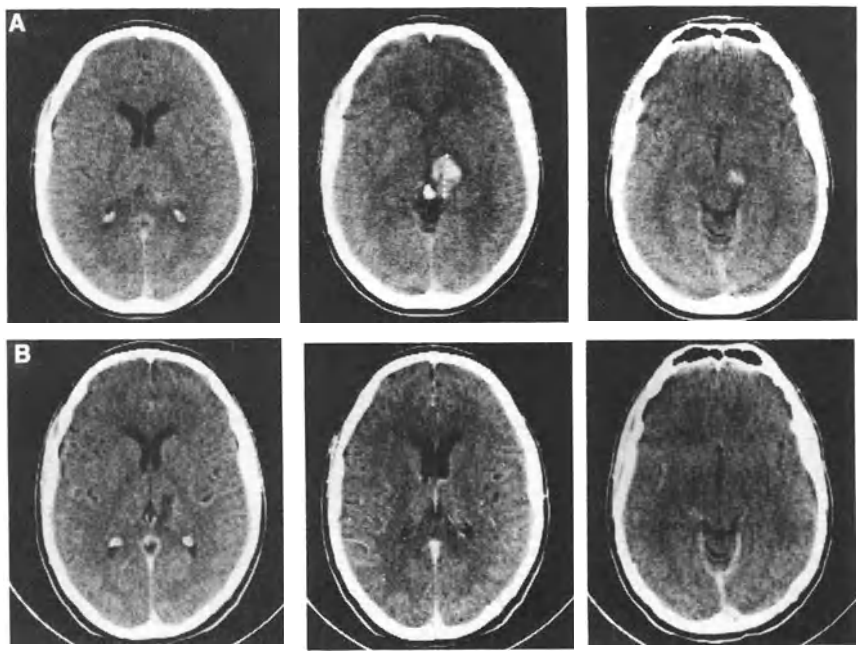

Figure 7. (A) CT scans of a 36-year-old man, demonstrating a small, hyperdense lesion in the right thalamus. (B) Postoperative contrast-enhanced CT scans of the same patient, demonstrating a postoperative cyst and no residual cavernoma or hematoma.

diversity and variety of symptoms, very careful attention should be given to obtaining an inclusive history from the patient and from relatives.

A CT and/or MRI scan cannot make up for a vague history and an incomplete neurological examination, and can even lead to erroneous decisions about therapy. It goes without saying that a CT or MRI scan cannot replace a histological examination.[8,9] In one of our cases (Fig. 5), a number of mistakes were made because of an incomplete history and wrong conclusions drawn from insufficient premises. The patient's history as given by his mother included deterioration of vision and headache, and a CT scan demonstrated a large tumor. The findings were interpreted as typical of a glioma of the optic nerve. Consequently, this patient was operated on by a pterional approach in two different institutions. In both hospitals the same histological diagnosis—glioma of the optic nerve—was established. The lesion was therefore thought to be inoperable and the patient was treated only by a shunt operation.

Postoperatively the child got worse, and his mother was referred to this department. When asked about the first symptom of her son's disease, she remembered that at the age of 6 months he began to refuse food and drink, which led to a considerable loss of weight. He was kept alive by forced nutrition. The information that the neuroendocrinological disorder occurred before visual impairment was of utmost importance for further planning of therapy.

We suspected that a hypothalamic tumor was responsible for the condition and that it compressed the chiasm, the optic nerves, and both optic tracts. The tumor was

subtotally resected through an interhemispheric–transcallosal approach. Histologically, the tumor was a Grade I astrocytoma. Prior to surgery the patient was confined to bed and showed marked disturbances of consciousness, but on appropriate substitution therapy given postoperatively, his condition improved and at discharge he was able to walk without support.

It would be beyond the scope of this presentation to deal with the manifold histological picture of tumors located in the third ventricle and the surrounding structures.[9,10] Yet, we cannot deny the fact that in these cases histology is a reliable diagnostic tool, provided that a sufficient number of specimens, taken from different parts of the tumor, are available for evaluation.

A direct approach to the lesion is therefore superior to stereotactic biopsy, except in those easily diagnosable cases (e.g., germinomas) in which chemotherapy and radiotherapy, rather than surgery, are indicated.

Generally, on the basis of microsurgical evaluation of the tumor and study of the frozen section, the most suitable therapy is devised for each particular patient, and it is decided to what extent the lesion can be safely removed.

We support the concept that in order to restore a normal CSF flow, it is better to remove the tumor than to insert a shunting system. We would point out here that in addition to the well-known complications of shunt operations, in malignant tumors the possibility of artificial dissemination of tumorous cells should always be kept in mind.

Highly elaborate surgical approaches to the third ventricle and the surrounding structures, which make use of the most advanced technologies, present no difficulties to a skilled neurosurgeon.[3,5–7,11] They make complete and atraumatic removal of a number of lesions possible and guarantee a complete cure of benign lesions. Proper positioning of the patient and the use of modern operative techniques and instrumentation make it possible for the surgeon to remove even giant tumors of this region without retracting the brain (Fig. 6). Yet, complete removal of a benign extracerebral tumor does not necessarily predict an excellent outcome of treatment. The associated neuroendocrinological disorders can pose unsurmountable metabolic problems and may even be fatal.

Although refined operative techniques are available for the treatment of lesions situated in the third ventricle and the surrounding structures, a successful outcome of treatment is sometimes compromised by a number of complex, still uncontrollable, pathophysiological mechanisms arising in the immediate postoperative period.

Therefore, treatment of these pathologies should not be left only to a neurosurgeon, but should be given by a well-coordinated team of specialists, including an endocrinologist.

DISCUSSION

VISUAL PRESERVATION AND RECOVERY FOLLOWING SELLAR AND THIRD VENTRICULAR SURGERY

For those not experienced with the phenomenon, I'd like to present a case regarding preservation of existing vision at the time of surgery and the recovery of vision after radical operation. This case involves a woman with endocrinological disturbances who was admitted to

the hospital and found to have a mass in the chiasmatic area. In 1952 or 1953, in Belgrade, she had been vaccinated against tuberculosis and suffered a number of complications from the vaccine. The patient suffered blindness and then recovered her vision.

The mass was densely calcified, and on histological examination was found to be a tuberculoma. The patient's vision was very poor before the operation and afterward she became blind. Visual evoked potentials and classical ophthalmological testing confirmed complete loss of vision. Remarkably, her vision began to return and, though it is still not perfect—it is a small central vision—she can move about freely, care for herself, and lead a useful life.

In view of our experience, we now routinely perform pre- and postoperative ophthalmological assessment to provide documentation regarding visual acuity and visual field changes that might occur during surgery.

Konovalov feels that the question of visual loss is complex because it is not only a reflection of optic nerve compression and increased intracranial pressure. Often after tumor removal from the third ventricle, there is improvement in visual acuity; conversely, there may be a decrease in visual acuity if the preoperative acuity was poor. In some patients with extremely poor vision before surgery, postoperative blindness is more likely. In his opinion, if a third ventricular tumor is approached via a transcallosal route without touching the chiasm, there is usually no change in visual acuity and postoperatively some improvement may be expected. In view of this, Konovalov feels perhaps the transcallosal approach is better.

Fukushima adds that in his experience, about one third of cases are rather easy to operate via a transcallosal approach. However, in larger tumors, he has noticed under the microscope significant adhesions of the tumor capsule and calcification to the pituitary stalk, the hypothalamus, perforating branches of the carotid arteries, and the optic nerves. If one does a "lateral" dissection—removing the tough tumor capsule from behind the optic nerves and chiasm—there is usually no improvement in visual symptoms. The key point concerns a given surgeon's microsurgical technique. The decision whether tumor capsule or calcification can be safely resected lies in the surgeon's judgment at that moment in the course of an operation.

Fukushima claims to have obtained the best results from the transsphenoidal approach and inferior results from the interhemispheric approach. The interhemispheric approach is for the removal of large intraventricular tumors. In his cases of transsphenoidal approach, the patients' visual acuity and visual field defects improved in 86% of cases. Using the pterional approach, improvement was seen in 83% and only one patient improved following an interhemispheric approach. In two instances postoperative visual acuity couldn't be measured—because of a mortality in one case, and because of a persisting obtundation precluding visual acuity assessment in the other. He offers that if one's resections exceed certain, as yet poorly defined, limits morbidity will ensue.

Patterson states that he had published results on 130 craniopharyngiomas with visual disturbances 1–2 years ago, and that 70% had improved and 1% had remained worse postoperatively. He is very cautious about the optic nerves, believing that stripping tumor from the underside of a threatened optic nerve implies that one will deprive that nerve of its blood supply and incur an infarction. Normal optic nerves will take quite a lot of retraction, but a nerve stretched by tumor and accompanied by diminished visual acuity may suffer further visual loss if manipulated. He contends that we'd all rather leave a little tumor behind than wind up with a blind patient.

Holtzman inquires whether a surgeon can tell to what degree an optic nerve is at risk by its appearance or configuration under the microscope.

Patterson replies that it's a question of looking at the nerve and seeing how fresh it is and remembering from the preoperative examination what the visual acuity is in the eye.

Holtzman inquires whether that judgment depends on the rapidity or chronicity of visual acuity loss preoperatively.

Long comments that at his institution, the neuro-ophthalmologists feel very strongly that the usual kinds of evaluation performed do not adequately describe visual problems. They utilize a technique of "quantification" preoperatively and postoperatively so they can compare those states. This assessment is well recognized in the ophthalmological literature, but not in the neurosurgical literature.

Long and his colleagues have taken pituitary tumors and meningiomas, but not craniopharyngiomas, and subjected them to this quantified comparison and then looked at factors that predict; they concluded that one really couldn't tell at surgery what was going to happen. The predictors were those you might expect: the age of the patient—with older patients doing less well than younger patients; the size of the tumor—with patients with big tumors doing less well than those with small tumors; and finally, not the rapidity of onset but rather the length of duration of the visual problem.

Those people who had a visual loss exceeding 2 years did less well than those with short-term visual loss. Long was unable to predict at surgery, from what he had done to the chiasm, what was going to happen to the patient's vision. Some of those patients in whom he was sure vision was lost made perfect recoveries, and vice versa. Those in whom Long thought he had done "the most beautiful operation in the world" came out with markedly diminished vision.

Post states that they have tried using visual evoked potentials during surgery at the Neurological Institute. It fits right on the eye itself. They have stopped using it because the neurologists in the Electrophysiology Laboratory were not satisfied with the electrodes, but have not yet found appropriate substitutes. Despite the apparent worth of this technique, Post is not sure if there is a good correlation between what is observed intraoperatively and the end result. It is similar to spinal cord monitoring for intramedullary tumor removal: The postremoval neural tissue looks bad, but the spinal cord works after the tumor removal.

THE TRANSSPHENOIDAL APPROACH

Patterson, referring to Fukushima's good results with vision using the transsphenoidal approaches, claims to have operated on about 15 transsphenoidal craniopharyngiomas, half of which were unanticipated preoperatively; he thought they were something else and they turned out to be craniopharyngiomas. He inquires as to the feasibility of achieving total removal via a transsphenoidal route and the advisability of operating transsphenoidally if one knows that the lesion is a craniopharyngioma.

Fukushima responds that in Group I and II patients who underwent multiple surgical procedures for small intrasellar tumors, or those with a small suprasellar extension, there were approximately half with verified craniopharyngiomas. This was similar to Patterson's experience. In half of Fukushima's cases he could achieve a radical total resection preserving the pituitary stalk and the pituitary gland. Fukushima suspects that the ability to achieve a total resection depends upon the origin, growth pattern, and degree of extension of the tumor.

Tew adds that a key to determining the use of the transsphenoidal approach is a significant amount of tumor in the sella, a point with which Fukushima agrees. Tew points out that the tumor planes can be followed far laterally, making the transsphenoidal approach less hazardous than approaches that begin lateral to the optic nerves.

Tew responds to Post's indication that transsphenoidal approaches are performed on a selected population by noting that if the tumor is intrasellar it may be confused with a pituitary adenoma, and is not a typical craniopharyngioma, and if it is extrasellar it may be a big cystic lesion or different entity. Tew maintains that one would expect patients operated upon transsphenoidally to do better in terms of preservation of their visual acuity.

Fukushima notes that tumors with suprasellar extension, those described as pituitary stalk types, and those of the third ventricle are difficult to dissect via a transsphenoidal approach.

Patterson remarks that some neurosurgeons do dissect such tumors transsphenoidally: Ivan Ciric talks about cutting around the diaphragma sellae and pulling the tumor down.

Post declares the real question is: If one finds an unanticipated craniopharyngioma coming through the sella, or a meningioma, how much can one, or should one, attempt in terms of its removal? Do you continue to dissect up and around it trying to follow planes of cleavage? Do you take the lower four fifths or seven eighths and return later for a transcranial approach? Post has had a few cases such as these, and when he presents them at different institutions he is surprised at the responses he encounters. He feels somewhat conservative upon finding one of those lesions from below, and likes to take the lower portion of it to a certain extent, but not to follow the superior capsule or pseudocapsule for fear of not being able to see the little perforators, small vessels, and adherences to the optic chiasm and nerves. Thus, Post feels strongly that if a tumor falls into his field then he will pursue it, but not in the same manner as he might an adenoma—using curets in a partially blind fashion.

Apuzzo asks whether one isn't guided by the corner of entry that one has and the size of the sella, the sellar opening, the texture of the lesion and one's ability to hold it. Those are all factors that are not openly discussed. Obviously, it's a horrifying thing to think that you might have a small sellar opening and a lesion which balloons out from the top without easy access to the dome and the structures behind it. At the other end of the spectrum is the soft lesion within the sella that folds in on itself. Apuzzo offers that these are the cases Ciric is talking about. That is, those types of cases where the surgeon can visualize what he or she is doing. Apuzzo cites a number of operations he has on videotape that he likes to call a blind type of surgery: Even though mirrors are used, there is still a fair amount of pulling and tugging on the tumor. Apuzzo declares that if we are going to optimize the results we get in the long term, we are going to have to try to achieve an exposure that gives the surgeon the opportunity to visualize what is being done—or at least maximize the time period of the operation during which the tumor planes are well visualized, rather than pulling blindly.

TRANSCALLOSAL APPROACHES

Long wonders how many members of the Stonwin Conference believe that simple section of the anterior corpus callosum produces any discernible or important neurological deficits. When Dr. Shelley Chou, Dr. Lyle French, and Long presented the transcallosal approach at the American Association of Neurological Surgeons (AANS) meeting as a feasible procedure in human beings, they were roundly attacked by people in the audience who were convinced that it would leave patients badly damaged. Long inquires, then, as to the experience of the Stonwin attendees.

Patterson replies that there is a psychologist at his institution, Dr. Michael Gazzaniga, who worked with Roger Sperry. Patterson cites 18 patients with total callosal section, from splenium right around through the anterior commissure. It is possible to demonstrate problems with the passage of information from one hemisphere to the other in those patients, but with incisions in the corpus callosum of 4–5 cm, Gazzaniga was unable to measure any deficit.

Apuzzo declares, in response to the question of deficits associated with corpus callosum section, that Long and Chou should be applauded for their article "Transcallosal Removal of Craniopharyngiomas within the Third Ventricle."[12] He states that it was a key article in bringing people back to Dandy's original concept that this was an excellent method of exposing the third ventricle. In the experience of Apuzzo and Joseph E. Bogen, who has recently reviewed all

studies in this area, it was not possible to detect a neurological or psychological deficit by present testing methodologies. There is some question that there might be some dicrotic hearing loss, depending on how this is measured. Certainly, from the functional standpoint, in the average patient there will be no noticeable deficit incurred by an incision in the trunk of the corpus callosum.

GASTROINTESTINAL HEMORRHAGE AND CORPUS CALLOSUM SECTION

Apuzzo cites the two of Long's six patients who succumbed to massive gastrointestinal hemorrhage following callosal sectioning. Apuzzo claims that at every meeting he is asked what percentage of his patients have postoperative gastrointestinal bleeding. He also usually asks people how many of them have seen gastrointestinal hemorrhage with dissection in the chamber of the third ventricle, because there is some question as to whether sympathetic outflow has been increased. He asks if Konovalov has seen gastrointestinal hemorrhage in patients in whom he has removed third ventricular lesions transcallosally.

Konovalov responds that it certainly can happen. He believes the reason for this is damage to the hypothalamus produced by the tumor itself. In more severe cases with large third ventricular tumors, gastrointestinal hemorrhage occurs, but the preoperative condition of these patients is often poor. In regard to the question of interhemispheric transfer of information, especially in children, he has found that interhemisphere relations may substantially improve postoperatively since the tumor can affect the interhemispheric relations as well as other functions.

Long, in answer to Apuzzo's reference to his two patients suffering gastrointestinal hemorrhage, claims never to have seen them again until this year, when a patient had a massive gastrointestinal hemorrhage while waiting for surgery. Long recalls that those two cases, although presented in 1970, actually dated back to 1965. The two who died were operated on before the use of the microscope in surgery, and Long concurs with Konovalov in that the cause was injury to the lateral hypothalamus, because not only did each have gastrointestinal hemorrhage, but each had a full blown lateral thalamic hemorrhage. Even though both awakened from surgery and did relatively well, they each had a later vascular injury to the thalamus with softening and massive hemorrhage. This sort of thing was never seen again once the microscope was employed in tumor removal.

MEMORY DISTURBANCES WITH SUBFRONTAL LESIONS

Holtzman raises the question of memory disturbances occurring as a consequence of damage to the subfrontal regions, including the septal nuclei and the septal region. Of course, this might well be due to the subfrontal region's contribution to the fornix and its role in memory pathways. The tumors discussed in this volume are often adherent to the subfrontal region. Are we encountering these kinds of memory disturbances postoperatively?

Konovalov responds that before surgery, these patients often have severe memory disturbances. In some cases, there can be improvement of memory function after surgery. In some cases, memory function becomes worse than preoperatively. It is always difficult to discern the reason for this deficit: Was it the cutting of the fornix, corpus callosum, damage to the walls of the third ventricle during the separation of the tumor, or were there subsequent problems with the vascular supply to these regions? There is no single explanation, and in each case it is very difficult to determine the real reason.

COLLOID CYSTS AND DELAYED POSTOPERATIVE DEATH

Patterson raises a problem he has encountered with removal of colloid cysts from the third ventricle. One patient, an 18-year-old woman whose colloid cyst was successfully removed 8 months previously and who had returned to college, died suddenly on a weekend. She developed a severe headache, went into a coma, and died. An autopsy was performed and nothing was found. There was no residual cyst. Patterson assumed she had died of some kind of acute problem of spinal fluid circulation. Patterson also cites the case of a 46-year-old man who herniated and died 6 weeks after successful removal of his colloid cyst. At autopsy he had no residual cyst; nothing was obvious. Again, Patterson concluded the patient must have had an acute problem of spinal fluid circulation.

Post asks if the pathologists looked closely at the aqueduct of Sylvius. Apuzzo reiterates: Was there atresia of the aqueduct of Sylvius? This is a critical point. The Swedes have reported that about one third of patients will have some evidence of aqueductal atresia, and one of the arguments that has been made for doing a transcallosal incision is that one gets better drainage in the postoperative period. If one has fenestrated the septum pellucidum along with cyst removal, they can drain ventricular fluid via the surgical route. If that route subsequently closes, and if there is aqueductal atresia, that patient could get into trouble.

Patterson concludes that he is more inclined to think that shunts are important in these cases of third ventricular colloid cysts than he used to be.

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12

Stereotactic Surgery of the Thalamus

Edward I. Kandel

The thalamus is the main and largest part of the diencephalon, the surgery of which is the subject of this volume. The original meaning of the Greek word "thalamos" is "connubial couch." It is difficult now to understand the fantasy of the ancient anatomists who gave it such an unusual allegorical title, but we may suppose that they did so because this part of the brain, like the connubial couch, was hidden from strangers' views.

Excluding animal experiments and morphological descriptions, the human thalamus remained inaccessible to investigators, including neurosurgeons, for more than a century during the development of neurophysiology and neurosurgery. Only stereotactic surgery, which began its rapid and fruitful development about 40 years ago, opened an essentially new way of investigating human thalamic functional organization.

Great efforts have been undertaken and many achievements made over the last four decades in developing new experimental and clinical methodologies for the investigation of the thalamus and other subcortical structures. These include: electrical stimulation during stereotactic operation, using chronically implanted electrodes; recording of biopotentials, including the microelectrode technique; very informative studies of different evoked potentials, including studies of neural pathways' velocity conduction; investigation of impedance profiles; H-reflex study; local cerebral blood flow (CBF) investigation, and many other neurophysiological methods.

Many methods of local neural tissue destruction have also been developed: the cryogenic method, which also allows the temporary, reversible "switch off" of a limited part of thalamic nuclei; radio frequency coagulation; anodal electrolysis; inductive heating, and others.

The precise and informative methods of morphological investigation—high-resolution electron microscopy and cytochemical, immunocytological, and other methods—were also developed over these years and successfully used. A real revolution, not only in clinical diagnostics but also in research, came about following the introduction of modern neuroimaging techniques—computerized tomography, nuclear magnet-

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ic resonance, and positron-emission tomography. The complete classification of numerous thalamic nuclei and pathways, initiated by Walker, was developed by Hassler.

Undoubtedly, such a "massive attack" on the thalamus yielded extensive and voluminous scientific information concerning its morphological and functional organization. Using all of the above-mentioned research methods, scientists explored and investigated practically all human thalamic nuclei and connections during stereotactic operations. Many significant discoveries were made. In the opinion of many, the greatest of these was the investigation of neurotransmitters, which disclosed the participation of the thalamus in the function of dopaminergic, serotoninergic, GABAergic, and other brain metabolic systems.

On the other hand, a general summary of thalamus studies gives, I think, grounds for a certain pessimism. Indeed, in spite of all the information obtained during the last decades, the functions of the thalamic nuclei, the thalamus as a whole, and the role of the thalamus in the integrative activity of the brain remain quite obscure.

Just as we did half a century ago, we know that the posterior ventrolateral nuclear complex is a relay station of general sensibility, but we can't explain the preservation of the sensibility after surgical destruction of this nucleus. The relationship of VPL to thalamic intralaminar nuclei and centrum medianum, which belong to the extralemniscal or medial pain-conducting system, has not been disclosed. We know that destruction of the ventrolateral nucleus may completely abolish tremor and rigidity, but we also know that the mechanism of these two pathological phenomena is not localized in this nucleus.

We know that the medial group of thalamic nuclei is connected with mental and psychological spheres, but these connections are not yet clearly established. The functional organization of the biggest thalamic nucleus, the pulvinar, and of the anterior nuclear group is obscure. The mysteries of the "connubial couch" still seem to be somewhat preserved, from the scientific point of view. Only a fundamentally new methodology of scientific investigation can solve the mysteries of the thalamus.

As has so often happened in the history of medicine, surgery itself developed much more rapidly than did its theoretical basis, our understanding of the pathological processes that are the objects of surgery.

In spite of sporadic and, as a rule, unsuccessful attempts, real thalamic surgery by the open approach did not exist practically in the past. The inception of modern thalamic surgery occurred about 40 years ago, when neurologist Ernst Spiegel and neurosurgeon Henry Wycis performed the first stereotactic operation on the human brain. These pioneers of stereotaxy developed a new methodology, which included the first modern stereotactic apparatus and the first stereotactic atlas of the human brain.

The aim of this chapter is to present the contemporary status of stereotactic surgery of the thalamus or, as we say now, the "state of the art," in this rapidly developing field of neurosurgery.

STEREOTACTIC SURGERY FOR DYSKINESIAS AND PAIN

Hundreds of papers devoted to the topic of stereotactic surgery for dyskinesias and pain have been published. These have proved that stereotactic surgery of the thalamus

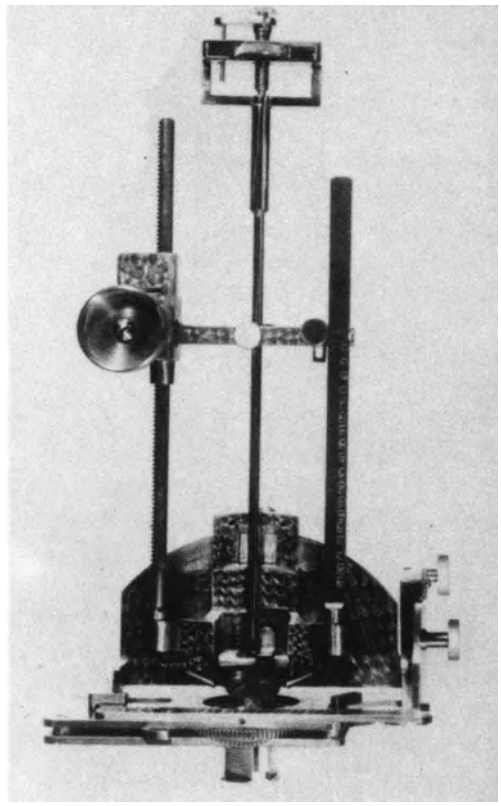

Figure 1. Stereotactic apparatus of the author's own construction.

is highly effective in the management of many severe chronic neurological diseases for which there is either no conservative treatment or for which treatment is of little effect. For efficacy, stereotactic surgery cannot be compared to any of the previously employed methods.

Since 1958, I and my co-workers have done more than 2000 stereotactic operations on thalamic nuclei.[1–5] The majority of the operations were done for extrapyramidal dyskinesias such as parkinsonism (880 operations); dystonia musculorum deformans (270); cerebral palsy (240); spasmodic torticollis (220); atypical dyskinesias (150); certain familiar degenerative diseases (e.g., essential tremor, hepatocerebral degeneration, Huntington's chorea, myoclonus epilepsy) (90); multiple sclerosis (40); pain (70); and others (40).

In the case of extrapyramidal diseases we performed cryodestruction of the VL complex (VOa, VOp, Vim) and subthalamic region; in pain syndromes, VPL, centrum medianum, or intralaminar nuclei; and in Tourette syndrome, medial nuclei. For these operations, we use the stereotactic apparatus of our own construction (Fig. 1) and our cryogenic device with liquid nitrogen (Figs. 2,3).[6,7]

To briefly summarize our clinical results, the VL-complex ablative operations are very effective for a variety of extrapyramidal disturbances. In the great majority of

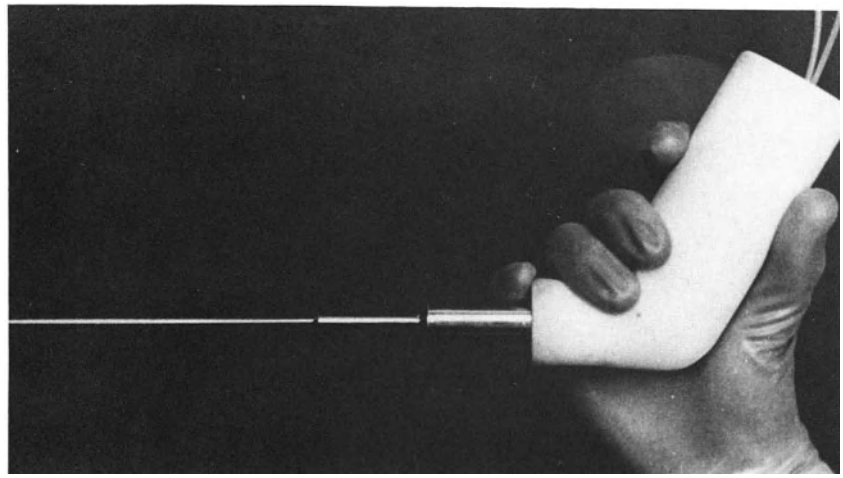

Figure 2. Device for cryosurgery, of the author's own construction.

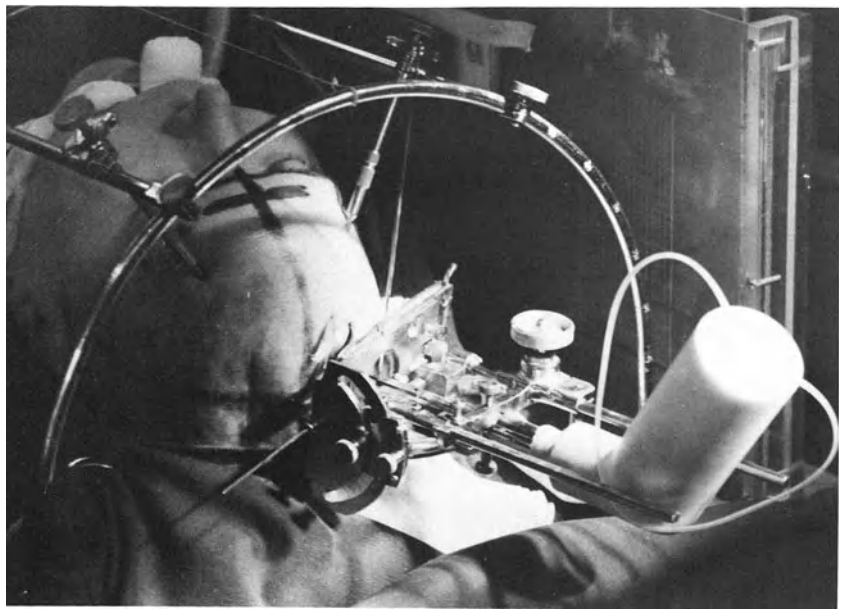

Figure 3. General view of a stereotactic operation on the basal ganglia, using cryoprobe shown in Fig. 2.

cases, these operations give stable and long-lasting therapeutic results, abolishing tremor, muscle rigidity, and to a much lesser extent spasticity and bradykinesia. The stereotactic surgery of parkinsonism, which affects about 50 million people worldwide, has been reconsidered recently because it has been proven that L-dopa loses its efficacy completely after 5–7 years of treatment. Because of the low risk connected with modern stereotactic surgery, the indications for these operations must be extended.

Stereotactic surgery remains the treatment of choice for dystonia musculorum deformans and spasmodic torticollis, for which conservative treatment is not practically effective. Only a partial effect may be obtained in cerebral palsy. The treatment of this severe disease, which affects millions of children, remains unsolved.

Excellent results have been noted in the great majority of cases of essential tremor. As palliative management, stereotactic thalamic operations are indicated in selected cases of multiple sclerosis with disabling tremor, Huntington's chorea, and myoclonus epilepsy.

Thalamic surgery for pain, considered as surgical management of pain in general, is a long-standing and very complicated problem of neurosurgery. Stereotactic operations for pain syndromes have not only proven to be an effective method of treatment, but have also played an important role in the study of the pathogenesis of pain. Destruction of various nuclei and pathways of the thalamus represents one of the main trends in contemporary stereotactic surgery for pain. Many specific and nonspecific thalamic nuclei are the target points for stereotactic destruction. These include sensory nuclei, VPL and VPM, centrum medianum, pulvinar, intralaminar, parafascicular and limitans nuclei, internal medullary lamina, dorsomedial and anterior nuclei, the basal medial thalamic region, thalamocortical pathways.

According to published literature and our own experience, the destruction of nonspecific thalamic structures is frequently more effective than destruction of specific sensory nuclei. One may also conclude that in the case of intractable pain, combined stereotactic operations involving destruction of both specific and nonspecific nuclei—in other words, the lateral and medial pain-conducting systems—are more effective than destruction of specific nuclei only. The main problem of thalamic pain surgery remains the frequent postoperative relapses of pain, the cause of which still has no adequate explanation.

A comparatively new trend in the surgical management of pain is electric stimulation of various thalamic nuclei with chronically implanted electrodes. This less traumatic technique has become more popular in the last decade, and chronic stimulation of periaqueductal and periventricular gray matter seems to be more effective, according to follow-up results.

THALAMIC TUMORS

Thalamic tumors constitute 1–2% of all primary brain tumors. About 25 years ago, my colleagues and I published an analysis of 72 cases of primary thalamic tumors—all observations made at the Burdenko Institute of Neurosurgery over a

period of many years.[8] The study showed that thalamic tumors do not have a specific neurological picture, and that the main clinical syndrome is caused by obstruction of the third ventricle and by development of occlusive hydrocephalus. Because at that time—before the advent of CT—neither clinical signs and ventriculography nor the partial surgical removal of deep-seated tumors provided exact thalamic localization, only morphologically verified cases were analyzed. Only partial removal of thalamic tumors was achieved, and postoperative mortality after several months was close to 100%. We did not come across a single proven case of total removal of a primary thalamic tumor in the 1960s and 1970s.

The introduction of the CT scanner about 10 years ago opened up new possibilities for early and exact diagnosis and for surgical extirpation of thalamic tumors. To date, there have been only a few reports in the world literature, and only a limited quantity of operated cases.

In spite of the many achievements of modern neurosurgery, removal of thalamic tumors by the open direct approach is still connected with high morbidity and mortality rates. Many cases are recognized as being completely inoperable, and only palliative operations (mainly ventricular shunting) are performed. Only a few dozen cases of radical removal of thalamic tumors are described in the world literature. For example, Konovalov et al.[9] have reported successful total extirpation of thalamic astrocytomas in three cases.

Because many patients with primary thalamic tumors are admitted in advanced stages of the disease, the problem of palliative treatment remains a priority. Besides CSF-shunting operations, an attempt to diminish tumor volume is indicated.

We have performed stereotactic biopsy followed by cryogenic destruction in seven cases of thalamic tumors. For the latter, we use the same cryoprobe that we employ in stereotactic operations. If the application of extreme cold, in the form of liquid nitrogen, is prolonged for up to 15 min the iceball on the active tip of one's cryoprobe may reach 45–50 mm in diameter (Fig. 4).

After CT diagnosis of primary thalamic tumor, we calculated the tumor's stereotactic coordinates, the cryoprobe trajectory, and the site of the burr hole. In the operating room, these data and tumor counters were recorded on x-ray film in both projections. The stereotactic biopsy, for which we used our own device or a Radionics probe, was then performed. Our seven cases included four astrocytomas, one cavernous angioma, one cyst, and one unidentified tumor. A biopsy was carried out in six cases, excluding the cyst, which was aspirated.[10]

Follow-up of these patients, lasting from 6 months to 7 years, has shown that this palliative surgery may improve the clinical picture and prolong the period of useful life (Fig. 5).

SPONTANEOUS THALAMIC HEMORRHAGES

Hemorrhage into the thalamus (or so-called medial hemorrhage) is the most severe and dangerous variant of spontaneous intracerebral hemorrhages due to hypertension and cerebral arteriosclerosis. The typical clinical features of the lesion are rapid

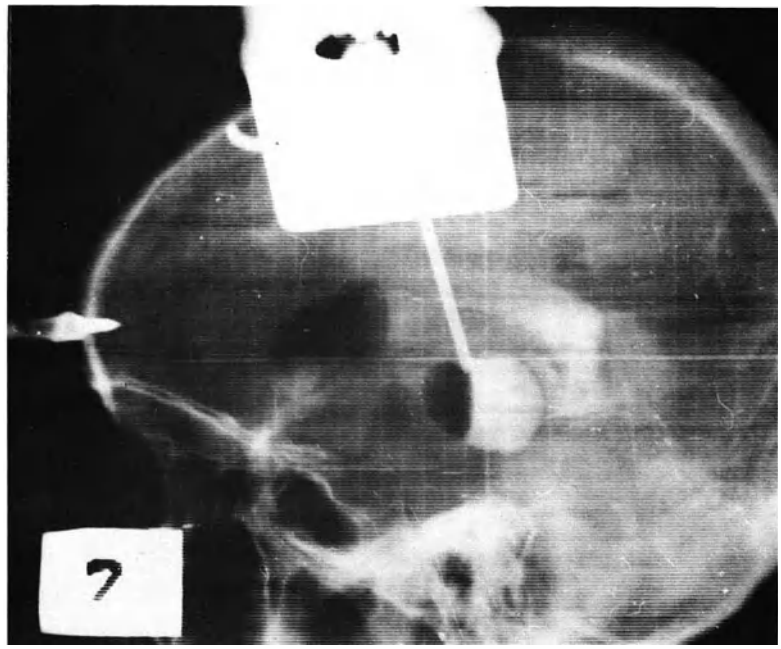

Figure 4. Stereotactic aspiration of a thalamic cyst. Contrast medium is inserted into the cyst cavity after removal of the colloid cystic fluid.

onset of comatose state and severe disturbances of vital functions, which may be partially explained as being a result of blood penetration into the whole ventricular system. According to many reports in the literature, and our own experience, the mortality rate due to these hemorrhages is extremely high—about 90%.

Despite many achievements in the surgery of intracerebral hematomas, many authors consider thalamic hemorrhages absolutely inoperable. Our personal experience with surgery of spontaneous intracerebral hemorrhages constitutes about 350 cases, including about 60 cases of thalamic hematomas. This experience has shown that the classic open approach to the hematoma by flap craniotomy and encephalotomy are often too traumatic and invasive in this most vulnerable contingent of patients.

A few years ago, my co-worker, Dr. Peresedov, and I developed an improved method of stereotactic evacuation of intracerebral hematomas.[11] For this procedure, we constructed a special device—a thin metallic cannula, 3.5 mm in diameter, with an Archimedes screw inside that is rotated with preselected speed by a small engine (Fig. 6). Preoperative CT scanning permits the exact calculation of hematoma volume and its stereotactic coordinates. The cannula is inserted stereotactically through the burr hole into the hematoma cavity, and the device is connected with an ordinary surgical aspirator.

The rotating screw destroys dense clots in the hematoma cavity, the pieces of which are removed by the aspirator into a calibrated bottle (Fig. 7). When the volume

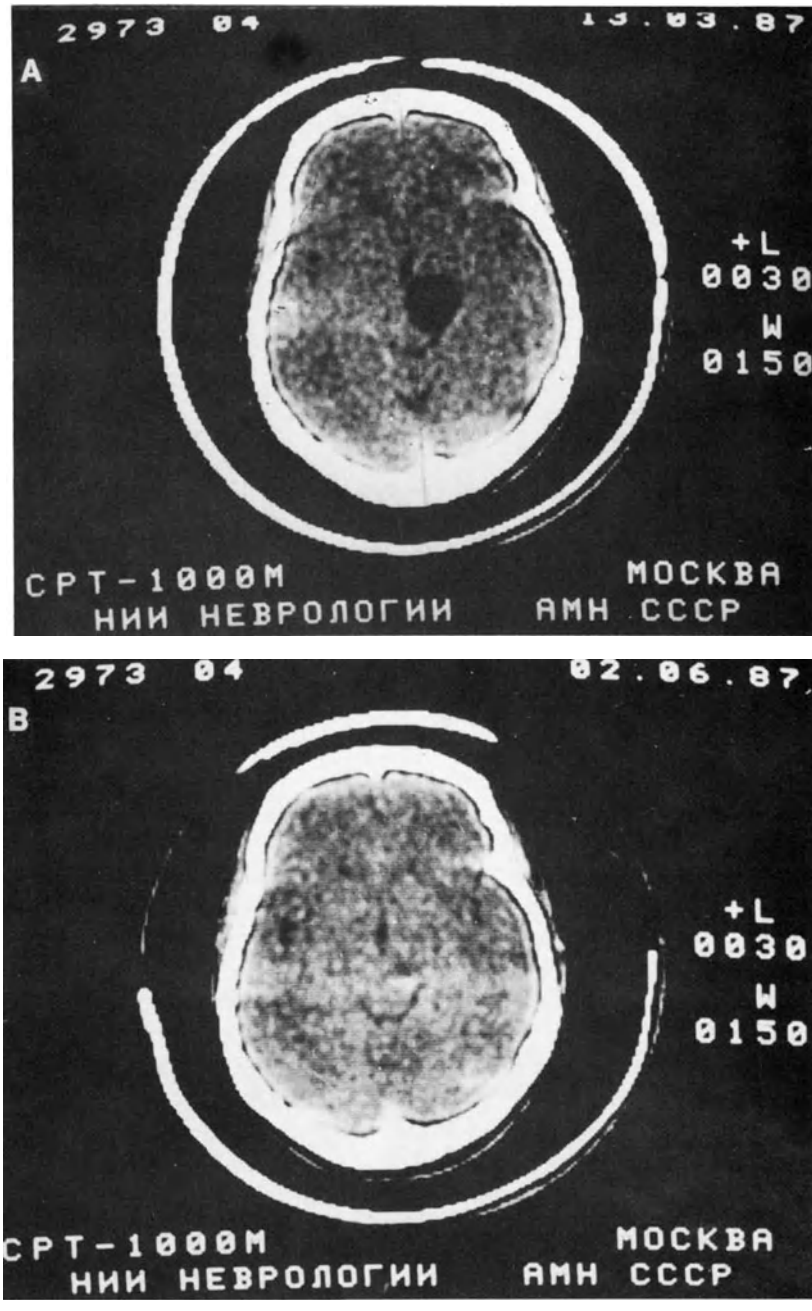

Figure 5. CT scans of a thalamic cyst before (A) and two weeks after (B) its stereotactic evacuation. There is no cyst after surgery.

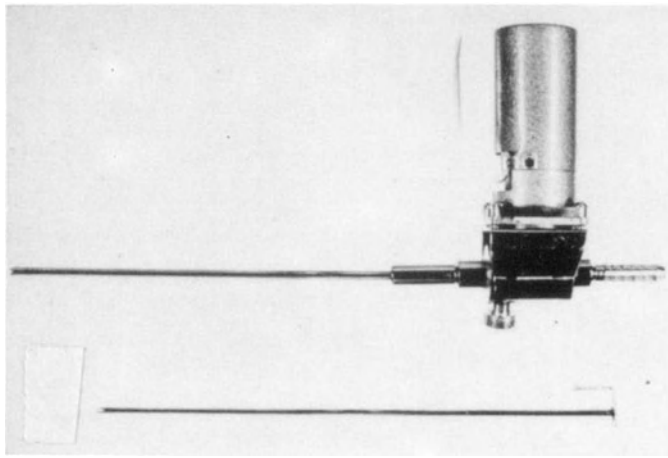

Figure 6. Device of our own construction for stereotactic aspiration of intracerebral hematomas. (See text for description.)

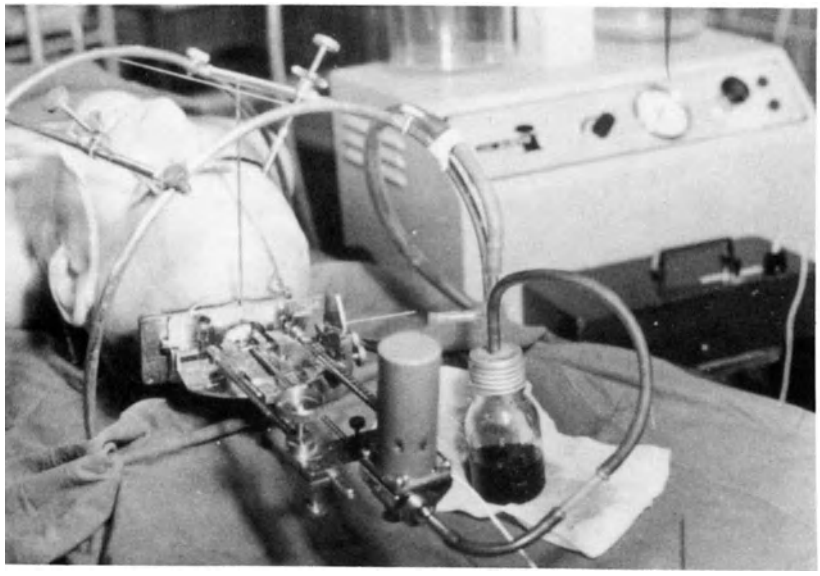

Figure 7. General view of the operative setup during stereotactic evacuation of an intracerebral hematoma. The device is fixed in the stereotactic apparatus. Blood clots from the hematoma are aspirated into the glass bottle. The volume of evacuated clots can be determined by the marks on the bottle and then compared with the volume of the brain hematoma as calculated using preoperative CT scans.

of removed clots and liquid blood in the bottle reaches a predetermined estimate, the operation is over.

It is known that the rate of recurrence of intracerebral hematoma after complete removal is about 15%. This remains a very important problem in the surgery of spontaneous hematomas.

For prevention and early detection of recurrence, we have developed the following method: For 3–4 days, postoperative pressure in the opposite lateral ventricle is monitored via a catheter introduced through a second burr hole on the other side. We also introduce a silicon rubber balloon into the hematoma cavity during surgery and inflate the balloon with a saline solution. After the operation, the balloon is deflated gradually and removed in 3–4 days.

Our experience with stereotactic evacuation of spontaneous intracerebral hematomas now consists of 64 cases, with a postoperative mortality rate of 21%. This figure is about two times less than before the introduction of this method. Among 64 cases, there were 16 cases of mostly thalamic (medial) hematomas. Each of these patients was in a comatose condition of varying severity (from 4 to 9 points on the Glasgow scale). Filling of the ventricular system with blood took place in 13 out of 16 cases. Ten patients survived after surgery and 6 died (three of them because of pulmonary artery embolism). An illustrative case is shown in Fig. 8.

We believe that the stereotactic removal of thalamic spontaneous hematomas is less traumatic and gives better results than the classic open approach.

ARTERIOVENOUS MALFORMATIONS OF THE THALAMUS

A small percentage of cerebral AVMs is located in the thalamus (about 8%). Previously, these deep-seated AVMs were considered inaccessible and inoperable. The introduction of microsurgical technique in neurosurgical practice has made it possible to perform radical excision of some kinds of subcortical AVMs, but thalamic AVMs have seldom been removed because of the risk of irreversible brain damage. In the literature, we found no more than a few dozen such operations. Each author has described only a few cases. Y. M. Filatov, of the Burdenko Institute of Neurosurgery in Moscow, presented seven cases of thalamic AVMs removed entirely by the direct open approach (personal communication, 1984).

Recently, Stein and Solomon published their outstanding experience with 22 AVMs of the thalamus and candate nucleus[12]: In 18 cases the AVMs were removed totally, and in four cases partially, by the interhemispheric approach, without postoperative mortality. All 22 patients returned to their previous occupations.

It is possible, in carefully selected cases, to radically remove small or middle-sized thalamic AVMs, but giant hemispheric lesions, which involve not only the thalamus but other subcortical structures, have remained absolutely inoperable up until now.

One decade ago, we developed a new method of stereotactically clipping cerebral arterial aneurysms and the feeding vessels of AVMs (Figs. 9, 10).[13,14] In our series, we had 12 cases of AVMs involving the thalamus that were considered undoubtedly

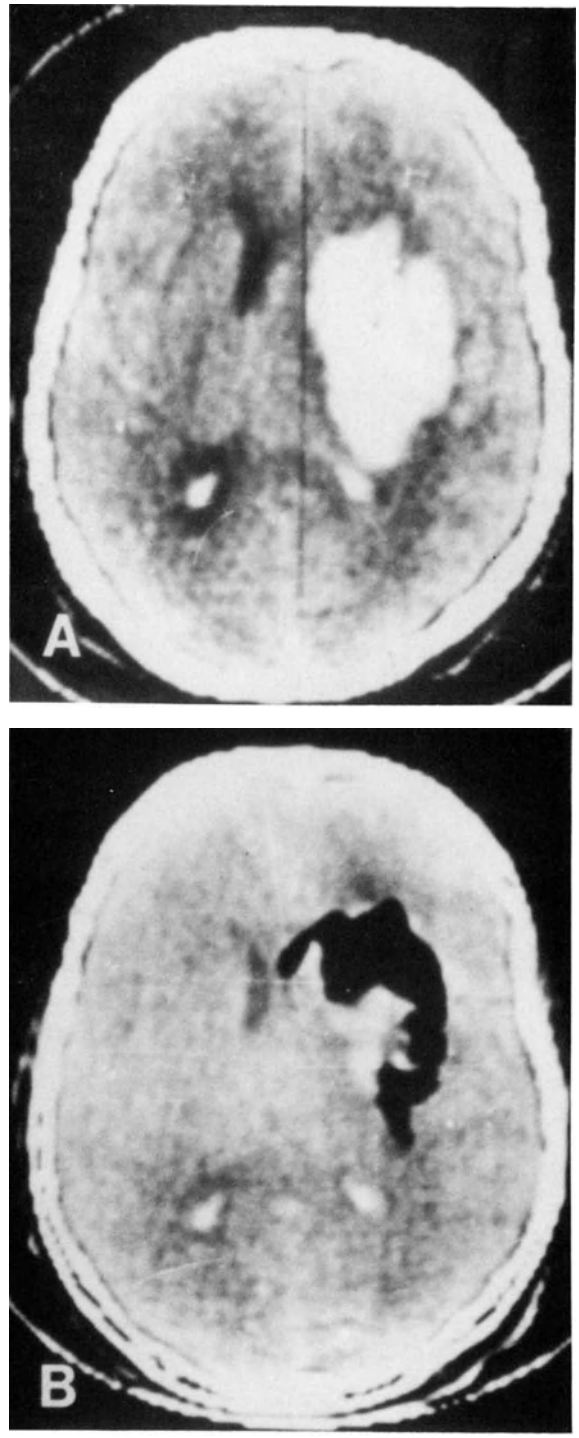

Figure 8. CT scans of a large intracerebral hematoma located in the thalamus and other subcortical structures. (A) Before surgery; (B) after stereotactic removal of the hematoma. The cavity of the removed hematoma is filled with air.

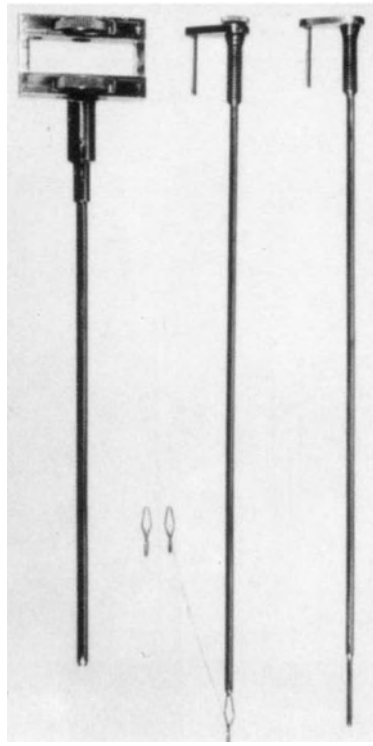

Figure 9. The author's device for stereotactic clipping of arterial aneurysms and AVMs of the brain.

inoperable in the sense of complete extirpation. Stereotactic clipping of the feeding arteries was done without any complications. In 10 cases, these operations were palliative, with the aim of diminishing AVM volume (Fig. 11). Two cases of small AVMs with one arterial feeder each may be considered as having undergone radical treatment (Fig. 12).

ERYTHROMELALGIA

There is one unexpected possibility for thalamic surgery that has not been described in the literature until now. We operated on two children with a mysterious and, fortunately, very rare disease called "erythromelalgia," or the Weir Mitchell disease. Both children—a 9-year-old boy and a 13-year-old girl—were in grave condition due to intractable burning pain in their legs. For a long time (9 months and 1.5 years, respectively), the children had been bedridden, constantly keeping their legs in cold water. The hot, reddish legs were severely macerated and covered with trophic ulcers.

After stereotactic operations on the thalamic nuclei ventral posterolateral (VPL) and centrum mediastinum (CM), pain disappeared; the ulcers healed, and strangely

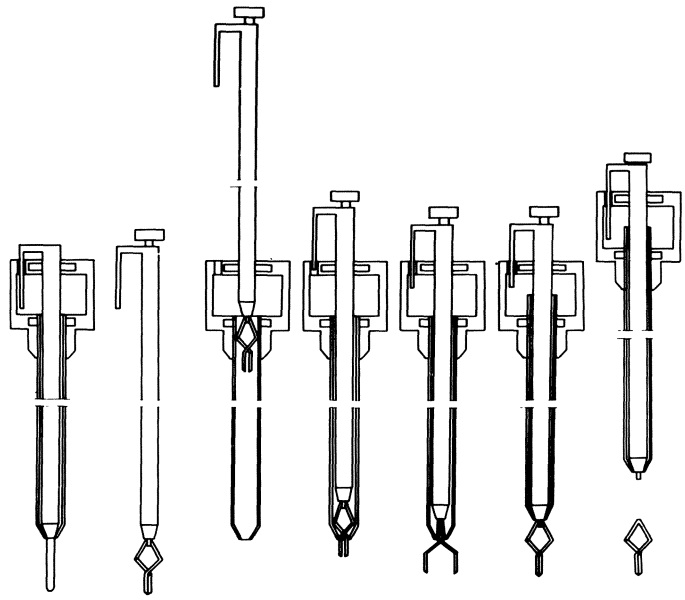

Figure 10. Schematic image of the sequence of working stages of stereotactic clipping.

enough, the erythromelalgia was abolished (Fig. 13). The children are now walking normally and studying at school (follow-up was 5 and 2.5 years, respectively). These results permit us to speculate that certain thalamic nuclei may influence peripheral vasomotor activity.

DISCUSSION

STEREOTACTIC CLIPPING OF ARTERIOVENOUS MALFORMATIONS

Hosobuchi points out that although there was temporary disappearance of the arteriovenous malformation with clipping of single feeders, we do know that subsequent collateral supply develops and the malformations recur. He inquires whether, with stereotactic clipping, we have repeat arteriography to see if the malformation is permanently obliterated.

Hosobuchi is absolutely correct. This method is a method of palliative treatment and is to be used in exceptional cases only. It may be considered as a radical treatment, but data from the literature indicate that only half of the cases of arteriovenous malformation may be operated radically, and the problem remains as to what to do with the second half. Certainly, this does not represent possible radical treatment in the future. Other avenues may be developed, but in my opinion, the experience of the last decade has shown us that the old opinion of clipping a feeding artery or maybe embolization or balloon occlusion with interruption of a feeding artery, is more effective than previously thought. Certainly, this diminishes the volume of the malformation. It may prevent, to a degree, subsequent intracranial hemorrhage and reduce the incidence of seizure activity. We have quite good clinical results after the palliative clipping of feeding arteries, but very clearly this is a palliative treatment.

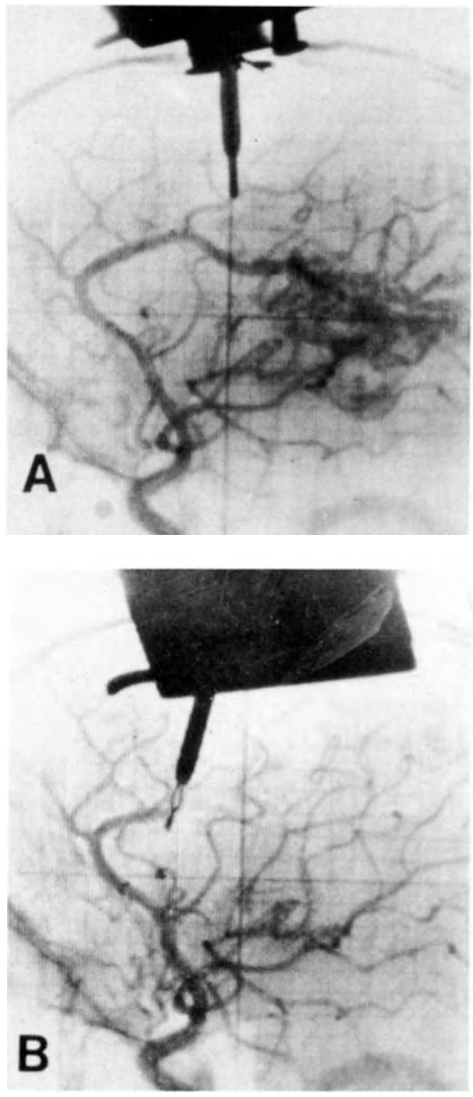

Figure 11. Giant inoperable AVM of thalamus and basal ganglia, fed mostly by the hypertrophied anterior cerebral artery. Stereotactic clipping of the artery serves as a palliative treatment. (A) Angiograph before surgery; (B) intraoperative angiograph after stereotactic clipping of the anterior cerebral artery. The volume of the AVM decreased substantially.

ERYTHROMELALGIA WITH BURNING FEET

Hosobuchi asks where we made the lesions. In what part of the thalamus?

The lesions were made in VPL and centrum medianum. My aim from the beginning was to treat the pain only, as I had never seen this disease before. Remarkably, the symptoms of erythromelalgia disappeared along with the pain.

Patterson comments that he and his colleagues had four children with unexplained pain in one foot—terrible pain that had gone on for months and months. They received psychiatric care, but were unable to stand on the painful extremity. Cordotomy was performed, and the pain in

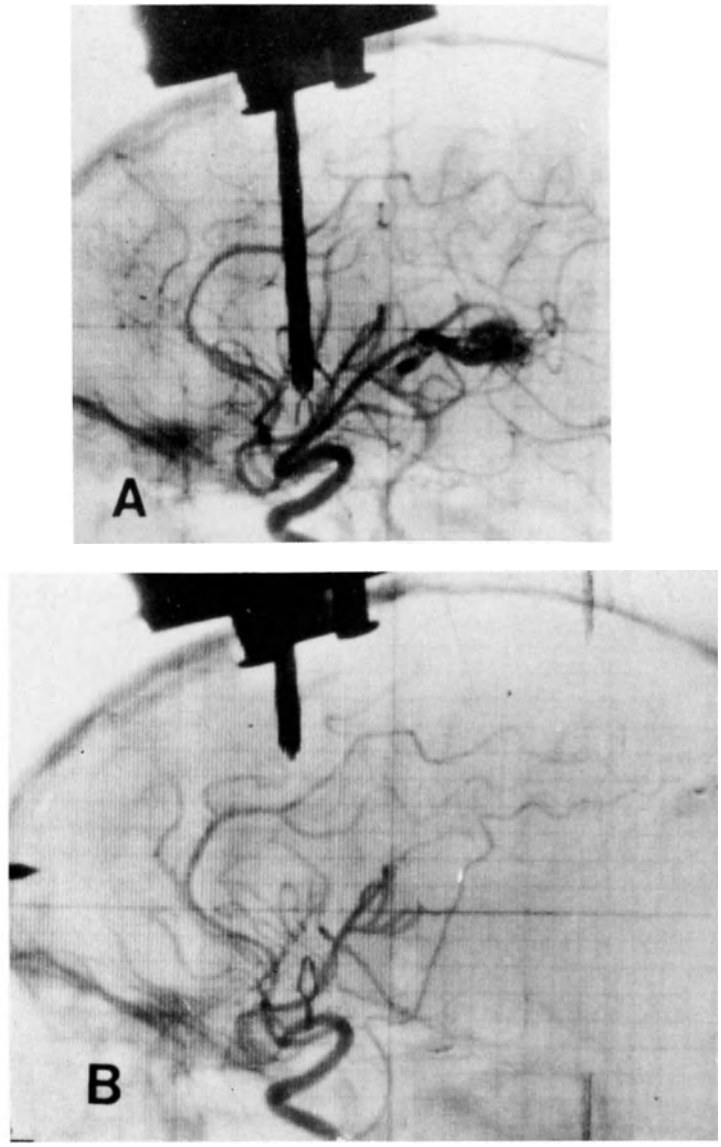

Figure 12. A small thalamic AVM fed by one branch of the middle cerebral artery. (A) before stereotactic clipping; (B) immediately after clipping of the feeding branch at its origin at the main trunk of the artery. Note that another branch, located close to the clipped artery, was left undisturbed.

each child was relieved for a long period of time. One child, who was able to walk after his cordotomy, fractured his leg because of the degree of bone demineralization. Patterson points out that these were clearly not cases of erythromelalgia, but rather represented unexplained severe foot pain.

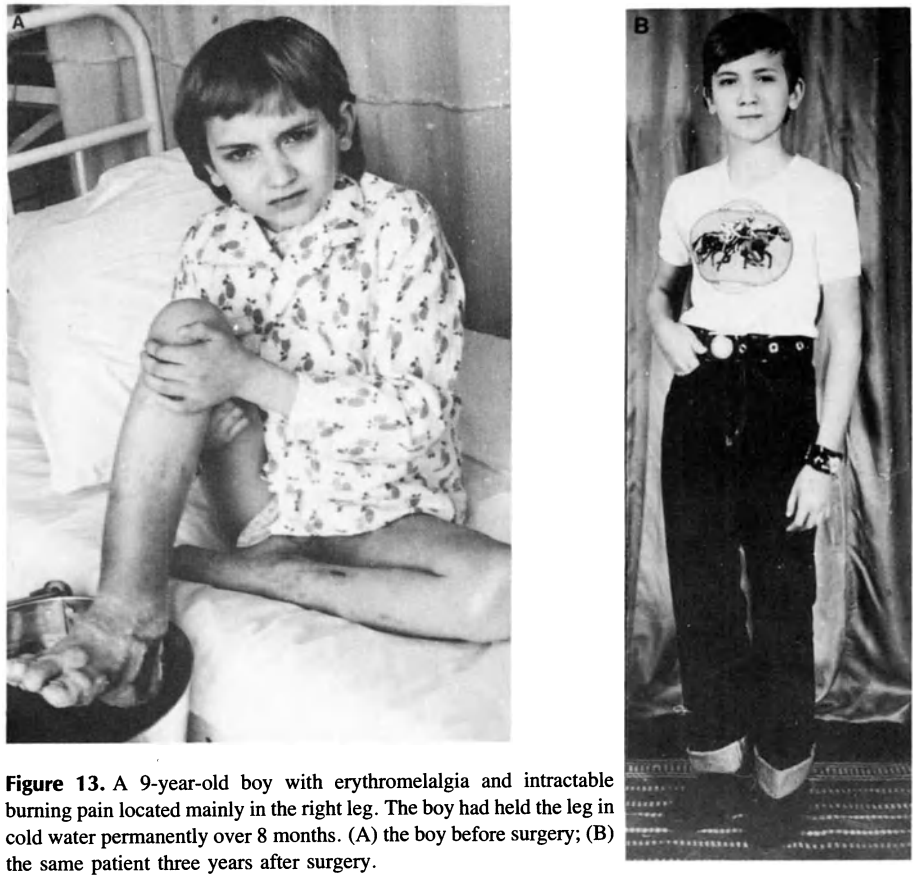

Figure 13. A 9-year-old boy with erythromelalgia and intractable burning pain located mainly in the right leg. The boy had held the leg in cold water permanently over 8 months. (A) the boy before surgery; (B) the same patient three years after surgery.

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13

Ventriculoscopy in Diencephalic and Sellar Neoplasm Resection

G. O. Mjavanadze

INTRODUCTION

The surgical resection of neoplasms of the diencephalon and sellar regions remains one of the most serious problems in neurosurgery. The success of an operation depends upon exact diagnosis: The size of a neoplasm, its location and extent, and its relationship to the ventricular system determine the choice of surgical approach. The relationship of a tumor to the third ventricular floor is important in choosing a transcallosal and/or a subfrontal approach for maximal tumor removal with maximum brain tissue protection.

MATERIAL

In our study, one group of about 350 patients with craniopharyngiomas was operated upon during the period 1974–1986. Approximately one third of these patients had a large tumor mass located in the cavity of the third ventricle.

Another group of 96 patients with arachnoidal cysts was also operated upon. Twenty-two percent of these had tumors that were localized in the suprasellar region and compressed the floor of the third ventricle.

CT scanning was performed and the tumors and cystic masses were clearly identified. However, only 15% of the intraventricular craniopharyngiomas and only 25% of the arachnoidal cysts were precisely localized.

For exact diagnosis, we used a ventriculoscope in 18 cases of craniopharyngiomas and in six cases of arachnoidal cysts. The Japanese "Olympus" fiberoptic ventriculoscope was used for these purposes.

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VENTRICULOSCOPY

Ventriculoscopy was indicated in cases of neoplasms located in the sellar region and extending into the third ventricle and/or the lateral ventricles with symptomatic severe hydrocephalus.

Preoperatively, the anterior horn of the right lateral ventricle was punctured in the usual region of the brain and ventriculoscopy was performed. The flexible tubing of the fiberoptiscope was covered with a plastic material to protect brain tissue.

With the help of the ventriculoscope, it was possible to see a tumor mass in the cavity of the third ventricle, and biopsy could be performed. In these cases, the transcallosal approach for tumor removal was recommended. In instances where craniopharyngioma cysts or arachnoidal cysts were found in the third ventricle or in the lateral ventricles, they were emptied with the help of the ventriculoscope prior to the microsurgical excision of the main tumor mass (see Figs. 1–3).

In cases where ventriculoscopic inspection through a deformed foramen of Monro disclosed that the upper part of the tumor or arachnoidal cyst was covered by the thin floor of the third ventricle, a subfrontal approach was suggested.

Intraoperative and postoperative ventriculoscopy made it possible to inspect regions otherwise inaccessible—such as the inferior surfaces of the optic nerves and chiasm, the internal carotid arteries, the inner surface of the sella turcica cavity, and other nerves and vessels of the sellar region.

Coagulation of some of the tumor vessels and remnants of tumor capsule was performed with endoscopy.

Blood clots were aspirated from the cavity of the third ventricle and inferior horns of the lateral ventricles.

Evaluation of the status of the floor of the third ventricle is important in predicting a patient's convalescence in the early postoperative period.

There were no complications during or after endoscopy.

CONCLUSION

Endoscopy provides important information for selecting optimum surgical approaches and for monitoring and refining the radical resection of diencephalic and sellar neoplasms.

DISCUSSION

THE VENTRICULOSCOPE

Carmel asks how many degrees of freedom the end of the ventriculoscope has. Can the operator look in every direction?

The tip of our ventriculoscope can move in two directions—90° and 120° from the original plane. The tip can be shaped somewhat like a hook in order to visualize the undersurface of the

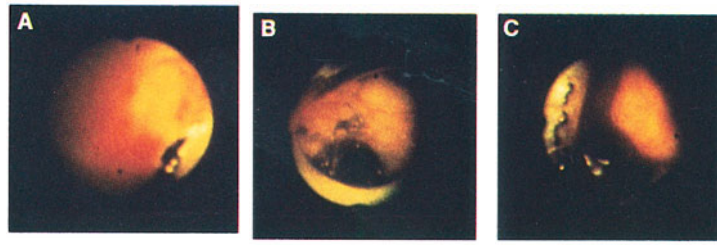

Figure 1. (A) Glial tumor inside the cavity of the third ventricle, viewed through the right foramen of Monro. (B) Craniopharyngioma inside the cavity of the third ventricle, viewed through the right foramen of Monro. (C) Floor of the third ventricle infiltrated by the tumor, viewed through the right foramen of Monro.

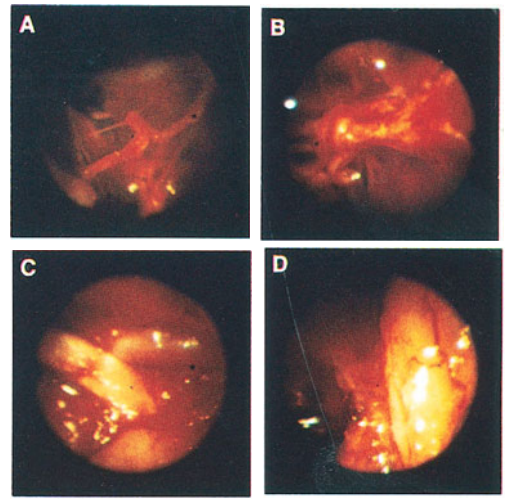

Figure 2. (A and B) Vessels of the circle of Willis after evacuation of a giant craniopharyngioma. (C) Third nerve and posterior communicating artery, covered by clots. (D) Opposite surface of the chiasm, with tumor remnants.

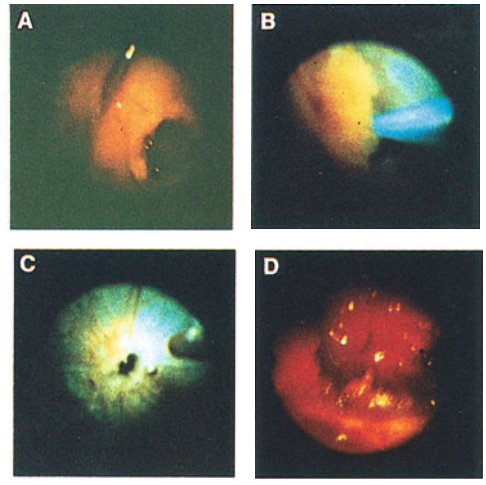

Figure 3. (A) Biopsy of a tumor. (B) Tumor-covered opposite surface of the chiasm. (C) Choroid plexus; closed foramen of Monro. (D) Under the choroid plexus wall of the arachnoidal cyst, which was punctured and emptied.

optic nerves and other basal structures. This particular ventriculoscope is flexible; its fiberoptic system is flexible.

Fukushima has had considerable experience with ventriculoscopes and has published his findings in the *Journal of Neurosurgery*.[1] He maintains that if one takes a conservative attitude toward the management of craniopharyngiomas in terms of preremoval definitive diagnosis or cyst aspiration, then the use of the fiberoptic endoscope is valuable and safe in achieving these aims. However, he claims to have been personally more inclined over the past 10 years to perform radical surgery with the microscope, and therefore his recent experience with ventriculoscopy is very limited. Since the publication of his report in the *Journal of Neurosurgery* Fukushima has developed other endoscopes for CT-guided endoscopy, cervical endoscopy, and spinal endoscopy with some flexible endoscopes as small as 2 mm.

To the question of whether the 2-mm endoscope has an internal channel as well, Fukushima replies that it does not; the smallest endoscope with an internal channel for biopsy, aspiration, or coagulation would be 3 mm. He believes that many people are now utilizing endoscopes with stereotactic laser capabilities, and that there are many applications for use of the endoscope.

Long inquires as to how many of the ventricular craniopharyngiomas in our study were entirely intraventricular, without a tumor component outside the third ventricle.

There is often tumor outside the third ventricle. When we say intraventricular tumor, we mean to say tumors with the major component of their bulk in an intraventricular location—that is, occupying the cavity of the third ventricle. Often these tumors grow upward from the sellar region.

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14

Surgical Treatment of Diencephalic Arteriovenous Malformations

Robert A. Solomon

INTRODUCTION

Arteriovenous malformations (AVMs) of the diencephalon are hazardous lesions. Rupture of an AVM in this location can lead to catastrophic intracranial hemorrhage and a devastating neurological picture. However, surgical therapy for these lesions poses a considerable risk to critical areas of the nervous system. The value of surgical treatment for diencephalic AVMs has therefore been controversial.

We have considered small malformations that primarily involve the diencephalon to be surgically resectable lesions.[1] Twenty-five patients with malformations within the thalamus and basal ganglia have been operated on during the past 6 years. The results of this experience have been gratifying, and indicate that deep-seated AVMs can be effectively treated by resection.

Representative Cases

Case Study 1. A 17-year-old left-handed female experienced a devastating hemorrhage into the right thalamus and ventricular system (Fig. 1). She was in a coma for several days and when she recovered she was left with a hemisensory loss and mild weakness of the left side of the body, as well as a significant recent-memory defect. One month following hemorrhage, she was admitted to the Neurological Institute for surgical treatment. Examination on admission showed a left inferior quadrantanopsia, severe impairment of recent memory, and mild weakness of the left side of the body. An arteriogram was performed and demonstrated an AVM fed by branches of the posterior cerebral artery and an aneurysm supplied by the lateral posterior choroidal artery on the right side (Fig. 2). Further characterization of the

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Figure 1. CT scan of the patient in Case Study 1, showing a large hemorrhage into the posterior right thalamus and ventricular system.

vascular malformation was performed with magnetic resonance imaging (MRI) (Fig. 3). This study demonstrated that the malformation was in the choroidal fissure near the trigone of the right lateral ventricle, with the aneurysm separated from the main mass of the malformation. Surgery was performed via a right parietal craniotomy with the patient in the semisitting slouch position. Through an interhemispheric transcallosal approach to the right lateral ventricle, the malformation was visualized and completely excised. Postoperative angiography demonstrated that there was no residual AVM and over the first couple of weeks following surgery, the patient made a gradual but very satisfying recovery. At 1-month follow-up, the patient continued to have a significant recent-memory deficit,

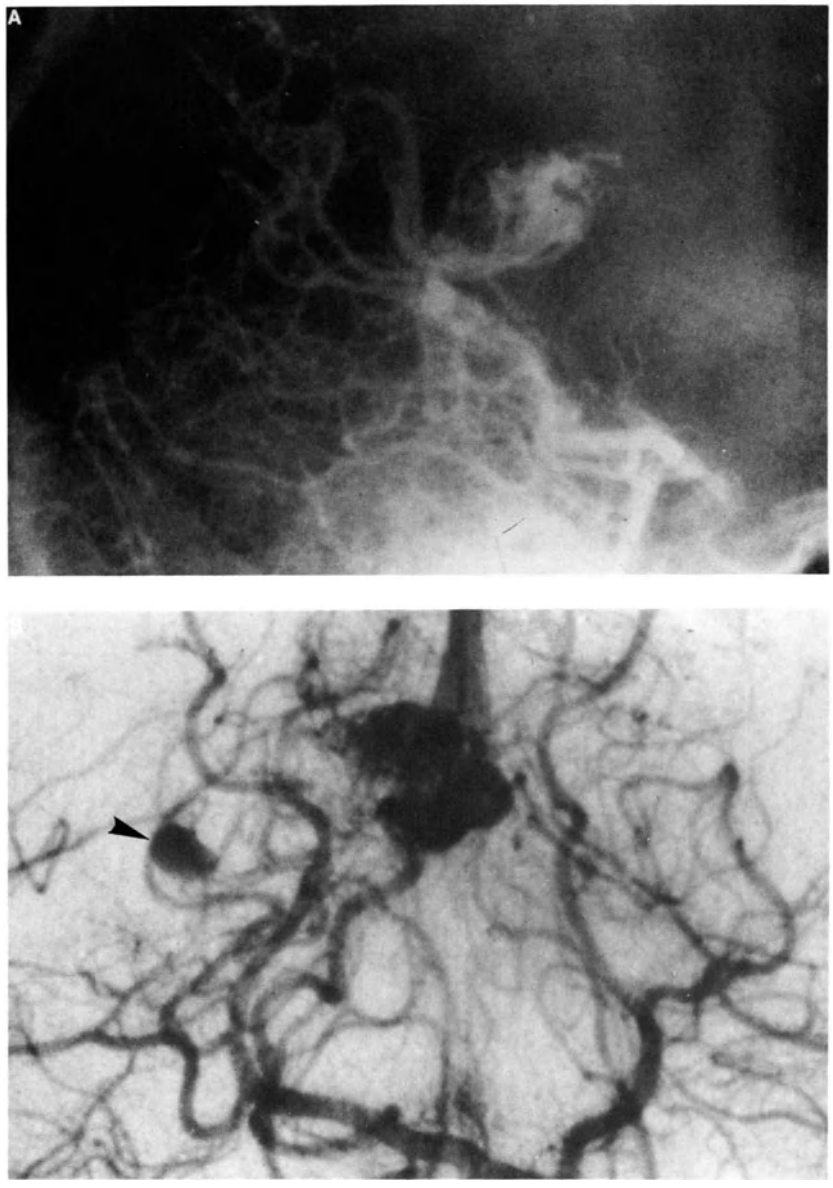

Figure 2. Cerebral angiography of the patient in Case Study 1. (A) Lateral vertebral angiogram showing a malformation fed primarily by posterior cerebral and posterior choroidal vessels. (B) Anteroposterior vertebral angiogram showing the medial malformation and the laterally displaced aneurysm on the posterior lateral choroidal artery (arrow).

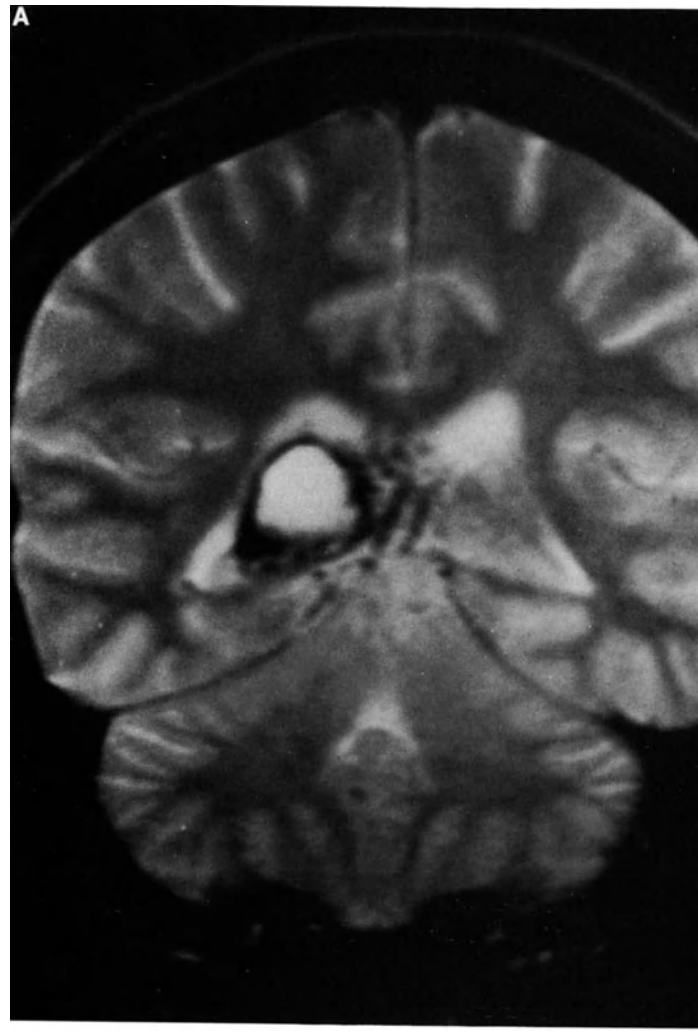

Figure 3. MRI scan of the patient in Case Study 1. (A) Coronal section through the posterior ventricular system, showing location of a blood clot with separation of the aneurysm from the more medially placed body of the malformation. (B) Axial MRI, demonstrating the location of abnormal blood vessels on the floor of the right lateral ventricle.

but her left-sided hemisensory loss had resolved, and her strength had improved essentially back to normal.

Case Study 2. A 23-year-old female had a sudden hemorrhage into the right thalamus and right lateral ventricle (Fig. 4) that left her with a severe left hemisensory deficit, a complete left homonymous hemianopsia, and a mild left hemiparesis. An MRI scan demonstrated a lesion in the region of the right posterior thalamus (Fig. 5). Angiography demonstrated that the patient did indeed have a malformation supplied by the right posterior lateral choroidal artery as well as the

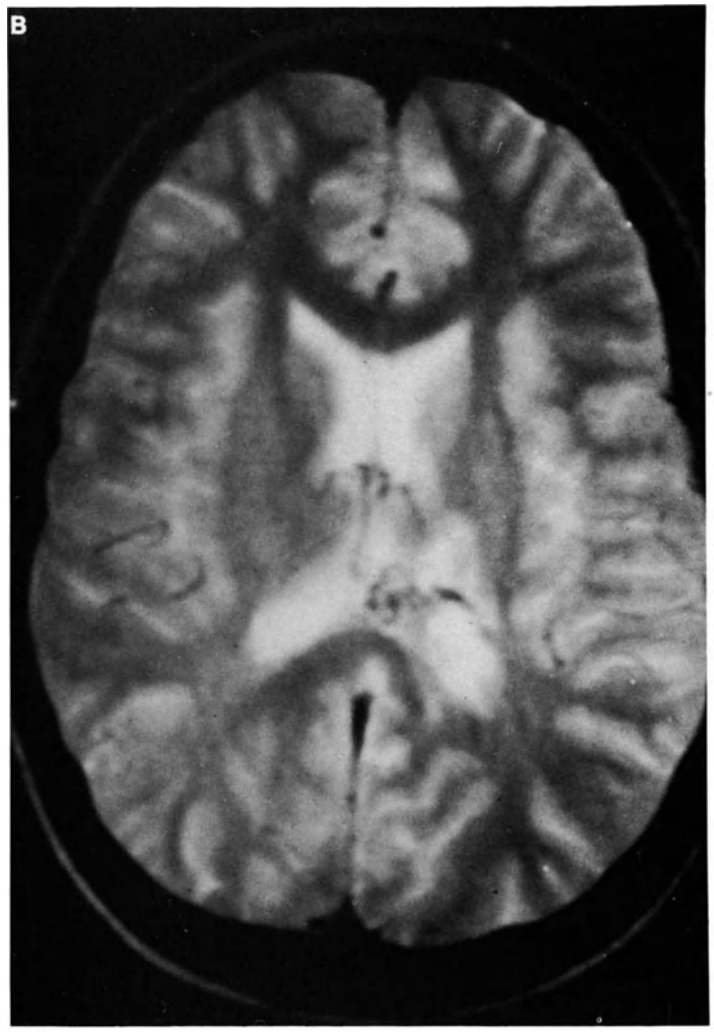

Figure 14. (*Continued*)

anterior choroidal artery on the right side (Fig. 6). Six weeks following her hemorrhage she underwent a right parietal craniotomy with total removal of the AVM. The operation was done with the patient in a semisitting slouch position and the AVM was approached through an interhemispheric transcallosal exposure of the right thalamus. Postoperative angiography confirmed that the malformation was completely removed, but following surgery the patient had slightly increased weakness on the left side of the body. Two weeks following operation she was transferred to an inpatient rehabilitation service, where she regained considerable neurological function. At 2-month follow-up she still had complaints of numbness over the left side of the body and somewhat diminished 2-point-discrimination sensation in the left hand. Although she was ambulatory without any assistance, she did have

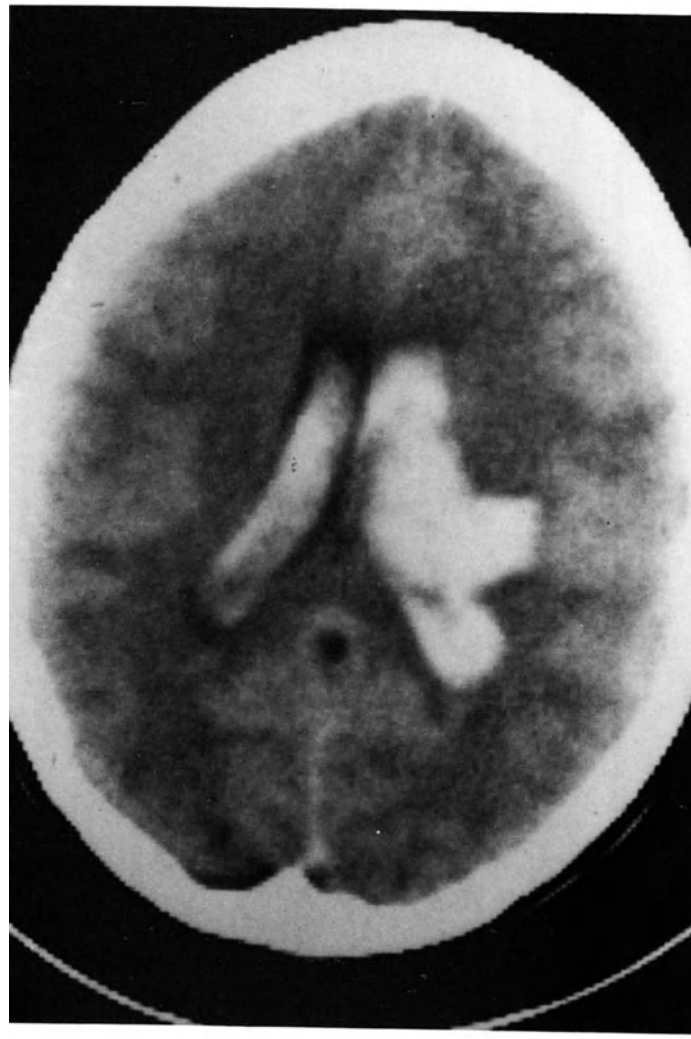

Figure 4. CT scan performed immediately after hemorrhage in Case Study 2, showing the blood clot in the ventricular system and the right thalamus.

a limp referable to a slight weakness of the left leg. The manual dexterity of the fingers of the left hand returned to an excellent functional level.

SUMMARY OF CASES

This series of 25 patients included 14 males and 11 females. Their ages ranged from 14 to 42 years (mean age, 27 years). A summary of these cases is presented in Table 1.

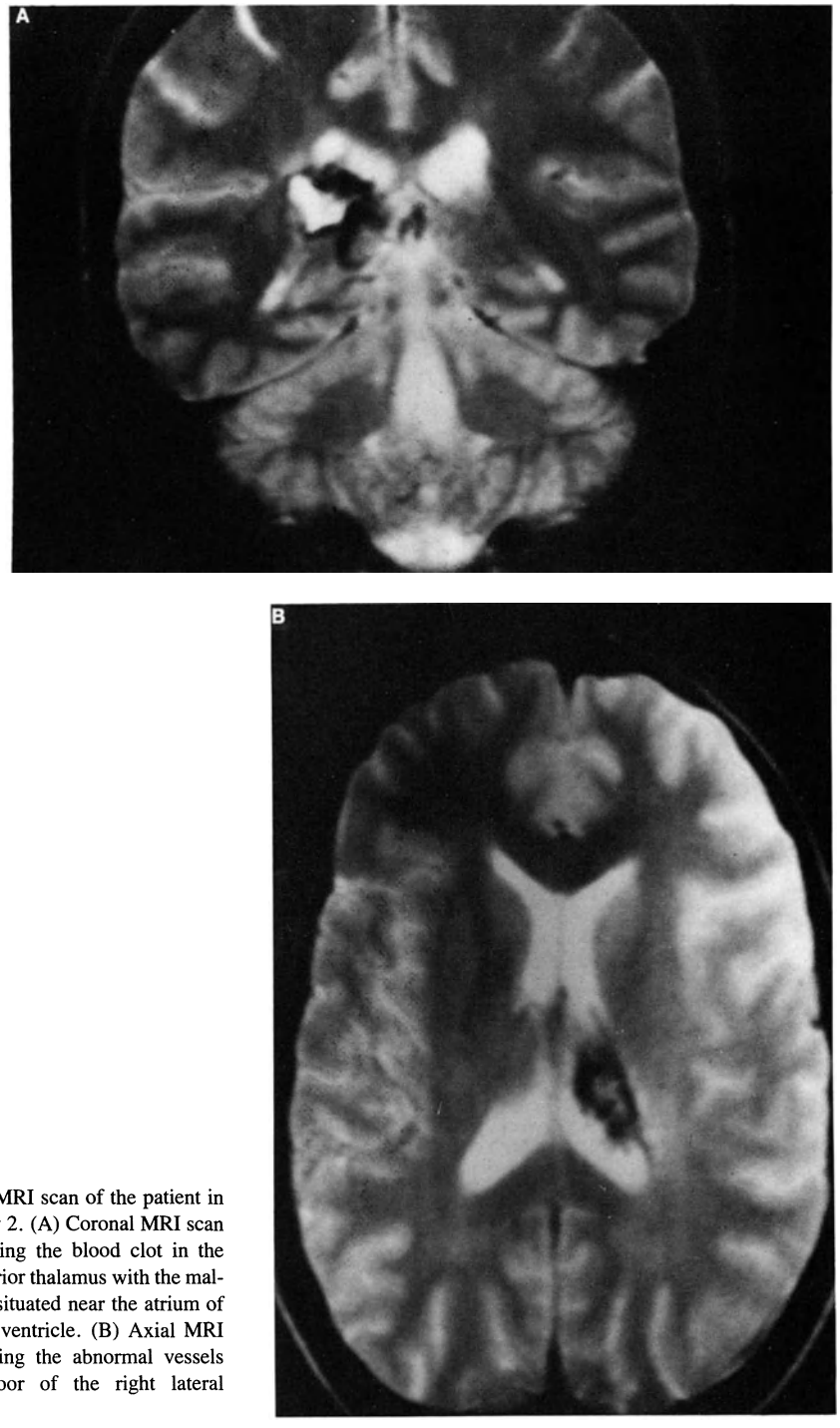

Figure 5. MRI scan of the patient in Case Study 2. (A) Coronal MRI scan demonstrating the blood clot in the right posterior thalamus with the malformation situated near the atrium of the lateral ventricle. (B) Axial MRI scan showing the abnormal vessels on the floor of the right lateral ventricle.

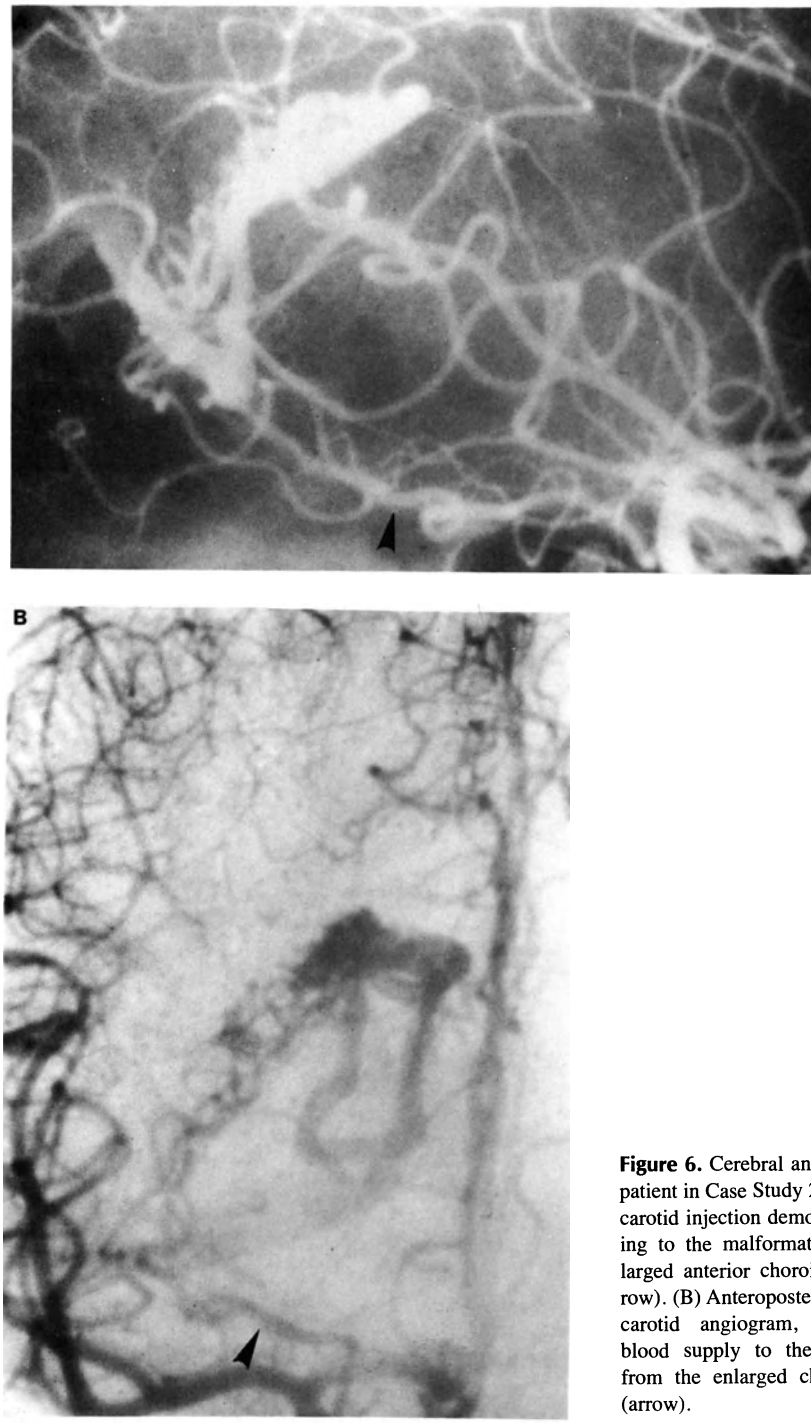

Figure 6. Cerebral angiogram of the patient in Case Study 2. (A) A lateral carotid injection demonstrating feeding to the malformation by an enlarged anterior choroidal artery (arrow). (B) Anteroposterior view of the carotid angiogram, demonstrating blood supply to the malformation from the enlarged choroidal artery (arrow).

Table 1
Clinical Summary of Twenty-five Patients with Thalamocaudate Arteriovenous Malformations

Factors compared	Number of patients
Clinical presentation	
Hemorrhage	24
Seizures	1
Location	
Right	16
Left	7
Bilateral	2
Surgical approach[a]	
Interhemispheric	
Parietal (semisitting)	24
Frontal (supine)	2
Inferior temporal (lateral)	1
Posterior fossa (sitting)	1
Subfrontal (supine)	1
Reoperation (residual AVM)	1
Operative results	
Total removal	21
Mortality	0
Return to premorbid occupation	25
Memory disturbance	13
Homonymous hemianopsia	8
Transient hemiparesis	5
Sustained hemisensory loss	2
Parinaud's syndrome	1
Recurrent hemorrhage	1

[a]Five patients had two operations each.

Clinical Presentation

Twenty-four patients presented with sudden intraventricular or intracerebral hemorrhage as the first manifestation of the AVM. One patient presented with sensory aberrations and headaches, and was the only patient in this series to come to medical attention for reasons other than a hemorrhagic event. In the immediate preoperative period, all patients were alert, oriented, ambulatory, and capable of independent lives. Five patients had a mild residual hemiparesis, four had hemianopsia, and eight had some disturbance of recent-memory function. Five of the eight patients with a preoperative memory disorder bled from lesions involving the left pulvinar, caudate, and fornix.

Location of the Arteriovenous Malformation

Two patients had bilateral involvement of diencephalic structures; one of these malformations extended infratentorially. The remaining patients had supratentorial AVMs that were lateralized; 16 were on the right side and seven were on the left side.

Twenty-three of the 25 malformations in this series were located adjacent to the atrium of the lateral ventricle. One patient had a malformation situated anteriorly in the septal region extending into the anterior aspect of the right thalamus, and one had an extensive AVM that followed the entire corpus callosum, the septal region, fornices, and roof of the third ventricle.

Vascular Anatomy

Although most malformations in this series were supplied by two or more major arteries, the choroidal arteries form the primary vascular supply to AVMs situated near the atrium of the lateral ventricle. Sixteen malformations were fed by the posterior choroidal arteries, and five received input from the anterior choroidal artery. The posterior pericallosal artery, as well as other penetrating branches from the posterior cerebral artery in the region of the fusiform gyrus, supplied 13 of the AVMs. The distal segment of the anterior pericallosal artery was involved in nine cases. Although thalamoperforating arteries were angiographically demonstrated to supply only three malformations, small penetrating vessels supplying the deep aspect of the malformations were encountered during surgery in almost all cases.

The venous drainage from these malformations was always toward the midline. In one case, the primary draining vein ascended in the interhemispheric fissure to reach the superior sagittal sinus. In the remaining 24 cases, the venous drainage was into the deep venous system of the brain: internal cerebral veins, the basal vein or Rosenthal, the vein of Galen, and the straight sinus.

Surgical Technique

Surgery was performed on all patients in this series via an interhemispheric route ipsilateral to the malformation (Fig. 7), the procedure for which follows. A spinal drainage catheter is inserted and the patient placed in a semisitting slouch position. The head is straight and maximally flexed to bring the curved portion of the parietal bone parallel to the floor. A 4 × 4-cm bone flap is formed to the right or left, including the midline. The medial burr holes are placed slightly to the opposite side of the superior sagittal sinus, with the posterior hole adjacent to the lambda. A dural flap is created along the sinus, and medially draining veins are preserved whenever possible. Retractors are placed on the falx and on the parietal lobe to expose the posterior aspect of the corpus callosum. At this point in the operation, some aspect of the malformation may be visualized. When the malformation lies entirely in the floor or wall of the lateral ventricle, the corpus callosum must be divided before the AVM can be appreciated. Resection of the malformation is begun, based on the CT scan, MRI, and angiographic

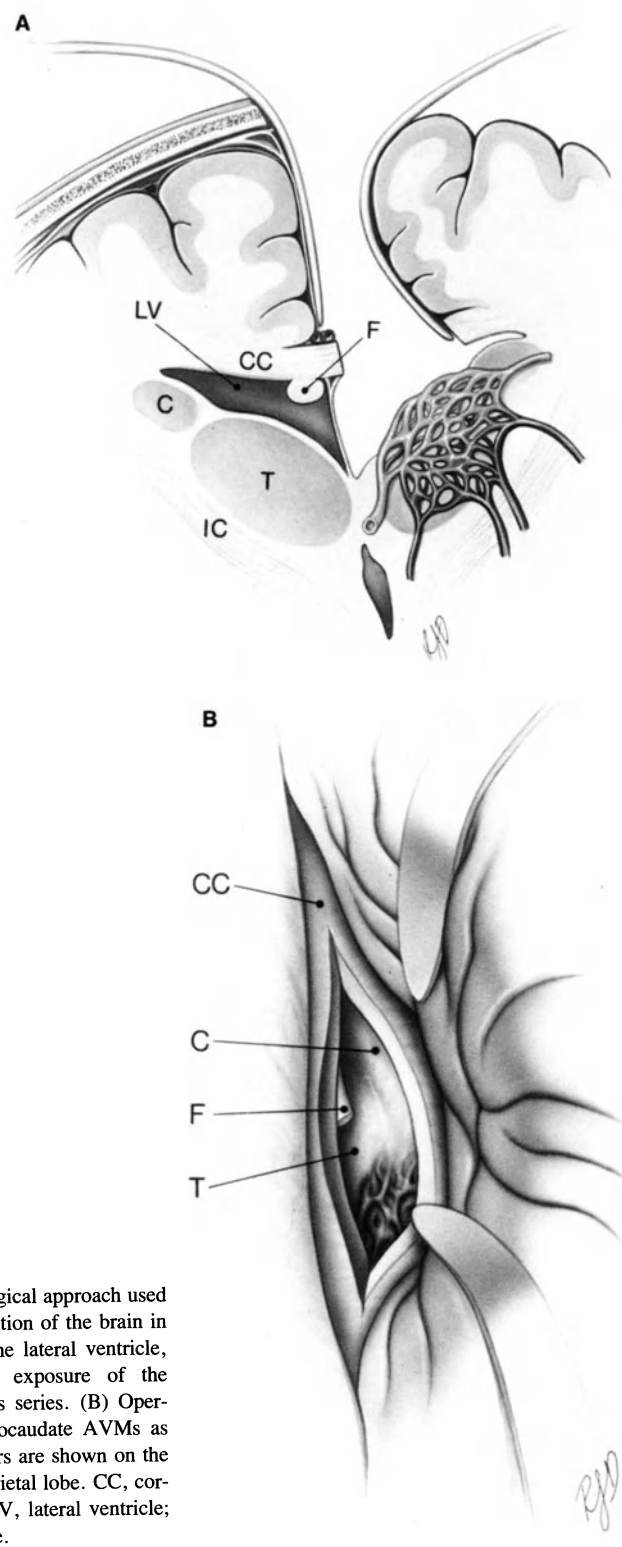

Figure 7. Drawings of the surgical approach used in this series. (A) Coronal section of the brain in the region of the atrium of the lateral ventricle, demonstrating the operative exposure of the thalamocaudate AVMs in this series. (B) Operative exposure of the thalamocaudate AVMs as seen during surgery. Retractors are shown on the medial surface of the right parietal lobe. CC, corpus callosum; T, thalamus; LV, lateral ventricle; F, fornix; IC, internal capsule.

information as well as defined principles of AVM surgery that have been outlined elsewhere.[1–6]

In all cases in this series, the corpus callosum was divided over a distance of about 1–2 cm, and the fornix, which lies just deeper than the corpus callosum, was sectioned ipsilaterally. These maneuvers were necessary to gain access to the atrium of the ventricle. In some patients, the malformation actually involved the corpus callosum and the ipsilateral fornix.

Five patients in this group required two operations: One patient had incomplete removal and required reoperation; one patient underwent a suboccipital infratentorial approach to remove residual malformation in the region of the quadrigeminal plate; one patient had a subtemporal operation to resect a residual malformation extending into the fusiform gyrus; one patient required two interhemispheric operations for a large AVM extending from the anterior third ventricle to the splenium of the corpus callosum; the fifth patient was first operated on by a subfrontal approach to eliminate feeding vessels entering the malformation through the anterior perforated substance—his second operation was an interhemispheric exposure of the anterior right lateral ventricle, in which the malformation was removed from the head of the caudate and the septal region.

Surgical Outcome

There were no operative deaths in this series, and all 25 patients were able to resume their previous occupations after surgery. The most common postoperative complication was a disturbance of recent memory. Thirteen patients were noted to have at least transient problems in acquiring new knowledge. However, eight of these patients had suffered a preoperative memory disturbance as a result of hemorrhage, and only three of these were believed to be worse after surgery. All patients showed considerable improvement with time.

Eight patients were found to have a contralateral homonymous field defect after the operation. Four of these patients had field cuts preoperatively. Two of the eight patients had visual loss in the dominant hemisphere; neither displayed a disabling disconnection syndrome and both were capable of reading and naming colors postoperatively.

There were five cases of postoperative hemisensory loss: Two cleared completely and three are persistent. Five patients had transient hemiparesis, and all of these regained essentially normal strength in 2–12 months. One patient with an AVM extending into the quadrigeminal region developed a profound eye-movement disorder after surgery. Another patient who was neurologically normal developed a sterile ventriculitis and required prolonged steroid therapy.

All 25 patients were studied with postoperative angiography. Total removal of the AVM was confirmed in 21 cases, and residual malformation was noted in four. Reoperation in one of these four patients again failed to obliterate the malformation. This patient rebled from the AVM 2 years after the second surgery, and a third operation at that time removed the residual lesion.

DISCUSSION

Operative resection of AVMs of the diencephalon can be performed with relative safety. The interhemispheric transcallosal approach to the deep paramedian lesions has been described previously in relation to medial hemisphere AVMs,[4] AVMs that follow the tentorial ring,[2] and thalamocaudate AVMs.[1] This approach was first used by Dandy,[7] for removing posterior third ventricular tumors, and we have found it ideal for treating vascular malformations in the region of the atrium of the lateral ventricle. These AVMs invariably drain into the deep medial venous structures of the brain, and the arterial supply derives almost exclusively from the pericallosal and choroidal arteries. With hemispheric retraction, one may reach the posterior cerebral artery as it courses around the lateral side of the brainstem and still have good visualization out to the atrium of the lateral ventricle. Therefore, a medial interhemispheric approach affords unequaled access to the arterial and venous components of these malformations.

Other surgeons have operated on AVMs in the thalamus and caudate region via a transverse incision in the parietal lobe,[8] the superior temporal gyrus,[9] the middle temporal gyrus,[10,11] or the inferior temporal gyrus.[12] These approaches have the disadvantage of transgressing normal-functioning brain before the malformation is reached. In addition, the AVM is first visualized on its lateral surface, whereas the blood supply and venous drainage are on the medial surface. The surgeon must then work around the margins of a tense malformation to secure the arterial feeders.

The postoperative complications and the neurological sequelae of hemorrhage observed in these patients with AVMs near the atrium of the lateral ventricle provide some insight into the functional neuroanatomy of this region of the nervous system (see Fig. 7). The roof and posterior face of the atrium is formed by the posterior body and splenium of the corpus callosum. The body of the caudate nucleus lies inferolaterally, while the floor is formed by the posterior thalamus. The fornix lies on the medial side in the region of the choroidal fissure. Seven patients in this series bled from malformations involving these structures on the left (dominant) side. Six of the seven patients developed memory problems consequent to AVM rupture. The other 18 patients had right-sided or bilateral lesions, and only three of these patients had a preoperative memory disturbance. One of these patients was left-handed. Postoperatively, five additional patients displayed memory dysfunction, and one of these patients had a bilateral AVM that required sacrifice of both fornices and the corpus callosum.

These data imply that dominance extends to the limbic system, and that the left fornix, thalamus, and/or caudate nucleus are critical for recent-memory function. Although considerable improvement in memory occurred in every impaired patient, in no instance did memory function return to normal once it had been damaged.

The experience of Drake,[9] Kunc,[13] and Yasargil et al.,[14] in dividing the posterior corpus callosum indicates that no serious functional impairment results. Several of our patients underwent psychometric testing following partial surgical division of the splenium of the corpus callosum. In all instances a visual disconnection syndrome was demonstrable, but no patient was functionally impaired by this disconnection. Preser-

vation of reading and naming functions, even when there was a dominant-hemisphere hemianopsia, was due to the limited section of the corpus callosum that we utilized. The splenium was never completely divided.

The preoperative preparation of these patients requires sophisticated neuroradiological studies. High-resolution CT scanning and, more recently, MRI have proved invaluable for the precise localization of AVMs, and for defining their relationships to the tentorium, brainstem, and ventricular system. Stereoangiography has been useful in appreciating the three-dimensional vascular anatomy, which is often critical for planning the surgical approach.

Embolization has been a useful adjunct to the surgical treatment of large supratentorial AVMs[6]; however, malformations deep in the thalamus and the caudate region are generally not suitable for this procedure. These AVMs tend to be supplied by distal branches of the major arteries, such as the choroidal, posterior cerebral, anterior cerebral, and thalamoperforating arteries. These vessels generally have small intraluminal diameters and arise from parent vessels at right angles. These factors make embolization hazardous and therefore not usually indicated for malformations in this location.

Gamma irradiation for the treatment of small AVMs has been advocated by Steiner,[15] who reported successful treatment of a large group of patients with complete obliteration of the malformations. The major drawback to this method is the long latency between treatment and obliteration of the malformation. In many instances, this period exceeds 2 years, during which time the patient is at risk for hemorrhage. Additionally, the long-term deleterious effect of this high-energy radiation is unknown. Therefore, patients should be chosen carefully for radiosurgery.

Four patients in this series had incomplete removal. One of these patients had two operations, both of which failed to obliterate the malformation. We have noted that many of these deep malformations have indistinct margins, and this factor is reflected in the increased technical difficulties that may accompany surgical removal of thalamocaudate AVMs. Only one patient rebled from an incompletely removed AVM, but the possibility of incomplete removal must be factored into the equation when considering operating on malformations in this location.

Reliable criteria for relating the surgical morbidity associated with diencephalic AVMs to their natural history will probably never be available.[16,17] Nonetheless, the incidence of death or serious morbidity from hemorrhage of deep-seated AVMs is substantial,[18] and this factor warrants surgical intervention. Compared to the risk of morbidity due to an untreated AVM, which approaches 50%,[6,19] no patient in this series of 25 patients was significantly impaired by surgery.

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15

Laser Surgery of Tumors and Arteriovenous Malformations of the Diencephalon

John M. Tew, Jr., and Mario Zuccarello

INTRODUCTION

The diencephalon is the part of the brain located between the cerebrum and the midbrain.[1,2] Most of the anatomical structures that constitute the diencephalon form the boundaries of the third ventricle, which is bounded laterally by the thalamus on either side. The anterior floor of the third ventricle is composed of the hypothalamus and the posterior floor is composed of the red nuclei and subthalamic structures. The posterior wall of the third ventricle is bounded by the Sylvian aqueduct inferiorly and the stria medullaris and habenula superiorly. The anterior wall of the third ventricle is bounded by the lamina terminalis inferiorly and the anterior commisure superiorly. The roof of the third ventricle is formed by the tela choroidea, containing the paired internal cerebral veins. These arise anteriorly at the confluence of the septal and thalamostriate veins, and are united posteriorly with the veins of Rosenthal to form the vein of Galen.

The foramen of Monro is bordered by the distinctive column of the fornix anteriorly and then superiorly as the fornix arches posteriorly near the midline. The columns of the fornix sweep laterally, splitting farther apart as they travel to each temporal lobe. Contiguous with and superficial to the fornices is the septum pellucidum, which is bounded superiorly by the corpus callosum. The body of the corpus callosum overlies the septum pellucidum and the third ventricle.

Although the tumors and arteriovenous malformations (AVMs) of the diencephalon are responsible for only a small percentage of the lesions affecting the central

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nervous system (2–3%), they present very difficult surgical challenges.[3,4] The major difficulties in dealing with diencephalic tumors are their intimate relationships to critical neural and vascular structures and their deep location. Furthermore, AVMs present additional difficulties because their feeding arteries are obscured on the undersurface of the malformation and because these AVMs have high-flow characteristics. For these reasons, tumors and AVMs of the diencephalic region have frequently been considered to be inoperable. A number of technological advances in the last few years have enabled us to meet these challenges.

First, the development of sophisticated neuroradiological diagnostic tools such as computed tomography (CT) scanning and magnetic resonance imaging (MRI) have made it possible to define the neuroanatomical construct with which we are dealing, and to plan the best surgical approach. Second, the introduction of the operating microscope has allowed us to approach deep, delicate structures such as the diencephalon. Finally, the use of a "no-touch," nonmanipulative technique—laser surgery—allows us to remove neoplastic and vascular lesions through the smallest exposures, minimizing retraction of vessels and other neural structures that may impede access. We believe that the use of the CO_2 and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers plays an important role in surgical removal of lesions located in the diencephalon.[5–7]

In this chapter, we will review our experiences with 38 tumors and 20 AVMs located in the diencephalic region that were operated on with the CO_2 laser and Nd:YAG laser.

Table 1 shows the histological classification of the tumors. Eighty-one percent of these lesions could be totally removed based on radiographic techniques. There was local recurrence in 12% and metastases in 4%. Radiation therapy was used in 48% of all cases. There was no operative mortality and morbidity was limited to short-term memory loss, hydrocephalus, and infection (Table 2).

This series consisted of 20 consecutive AVMs with a primary thalamic component (Table 3). All 20 patients presented with symptoms related to cerebral hemorrhage.

Table 1
Laser Removal of Third Ventricular Lesions

Type of lesion	Number of cases
Arteriovenous malformation	20
Colloid cyst	12
Astrocytoma	9
Pinealoma	4
Ependymoma	3
Meningioma	3
Neuroectodermal tumor	3
Metastatic tumor	2
Epidermoid	2
TOTAL	58

Table 2
Laser Removal of Third Ventricular Tumors via the Transcallosal Route[a]

Result	Percentage of total cases
Mortality	0%
Complications	
Disconnection syndrome	0%
Short-term memory loss	19%
Hydrocephalus	31%
Infection	2%

[a]Sampling of 38 cases.

The incidence of multiple recurrent hemorrages was 82%, with one patient suffering five hemorrhagic episodes. Preoperative neurological deficits are shown in Table 3. The malformation was identified angiographically in 19 patients and remained occult in one patient. Primary arterial supply included the anterior and posterior pericallosal arteries and perforating branches of the anterior and posterior choroidal arteries. AVMs ranged in size from 2–8 cm. The postoperative status was generally unchanged (Table

Table 3
Laser Surgery of Thalamocaudate Arteriovenous Malformations[a]

Clinical presentation
Hemorrhage (20 cases; 17 multiple)
Hydrocephalus (2 cases)
Preoperative status
Paralysis (16 cases)
Dystonia (4 cases)
Visual field deficit (6 cases)
Hemisensory deficit (7 cases)
Memory deficit (15 cases)
Hydrocephalus (7 cases)
Results
Mortality (0 cases)
Total removal of tumor (19 cases)
New memory deficit (0 cases)
New hemianopsia (3 cases)
New paralysis (2 cases)
New hemisensory deficit (2 cases)
Recurrent hemorrhage (0 cases)

[a]Sampling of 20 cases.

3); in several of the patients there was some worsening, but this was not significant. There was no operative mortality. We had total removal in 19 of the cases and had to reoperate on one irradiated patient twice to achieve a total removal.

TECHNICAL DATA

We prefer the transcallosal approach in dealing with diencephalic lesions.[8,9] Only three cases of AVMs were approached via a transcortical leukotomy, principally because of the bulk of the malformation and because there was so much in the atrial area that we did not feel we could get all of the AVM out through a transcallosal approach.

Using a microoperative technique and a microretractor system with blades as small as 2 mm in width, and laser vaporization and coagulation, tumors and AVMs can be removed through a callosal incision measuring no more than 2.0 cm in length. The interhemispheric approach requires particular consideration in the areas of head positioning, bone-flap shaping (because of the presence of sagittal sinus), and location of cortical veins. For excellent references on the various approaches to the ventricular structures, the reader is referred to the references at the end of this chapter.[8,9] Exposure of the corpus callosum is gained by retraction of the medial bank of the ipsilateral hemisphere laterally. The deep, free edge of the falx can be retracted somewhat by a retractor blade placed opposite the retracted hemisphere. As soon as the cingulate gyrus is dissected, the pericallosal arteries identified, and the corpus callosum recognized, a callostomy is performed with a focused continuous-mode CO_2 laser beam of 3 W. Most openings can be limited to 2.0 cm. In the case of diencephalic tumors the CO_2 laser is most often used.[7,10,11] It produces an invisible beam in the far-infrared wavelength (10.6 μm). The energy is absorbed onto the surface to which it is applied; a thermal reaction causes vaporization of intracellular water and tissue ablation by a "no-touch," nonmanipulative technique. Moreover, CO_2 laser energy is not pigment-specific, and therefore vaporizes tissue with an efficiency that is independent of vascularity.[12]

Using a central coring technique and application of focused laser energy at 5 W, one can remove the entire lesion as the capsule collapses inward, delivering more mass to the exposed area. Great care must be exercised to avoid laser injury to the internal cerebral veins. We prefer to use the CO_2 laser attached to the micromanipulator, which mounts to the base of the microscope. The micromanipulator provides precise control of the laser beam, which is coaxial with vision through the microscope. The obvious advantage of this technique is that it allows the surgeon to directly observe the removal of neoplastic tissue through a small exposure, minimizing retraction and manipulation of vascular and neural structures.[7,10] All of these factors contributed to the low morbidity in these cases.

We excised all 20 AVMs utilizing the Nd:YAG laser. A Nd:YAG surgical laser was also used for most AVMs. This laser emits a continuous wavelength of energy at incident powers from 0–100 W. The laser light, with a wavelength of 1.06 μm, is delivered via a 300-mm quartz crystal fiberoptic handpiece or via a focusing micromanipulator attached to the surgical microscope.[7] The Nd:YAG laser functions pri-

marily as a hemostatic device because of its selective affinity for hemoglobin pigment.[13] During surgery, the spot size of the laser beam can be changed depending upon the size of the vessel that needs to be occluded. With a handheld probe, a focused spot size of 2 mm at powers of 10–20 W is recommended. With a micromanipulator, infinite focus size is provided and it can be adjusted to the size of the vessel to be occluded. Defocusing the laser beam results in increased focal size, which will vaporize more superficial volumes of tissue over a larger area. Because of the longer extinction length of Nd:YAG energy in neurological tissue, the beam tends to penetrate to a variable depth below the surface.[7,14,15] The scatter effect caused by this penetration results in deep heating and coagulation throughout the tissue. But effective heat dissipation, with sparing of viable neural tissue, is promoted by the selective absorption of laser light by hemoglobin and by the ability to limit laser exposure to the desired vessels.

Histological study of AVMs excised with the use of the Nd:YAG laser shows that the most prominent effect of laser coagulation is shrinkage of collagen of AVM vessels, which leads to laser-induced obliteration of blood vessels.[13,16] Moderate contraction of the muscular media and corrugation of the elastica are associated features. At a tissue penetration depth of 2–3 mm, brain parenchyma is selectively preserved in acute studies while small diameter vessels show contraction of collagen.[16]

CONCLUSION

The CO_2 and Nd:YAG lasers have become standard surgical tools for the removal of diencephalic lesions.[7] The CO_2 laser plays an important role in surgical removal of tumors because of the improved ability to work on deep lesions with minimal neural and vascular retraction. The risk of damage to vascular structures such as the internal cerebral veins needs to be kept in mind.

The Nd:YAG laser is an effective adjunct to bipolar coagulation in removing deep-seated AVMs.[17] The biophysical properties of this laser and the clinical results of its use demonstrate its ability to enhance AVM removal. Our results provide documentation that diencephalic lesions can be treated with an acceptable rate of morbidity.

The CO_2 and Nd:YAG lasers are important adjuncts in achieving the best results of therapy. Careful training and judicious use of these new techniques increase the neurosurgeon's capabilities to extirpate diencephalic tumors and AVMs.

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16

The Relationship between Pituitary Adenomas and the Diencephalon

Kalmon D. Post

INTRODUCTION

Pituitary tumors are discussed in some depth throughout this volume. This chapter will focus on a few ways in which pituitary tumors interact with the hypothalamic and diencephalic regions.

Very large tumors may present as a mass effect, with neural compression and visual problems. It is interesting that we rarely see other types of mass-effect problems due to hypothalamic compression. On the other hand, the case of a 3-mm tumor in a young lady presenting with infertility reflects the difficulties we have to consider regarding hypersecretion and the possible etiological role of the hypothalamus. Particularly as regards Cushing's disease, an argument could be made that the problem is in the hypothalamus rather than in the pituitary. However, I am going to advance the opposite position and I will not discuss the relationship between the hypothalamic releasing factors and the pituitary hormones, which has been summarized in Chapter 2 of this volume.

NONSECRETING ADENOMAS

Case Study 1. Figure 1 represents a 50-year-old gentleman who merely banged his head in a minor automobile accident. Because he had some mild persistent symptoms, he underwent an MRI scan, which demonstrated a tumor. The tumor was nonsecretory. His pituitary function and vision were normal, and yet the tumor came within about a millimeter of the optic chiasm.

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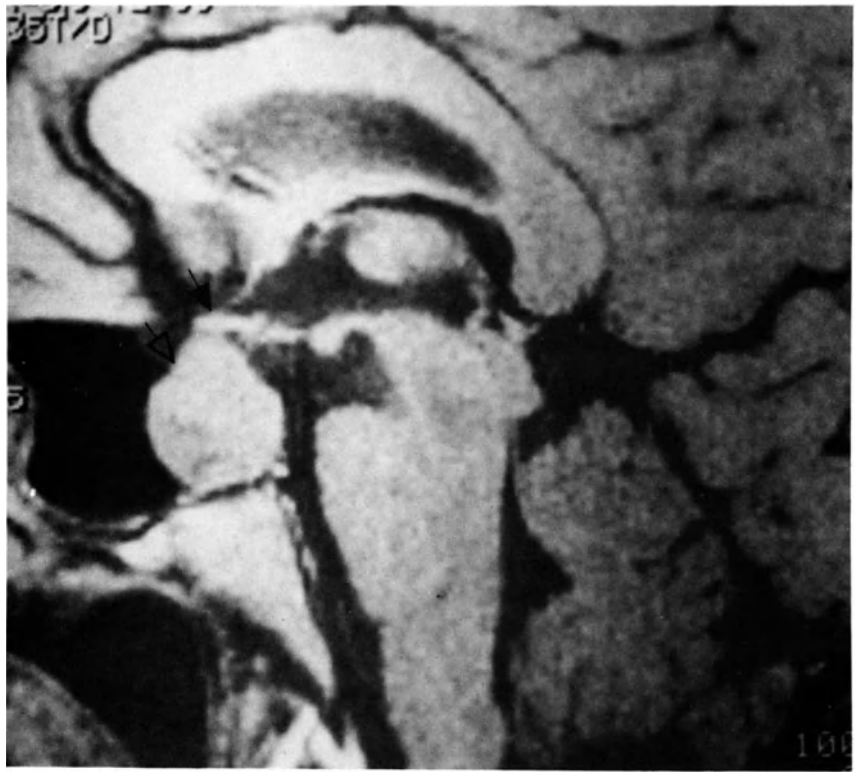

Figure 1. Sagittal T_1-weighted MRI demonstrating sellar tumor (open arrow) with suprasellar extension (SSE) up to the optic chiasm (black arrow).

In the span of 6 weeks, I may see three patients like this, all with incidental findings consistent with nonsecretory adenomas just about touching the chiasm. The real issue is, how do you treat patients like this? Do you follow them? Do you wait until they develop visual changes?

In the past, radiation therapy might have been recommended, but I do not think that course would be considered now. Likewise, medical therapy would not be of any benefit in this situation. There are two possible approaches. Transsphenoidal resection of such a lesion aids diagnosis of the problem, as well as providing the opportunity to cure it at the earliest time, when it is most curable. The other option is to follow the lesion's progress with only observation. Certainly, there would be various recommendations. My personal preference is for surgery, since we can operate transsphenoidally with a high rate of success and a low rate of morbidity.

Case Study 2. Figure 2 represents a 39-year-old gentleman who had had several refractory colds and upper respiratory infections during the year. He also had some mild headaches and, more recently, over a period of about a month, some very mild visual problems. His pituitary function was entirely normal and, in fact, his wife was 6 weeks pregnant. This is an example of someone with an enormous mass that

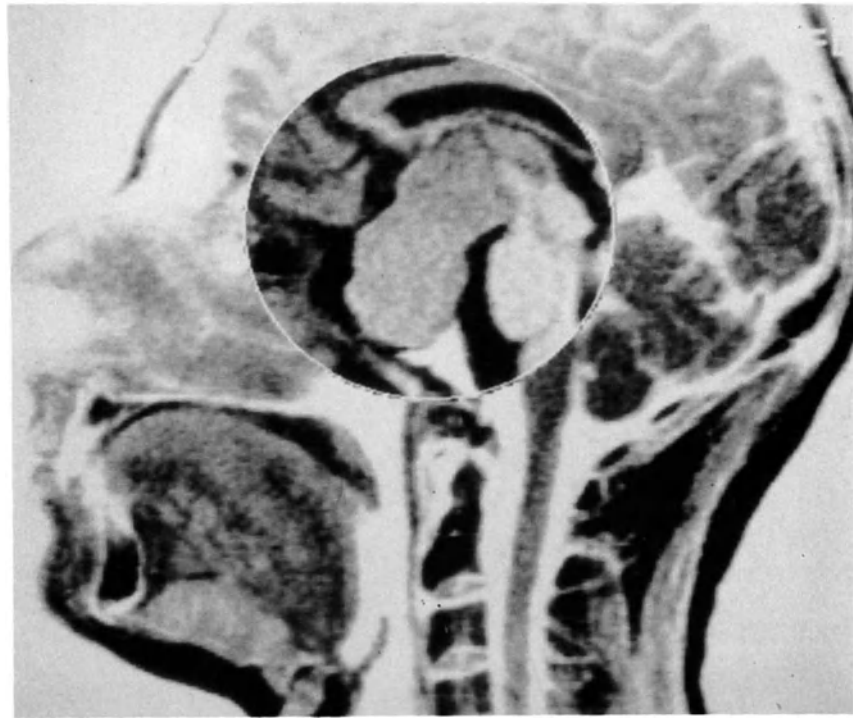

Figure 2. Sagittal MRI demonstrating sellar adenoma with suprasellar extension (SSE) reaching the foramen of Monro.

goes up quite high, clearly distorting the hypothalamic area. Yet, on endocrinological evaluation, this patient's function was entirely normal. He had a visual field defect that was relatively mild, considering the size of the mass. There was a wide communication between the sellar and the suprasellar mass.

The wide communication between the sellar and the suprasellar mass made this an ideal case for transsphenoidal surgery. While I do not believe this tumor could be cured entirely by surgery from any direction, I believe this is one I would do from below, without considering craniotomy. In fact, transsphenoidal surgery was performed in this case, followed by radiation therapy. The patient's vision improved, although it had not been that badly compromised prior to surgery, and he continued to do well. This case demonstrates that, with a slow process, the hypothalamus and diencephalon can tolerate great compression and distortion and still function.

Case Study 3. Figure 3 shows a 28-year-old woman in her sixth month of pregnancy who suddenly developed a severe headache with some visual loss. An MRI scan showed this lesion to be blood, consistent with pituitary apoplexy.

How would one handle a patient who is 6 months pregnant and has had some visual loss, but no pituitary dysfunction? Her prolactin was normal, so bromocriptine could

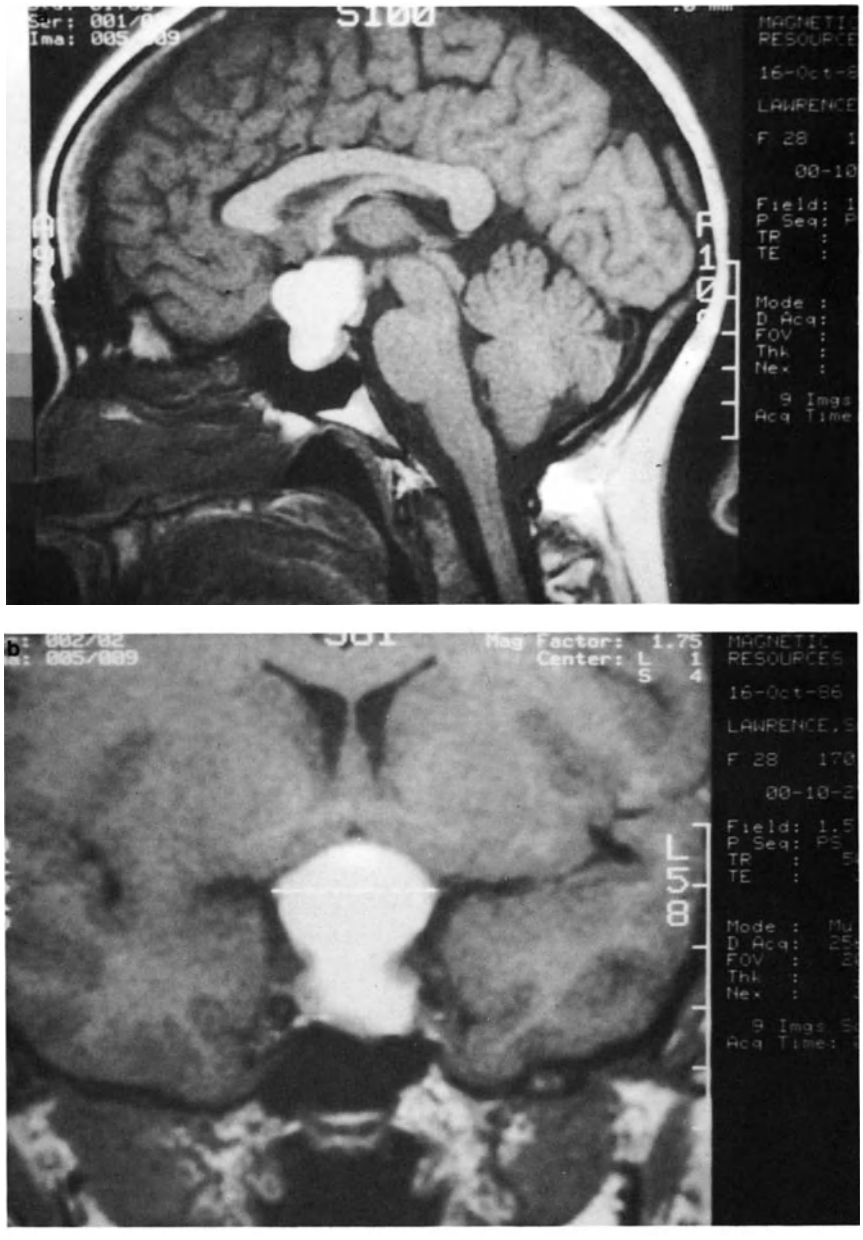

Figure 3. (a) Sagittal T_1-weighted MRI demonstrating large sellar mass with suprasellar extension (SSE). The intensity of the signal is consistent with fresh blood. (b) Coronal T_1-weighted MRI of the same patient. The optic chiasm is compressed.

not be used. We could have opted for steroid therapy throughout the pregnancy while following her vision, or we could have elected to operate. After our team discussed the situation with our obstetrics/gynecology and anesthesia consultants, we performed what I consider to be a conservative transsphenoidal procedure. The patient tolerated surgery very well, but had a little bit of CSF leakage during and after the operation, so we eventually had to rehospitalize her and keep her at bedrest with spinal drainage for several days. She recovered nicely and subsequently completed her pregnancy successfully. A particular dilemma is encountered with this type of patient, who presents during pregnancy either with tumor enlargement or, as in this case, with apoplexy.

A spinal catheter for either CSF drainage or instillation of air is very helpful in many of these operations. A couple of years ago, I used the catheter in every transsphenoidal patient. Now, with large tumors, I put in air and try to outline the top of the tumor. In this way, it is possible to see air descend, while visualizing the stalk above the larger tumor. With small tumors, CSF can be removed if arachnoid comes down into the sella as the tumor is excised. The arachnoid is elevated, permitting a much easier and safer look throughout the sella for microadenomas. We have seen a number of patients who have had some bothersome headaches afterwards, so we are a bit more selective now in using this technique with large tumors. I think the catheter-and-air procedure is helpful with the smaller tumors in Cushing's disease patients, and I still tend to use it when I really need a good look within the sella.

> *Case Study 4.* Figure 4 is a CT scan from an acromegalic patient who had had transsphenoidal surgery in another hospital. She also had had proton-beam therapy, but was still acromegalic.

The CT scan shows a pituitary tumor with a very large subfrontal component. This was an adenoma that I believed needed a craniotomy. When the extension is into the middle fossa, as in Figure 5, I have been leaning more and more toward the transsphenoidal route rather than craniotomy, because I do not think surgery is going to cure this type of tumor. As long as I can adequately decompress the tumor from below, particularly in an older patient, I prefer to do that and offer radiation postoperatively. Nevertheless, we still consider craniotomy for a few patients.

> *Case Study 5.* Figure 6 shows a recurrent adenoma in a patient who had been operated on numerous times before coming to us. He was an avid tennis player, and whenever he started losing to his partner, it was because he could not see the ball on his backhand side. He knew from this that it was time to have another craniotomy. He had a tongue of tumor coming forward, overlying the planum.

For a patient like this, who has been opened from above, has lost the normal planes, and has eccentric extension anteriorly with significant visual problems, I believe surgery from above is safer. If this were the initial presentation, I could argue the other way, but I would probably still lean toward craniotomy because of this anterior component.

> *Case Study 6.* Figure 7 shows a tumor with enormous lateral extension, a necrotic central portion, and a different presentation. This represents a 58-year-old woman who presented with meningitis and CSF leak.

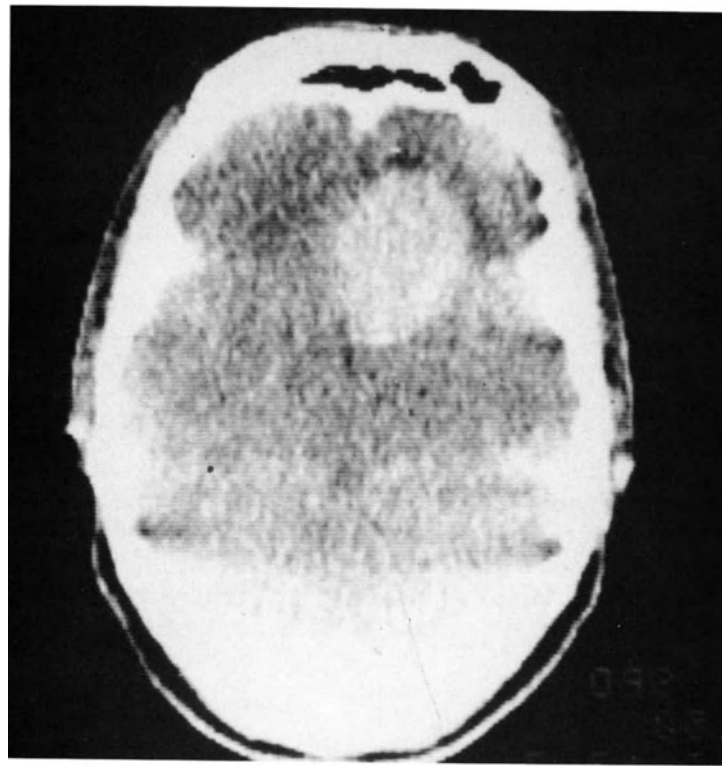

Figure 4. Enhanced axial CT scan of a patient with acromegaly. A large subfrontal extension of tumor is evident.

Here, I believe the surgeon's hand was forced, no matter what the degree of lateral extension. The patient had a trace visual field defect from the upper component, the main part going laterally through the cavernous sinus. We did this procedure transsphenoidally, both to decompress the tumor and to seal the leak. This approach also allowed the patient to have radiation therapy safely, with her optic nerves completely decompressed.

I have presented various nonsecretory tumors with extension in different directions, all of which I believe can be handled transsphenoidally. These types of tumors force the surgeon to carefully consider the therapeutic options. In addition, I am impressed, each time I see large adenomas like these, that so many of the patients can be endocrinologically and/or neurologically intact. This is especially surprising considering the complexity of the diencephalon.

ACTH-SECRETING ADENOMAS

In Cushing's disease more than in any other pituitary entity, perhaps, arguments have been made for the pathological substrate being in the hypothalamus rather than in

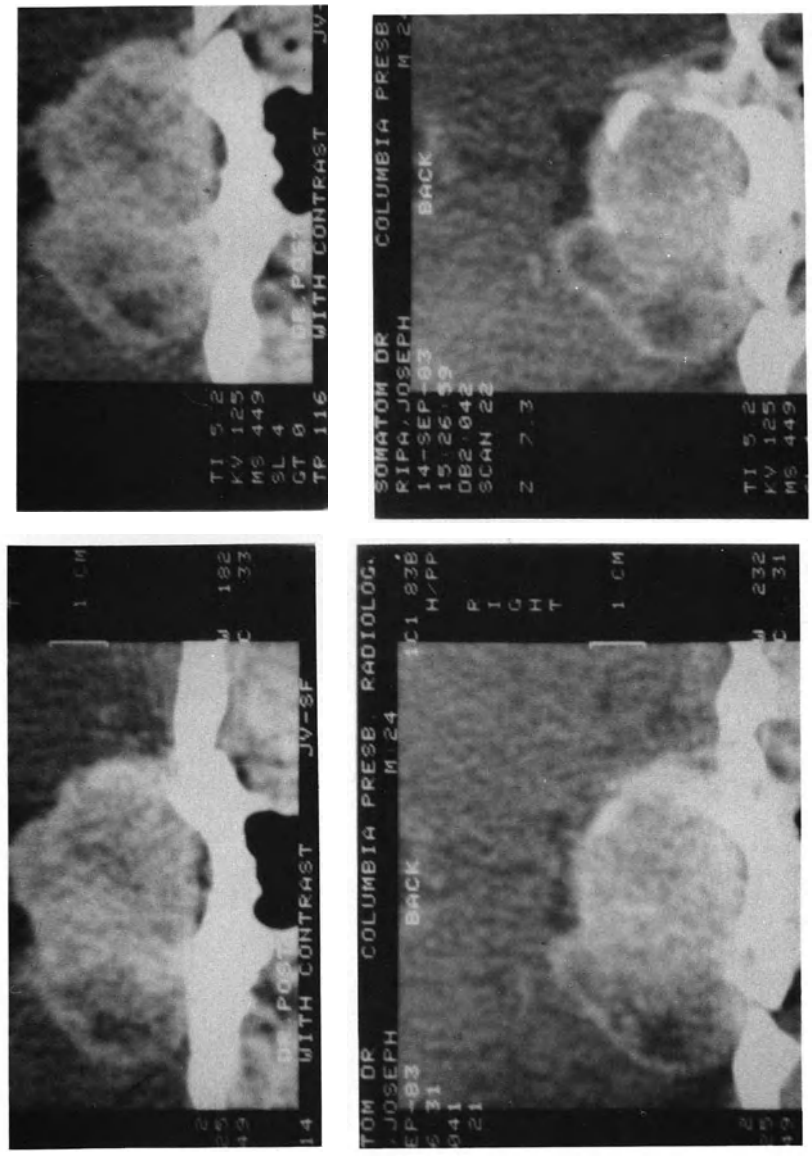

Figure 5. Coronal enhanced CT scans of a patient with a large pituitary adenoma and left lateral parasellar extension through the cavernous sinus.

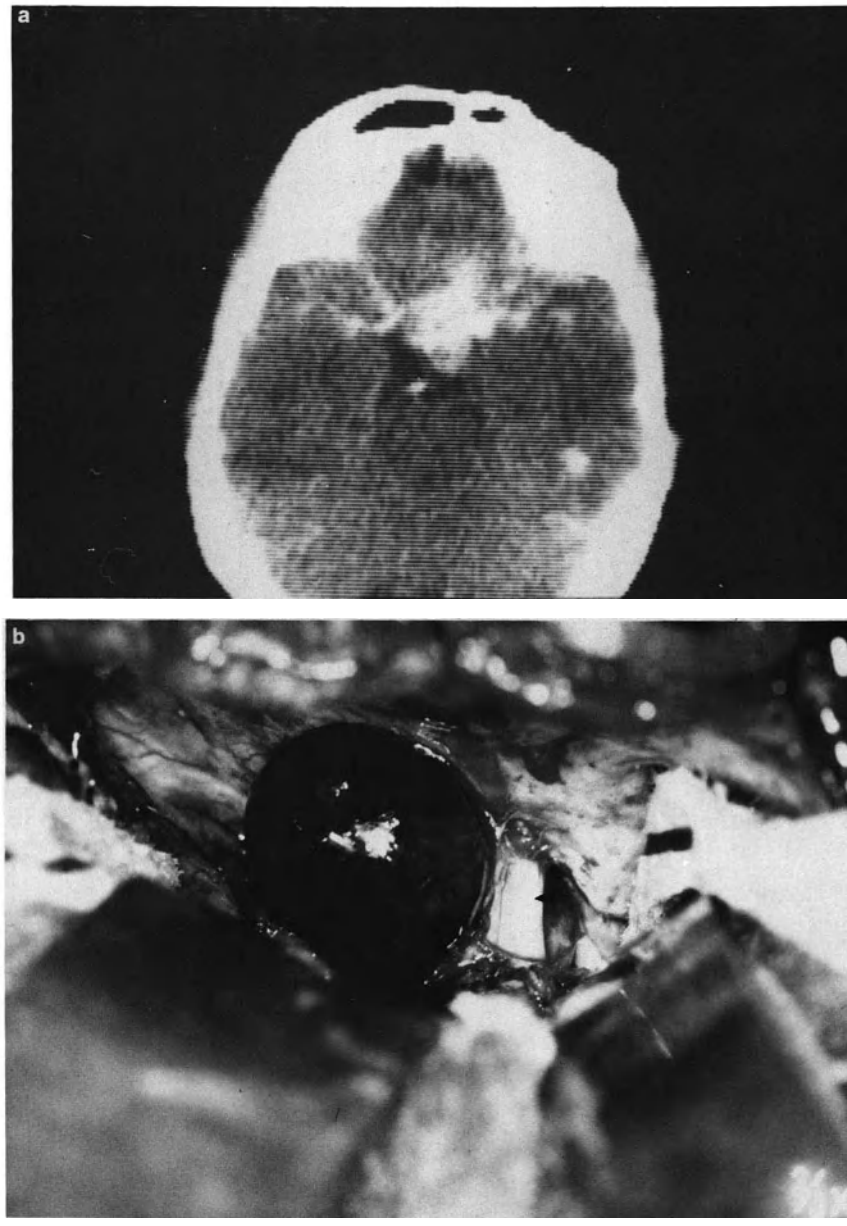

Figure 6. (a) Axial enhanced CT scan of a patient with a recurrent nonsecretory pituitary adenoma and subfrontal extension. (b) Operative photograph of the same patient, demonstrating the adenoma adjacent to the right optic nerve (black arrow) and overlying the planum sphenoidale.

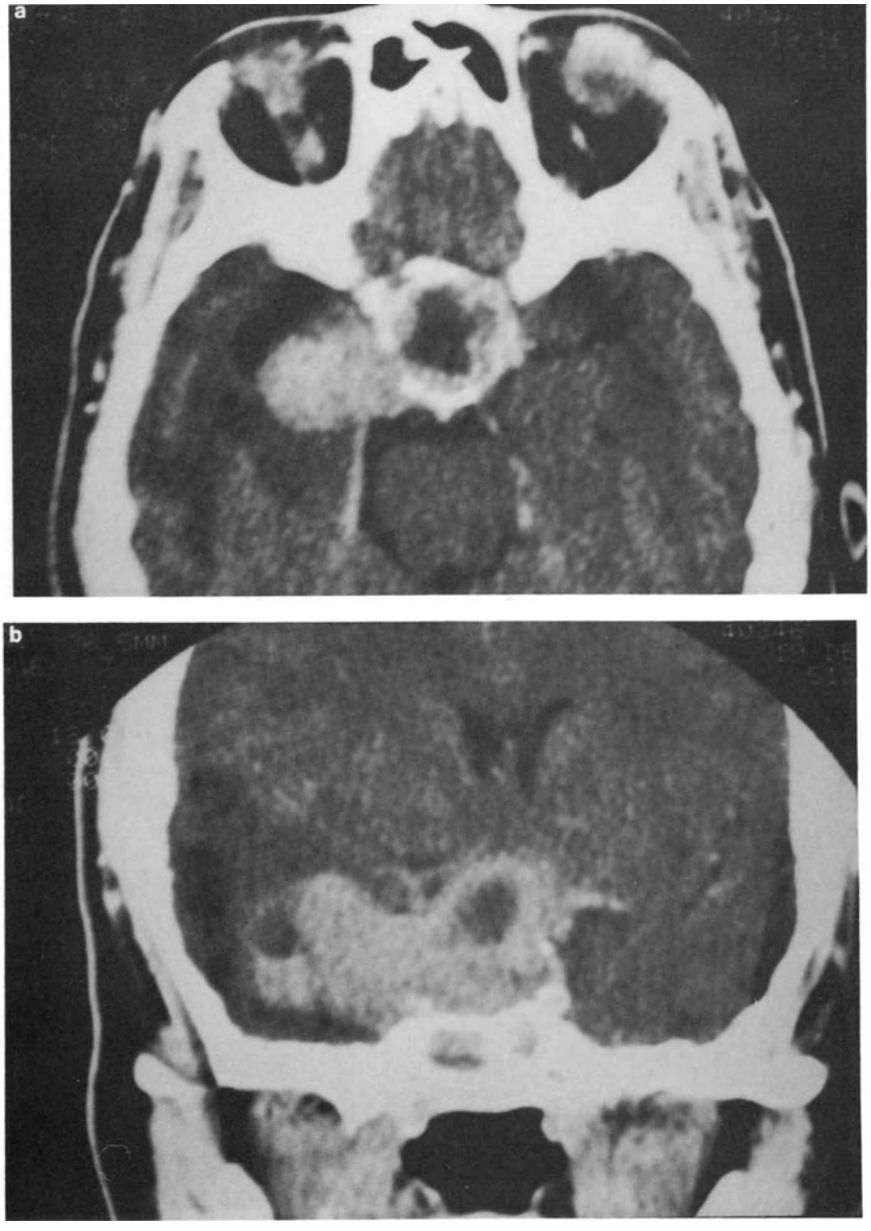

Figure 7. (a) Axial enhanced CT scan demonstrating a large sellar adenoma with parasellar extension into the right temporal fossa and a necrotic central portion. (b) Coronal enhanced CT scan of the same patient.

the pituitary gland.[1–4] An antiserotonergic drug, cyproheptadine, has been suggested to treat Cushing's disease, since there is a positive serotonergic control.[5] I find no support for this idea and I do not find this treatment effective. So, despite the irregularity in circadian rhythms and despite the depression that is seen, the fact that when the tumor is removed we appear to have long-term cures of Cushing's disease argues strongly against a hypothalamic etiology.[1–4]

The ACTH levels tend to be much higher in patients with ectopic secretion. With a corticotropin-releasing-factor test, it should be possible to differentiate between a pituitary adenoma and an ectopic source. An adenoma should stimulate with CRF, while an ectopic source usually does not.

In 43 consecutive patients of ours, with only one exception, ACTH levels were not overwhelmingly high. They were often in the 30–70 pg/ml range. The normal level in our laboratory is up to 100 pg/ml, although these "normal" levels are inappropriately high for a hypercortisol state. There is usually no great difficulty in distinguishing an adenoma from an ectopic source, but either the petrossal sinus venous blood collections[6,7] or the CRF test should be able to make the distinction.

The therapeutic choice of surgery, I think, is very clearcut, and we operate on every Cushing's disease patient. Most series show a greater-than-70% control rate of hypercortisolism. In about 10%, a hypophysectomy will be required, since the adenoma cannot be located.[4,8]

Cyproheptadine and bromocriptine are not very effective, but adrenalectomy, whether medical or surgical, still has a place in treatment, as does radiation therapy.

> *Case Study 7.* Figure 8 is a CT scan from a man who had had surgery elsewhere. The sella was explored, normal gland found, and an adenoma suspected. The pathology showed only normal gland. Laterally, there was tumor in the cavernous sinus surrounding the carotid artery. The patient's second operation was transsphenoidal, and the front wall opened very laterally into the cavernous sinus. A tiny branch of vessel that bled like a little artery was followed back to the main trunk of the carotid artery. It was possible to dissect medially and inferiorly to the carotid with no venous bleeding; clearly the tumor had compressed this portion of the cavernous sinus and closed it.

I chose in this case not to go above or posteriorly, which would have jeopardized the carotid artery. This is a type of tumor I do not think is curable surgically. If surgical attempts do not achieve a cure, radiation therapy is given. The patient was radiated and still was not cured of his Cushing's disease. This was a patient who required a full armamentarium of treatment, possibly including adrenalectomy. However, I do not think that I would recommend implanting radioactive seeds in this area around the carotid wall.

Two of our Cushing's disease patients have had multiple intrasellar pathology. One had a prolactin-secreting adenoma and the other had a Rathke's cleft cyst. Both patients required a second operation because I was fooled. With Cushing's disease in particular, it is helpful to have some confirmation on frozen tissue that the adenoma has indeed been resected. At times, a reasonable answer is possible if the tumor is not really microscopic. Therefore, while I do not usually rely on frozen-tissue confirma-

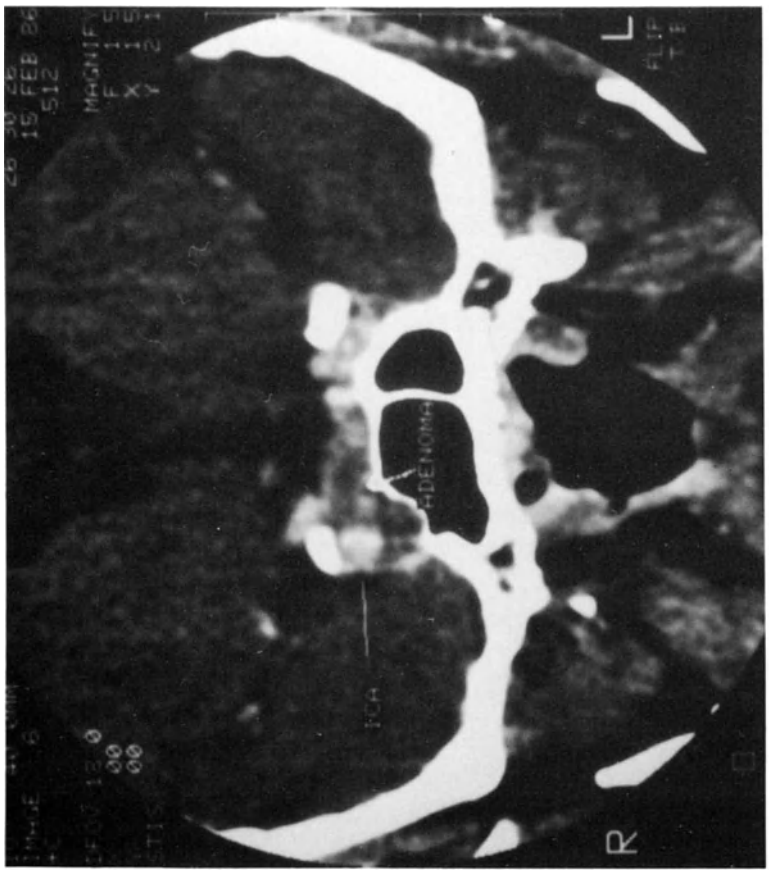

Figure 8. Coronal enhanced CT scan of a patient with Cushing's disease. Note the right lateral extension of the adenoma into the cavernous sinus where it surrounds the carotid artery (ICA).

tion when dealing with other adenomas, I find it especially useful in treating Cushing's disease.

GROWTH HORMONE-SECRETING ADENOMAS

The control factors between the hypothalamus and the pituitary gland in regard to growth hormone and acromegaly are discussed in Chapter 2 of this volume. They are perhaps more important in these cases than in Cushing's disease, because now we are seeing more reports about somatostatin analogs (e.g., sms 201-995 Sandoz Pharmaceuticals, East Hanover, New Jersey 07936). The drug controls growth hormone levels well, but shrinks the tumor in only approximately 25% of cases. It usually causes a dose-dependent steatorrhea that resolves. It may be used to shrink the tumor preoperatively or as an adjunct to surgery.[9]

Bromocriptine, in our experience, is not nearly as effective for acromegalic patients as it is for those with prolactin tumors. Since growth hormone-secreting tumors do not shrink, bromocriptine is only adjunctive therapy for acromegalics, using much higher doses than for prolactinomas, until somatostatin analogs become available in this country.[10]

> *Case Study 8.* While we operate on virtually every acromegalic patient, there are still some difficult decision cases. Figure 9 shows a rather large lesion. It extends into the cavernous sinus and around the carotid artery, and there is a finger of tumor coming up through the top of the cavernous sinus. It is noteworthy that this patient's vision was perfectly fine.

Here again is an interesting question: Does one treat this case surgically and, if so, in what manner? I was convinced I could not cure this patient surgically, either by craniotomy or a transsphenoidal approach. I knew I would have to irradiate her, so the question was should we do a craniotomy and take out the finger that was up above, or should we irradiate her, see what happened, and then operate later if the tumor grew? My preference in an adenoma like this is to operate transsphenoidally, taking out as much tumor bulk as I can. It is possible to decompress the cavernous sinus area, although clearly it must be done without going up through it to the supracavernous part. Although we used this technique and followed with radiation therapy, I am certain others might recommend different approaches.

> *Case Study 9.* The next case is that of a 17-year-old boy who began to grow considerably during high school. He grew not only taller, but also broader and heavier. His football coach was delighted, but his parents thought he was getting lazy and fat. He dropped out of high school and took a job, but this was also unsuccessful and he became withdrawn and lethargic. It was not until he became comatose and was admitted to a local hospital that medical attention was obtained. He had acromegaly, with an enormous erosion of the sella and a tumor that went up to the foramen of Monro, causing obstructive hydrocephalus.

What is the best way to treat someone like this—having an enormous tumor—after he has been shunted? Neurologically, this patient improved dramatically and again was

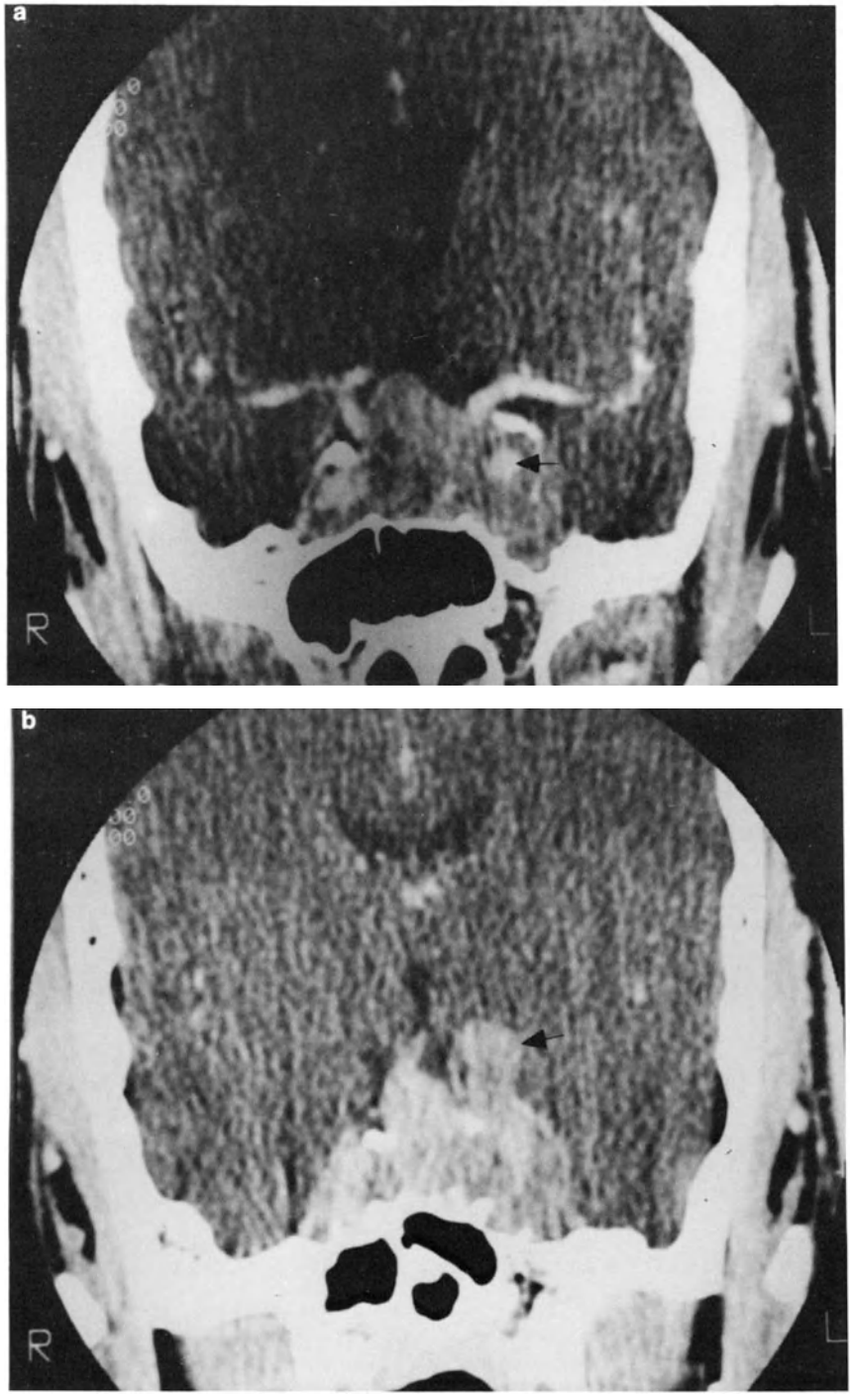

Figure 9. (a) Coronal enhanced CT scan demonstrating a large growth hormone-secreting pituitary adenoma with suprasellar extension (SSE) and left lateral parasellar extension surrounding the internal carotid artery (arrow). (b) Coronal enhanced CT scan of the same patient demonstrating extension of the adenoma (arrow) through the top of the left cavernous sinus.

quite normal. Although it was not obvious to him, a trace of a visual field defect was present on formal testing. With a tumor this high, should one operate subfrontally? Should one operate transsphenoidally? Would it be reasonable to go transsphenoidally before shunting him and use the pressure of the ventricles to try to force the tumor? I might have considered this approach if he had not been comatose. Since he was, I elected to operate transsphenoidally. There was a large open communication between the intra- and suprasellar components. As it turned out, in this particular case the tumor was firm in consistency and we could not resect nearly as much as I would have liked. It might be argued that this procedure could be done from above, transcallosally. We put the patient on bromocriptine, with a good response in GH level. We have given him radiation therapy and he has now been in remission and neurologically normal for 4 years. However, I think that with a tumor this size, the story is not over, which underscores the importance of considering all the therapeutic options.

PROLACTIN-SECRETING ADENOMAS

The control of prolactin secretion by the hypothalamus is well known. There may be several prolactin-releasing factors, such as vasointestinal peptide (VIP) and TRH.[11] Primary hypothyroidism can cause secondary hyperprolactinemia.

There is some evidence that prolactinomas arise from a cellular defect in the pituitary gland, especially in view of the low incidence of tumor recurrence after surgical "cure," as well as the low incidence of lactotroph hyperplasia.[12] There is still controversy, however, about the possibility that prolactinomas arise secondary to a defect in the normally inhibiting dopaminergic neurohypophyseal axis.[13]

In our series of 14 men with prolactin-secreting adenomas, there were 12 macroadenomas with suprasellar extension, two macroadenomas without suprasellar extension, and no microadenomas. In the male group, the adenomas at the time of surgery were significantly larger than those seen in the female group.[14–16] Prolactinomas in men generally are associated with impotence and hypogonadism, independent of tumor size. Laboratory studies show low serum testosterone and low or normal gonadotropins with elevated prolactin.[14]

The incidence of visual symptoms was much greater in the men in our series, which was consistent with the larger size of their tumors at the time of surgery. Numerous explanations have been proposed for the larger size of tumors at surgery among males, including (1) psychological barriers precluding admitting sexual impotence; (2) impotence often being interpreted as a psychological phenomenon; (3) physicians being less aware of the clinical entities in men than they are of those in women; and (4) hyperprolactinemia possibly having less influence on male physiology than it does on the female menstrual cycle.

My indications for surgical removal of microadenomas are summarized in Table 1. In the younger patient, below age 30, I generally recommend surgical intervention if the tumor is demonstrated on CT scan. In the patient beyond childbearing years with a microadenoma, observation or treatment with bromocriptine for symptomatic relief may be recommended. In the intermediate stage, there is no clear choice and each case must be evaluated individually, but I tend to favor surgery.

Table 1
Indications for Surgical Removal of Adenomas

Microadenomas
Bromocriptine intolerance or refusal
Progression of size
Progressive rise of prolactin
Pregnancy desired
Macroadenomas
Progressive visual loss (acuity or fields)
Extraocular motor cranial nerve dysfunction (e.g., III, IV, VI)
Increased intracranial pressure from local mass effect
CSF obstruction and hydrocephalus
Pituitary apoplexy
Uncertain diagnosis
Tumor recurrence after radiation treatment
CSF leak

Macroadenomas are less controversial when they present with neurological dysfunction because of mass effects. The endocrine dysfunction assumes less prominence. Bromocriptine, if tolerated in adequate doses, may normalize prolactin and may shrink a tumor by 20–50%.[17,18] However, there is ample evidence to demonstrate that the drug is not tumoricidal and needs to be taken continuously.[19–21] When medication is discontinued, the prolactin rises and the tumor may re-expand rapidly.[22] Therefore, all macroadenomas are considered surgical candidates, although bromocriptine may be used as adjunctive therapy pre- and postoperatively.

The results in the women studied show a 71% "cure" rate for all groups, whereas an 85% "cure" rate can be demonstrated for the microadenoma subgroup. When the group was restricted to those with preoperative prolactin levels of less than 200 ng/ml, the overall "cure" rate increased to 85% while that for the microadenoma group increased to 89%. The interval between surgery and return of menses varied from 10 days to 3 months, the average time being about 1 month. The cessation of galactorrhea was more difficult to determine. Normal menses and fertility may be restored even when postoperative prolactin values remain slightly or moderately elevated.

We have not seen prolactin levels continue to decline over the course of time. If prolactin remains elevated, the cause is presumed to be remaining tumor, rather than stalk irritation and reduced prolactin-inhibiting factor (PIF).

In the male group, the results are entirely different. All but two patients presented with mass effects and treatment was directed toward tumor control, rather than endocrine "cure." All patients remained hyperprolactinemic, requiring adjunctive therapy with bromocriptine, radiation, or a combination of the two.

Surgical results are not as good in men, because men tend to be seen later in the course of their disease. Moreover, more tumors are larger, have higher prolactins, and perhaps are more biologically aggressive.[14,15] Whether very high prolactin levels indicate invasion of the cavernous sinuses, as suggested by Shucart,[23] is not clear. The

surgical implications of this, if true, would be significant and would mandate adjunctive therapy preoperatively, postoperatively, or both.

With large tumors, the mass effect, such as visual defect, is dramatically improved. Vision is restored to normal in more than 85% of patients who had loss of acuity and visual fields prior to surgery.[24]

The mechanisms by which prolactin-secreting adenomas develop and the role of abnormal hypothalamic function in their pathogenesis are still obscure.[11] A recent report documenting a high rate of recurrence of hyperprolactinemia in surgically treated patients supported the view that these patients may have an underlying abnormality in the pituitary or hypothalamus, raising serious questions about the optimal management of prolactinoma.[25] This high rate has not been observed in other series.[26]

We reported a long-term follow-up study of a series of patients who had transsphenoidal selective adenomectomy.[26] In our series, prolactin levels returned to normal following selective microadenoma resection in 85%, but there was a 17% incidence of late relapse. In patients with macroadenomas, there was an early return to normal prolactin levels in 46%, with a 20% rate of relapse.

It is not known whether these relapses were due to late regrowth of tumor remnants left behind at the time of surgery or whether they represented new tumor formation, perhaps due to underlying hypothalamic or pituitary abnormality. The return to normal prolactin secretory dynamics in many patients 6–8 weeks postoperatively, and the continuing trend toward normalization found in the majority of patients tested 57 months postoperatively, suggest that underlying hypothalamic regulation is normal in most patients.

Stimulatory testing of nonrecurring adenoma patients at 6 weeks with insulin-induced hypoglycemia showed normal responses in 38%, while at 5 years, there was a 62% rate of normal response. With TRH stimulatory testing of nonrecurring adenoma patients at 6 weeks and 5 years, there was 55% and 82% rate of normal response, respectively. Two patients went from being normal in their stimulatory response at 6 weeks, to abnormal after 5 years, yet never showed recurrence of tumor or hyperprolactinemia.

On the basis of these long-term surgical cases, we offer several thoughts:

1. The continued conversion to normal testing in most patients suggested that the early postoperative abnormal results were probably secondary to the effects of the tumor on hypothalamic–pituitary function and not to underlying hypothalamic dysregulation. Those patients with continued abnormal secretory dynamics may have underlying hypothalamic dysregulation, slowly growing tumor remnants, or even generalized pituitary abnormalities.
2. Abnormal secretory dynamics at 6-week-postoperative testing are not predictive of which patients will relapse, since many patients who had abnormal dynamics did not relapse even during prolonged follow-up. Conversely, a normal response to provocative testing does not preclude relapse.
3. The underlying pathophysiology of prolactinomas is still not completely understood. The late recurrences seen after successful adenomectomies require indefinitely long follow-up of patients felt to be "cured" by surgery. The

relatively high incidence of late recurrence tempers enthusiasm for surgical intervention and does not end the debate between the proponents of medical versus surgical therapy.

Bromocriptine in the Treatment of Prolactin-Secreting Adenomas

Dopamine constitutes the major hypothalamic factor inhibiting prolactin. Bromocriptine, a dopamine-receptor agonist, delivers sustained and direct action on the dopamine receptor of the pituitary gland. It is also possible that bromocriptine has a similar effect on dopaminergic pathways in the hypothalamus. The efficacy of bromocriptine has been demonstrated in studies in which its use resulted in 80–90% of women experiencing return of ovulatory menses and the reduction of elevated prolactin to normal levels.[27]

Subsequent pregnancies do not appear to have been jeopardized by this therapy, and bromocriptine has not been associated with increased congenital malformations, multiple pregnancies, or spontaneous abortions.[28]

Bromocriptine also effectively reduces the size of prolactin-secreting macroadenomas by at least 50% in over 50% of patients, according to most series.[27] Indeed, the results in a recently completed prospective multicenter study were even more positive. Twenty-seven patients with prolactin-secreting macroadenomas were treated with bromocriptine. In 13 patients, the tumors were reduced by much more than 50% of their original size, in five patients the tumors were reduced by 50%, and nine patients showed reductions in tumor size of 10–25%.[29] Two thirds of the patients showed tumor reduction within 6 weeks, but others did not demonstrate reduction until the 6-month evaluation.

If therapy has been of less than 1-year duration, most tumors expand once bromocriptine is discontinued. For this reason, it is disturbing to consider bromocriptine as the primary modality of therapy for macroadenomas, despite the significant tumor shrinkage attributed to the drug. Reported rapid tumor enlargement after cessation of bromocriptine therapy renders the patients vulnerable to serious neurological deterioration should the medication be stopped for any reason.[22]

After 2 years of therapy, however, a lower dose of bromocriptine may control tumor growth and prolactin secretion.[30] Most tumors do not re-expand with therapy of 2–7-year duration, although less severe hyperprolactinemia usually recurs. Complete withdrawal of the medication after 24 months of therapy may produce a total remission in 11% of patients.[31]

The effects of pregnancy on prolactinoma growth have been reviewed using 16 series totaling 246 microadenoma patients who became pregnant.[32] These series also included 45 patients who had macroadenomas and became pregnant. Although the risk of clinically important microadenoma enlargement during pregnancy was 5.5% in the series reviewed by Gemzell and Wang,[33] it was only 1.6% in the Molitch review.[32] The risk of symptomatic macroadenoma tumor enlargement was significantly greater in the Molitch study, ranging from 15.5% to 35.7%, although previous surgery or irradiation appeared to greatly reduce this risk.[32]

Surgery used to be necessary in about 25–50% of cases of symptomatic tumor

enlargement during pregnancy before bromocriptine effectiveness in shrinking tumor size was determined. In a number of recent cases, however, bromocriptine has successfully reduced symptomatic tumor enlargement during pregnancy.[34,35] No ill effects on the infants were observed in these cases. Although this limited data implies that bromocriptine may be used safely late in pregnancy, there have been no large-scale or long-term studies to corroborate these findings.

The effectiveness of bromocriptine in reducing both prolactin and tumor size cannot be ignored. The results clearly demonstrate that surgical resection is far superior in patients whose prolactin is less than 200 ng/ml and whose tumor is less than 10 mm in size. Tumor shrinkage and prolactin reduction, combined with the increased surgical cure rate in these groups, have raised the question of whether preoperative bromocriptine therapy would be beneficial to surgical results. Reports provide contradictory answers.[21,36–39]

Weiss showed that 70% of those who responded to this preoperative medical regimen seemed to be chemically "cured" after surgery, as evidenced by sustained normal levels of prolactin postoperatively.[40] This is in comparison to the less than 25% of those who were not responsive to bromocriptine therapy prior to surgery. Return to normal prolactin levels with bromocriptine alone was not considered a favorable parameter; it was necessary that tumor shrinkage be demonstrated by CT scan as well.

At the opposite end of the spectrum, Landolt has reported poorer surgical results in the patients pretreated with bromocriptine, and has raised the question of whether pretreatment causes increased fibrosis of the adenoma, making it harder to distinguish the adenoma from the normal gland.[37,38]

At our institution, macroadenomas are pretreated with bromocriptine in the hope that shrinking the tumor will increase surgical success. Bromocriptine is not considered a primary modality of therapy for the macroadenoma. We currently use 7.5 mg/day and repeat the prolactin levels. If prolactin is significantly decreased or normalized, medication is continued and CT scan is done after 4 weeks. If tumor shrinkage is demonstrated, the medication is continued for 3 months, at which time elective transsphenoidal resection is performed.[39] If prolactin is not significantly altered or there is no tumor shrinkage, surgical intervention is not delayed. In addition, if there is serious visual loss, bromocriptine may be initiated; if there is no rapid improvement in neurological function, we switch to surgical intervention.

When bromocriptine is the only therapy, the larger macroadenoma with possible suprasellar extension presents a 15–35% risk of clinically serious tumor enlargement during gestation. Transsphenoidal surgery before pregnancy minimizes the risk by preserving the normal pituitary while removing sufficient tumor to allow for possible tumor expansion during pregnancy. These surgically conservative goals derive from the increased morbidity and low surgical rates of cure seen in these patients when more aggressive procedures are attempted. Postoperative restoration of normal prolactin levels and ovulation may require bromocriptine therapy.

Continuous administration of bromocriptine throughout pregnancy to women with macroadenomas is an approach that has been suggested. The regimen cannot be advocated at this time, however, as the effects of continuous bromocriptine on the developing fetus are still unknown.

In the microadenoma group, the issue is less clear. We attempt to present both alternatives to our patients, so they can arrive at their own decisions. Our preference is for surgical intervention, because the rate of success is extremely high if these tumors are removed when they are small and prolactin levels are below 200 ng/ml. Although only a small percentage of the microadenoma will enlarge to macroadenoma size,[41] it cannot be predicted which will follow the more benign course and remain inconsequential microadenomas. As the issue of osteoporosis has not been totally resolved, we believe that these tumors should be treated without prolonged bromocriptine therapy.

Bromocriptine is also used as adjunctive therapy postoperatively in those patients who are not surgically cured, can tolerate the medication, and either desire to become pregnant or are receiving radiation therapy.

> *Case Study 10.* The last case I wish to discuss is that of a 40-year-old man who presented with increasing headaches and some visual loss and had a tumor that went up and obstructed the foramen of Monro with consequent hydrocephalus. By the time I saw him, he already had a shunt in place and his ventricles were decompressed. His prolactin was extremely high at 8000, and his testosterone, LH, and FSH were not markedly suppressed. His wife was pregnant. The tumor was so large it completely encased both the carotid artery and the anterior cerebral artery.

The therapeutic issue is how to treat someone like this whose headaches are now relieved by the shunt, and who has marked hyperprolactinemia and mild visual problems? I elected to put him on bromocriptine to see if we could shrink the tumor. Within 2 weeks, he called to tell me he was starting to develop ptosis of his left eye and his vision was getting a little worse. We operated on him, keeping in mind where we saw the carotid arteries and just staying away from that side of the tumor. We did not push this one at all: Whatever tumor wanted to come out easily was removed. The patient's vision actually stabilized and he did quite well. We kept him on bromocriptine the entire time, and he is now having radiation as well, since we did not have adequate shrinkage of this tumor within 3 months. In the multicenter study to which I alluded earlier, it took 6 months to have significant shrinkage in a small percentage of the patients. The majority, however, demonstrated adequate shrinkage within 3 months. On our most recent scan of this patient, the lesion appears smaller and one can still see vessel in the center of the tumor. This is one case that requires the use of every therapeutic trick we have, but, despite how high the tumor goes, I do not think a craniotomy is required.

The transsphenoidal operation carries few complications, despite the size of these tumors. We have had no deaths in any transsphenoidal patient. Only three cases of meningitis occurred, but a few more easily treated leaks were noted. I have had one woman who developed complete loss of vision in one eye 2 days after surgery. We reopened her, thinking she had a clot, but she had minimal internal abnormality. I never really knew why she had the loss; it may have been a vascular spasm or some change in position of the nerve or chiasm. Prolapse of the chiasm into an empty sella with some of these very large tumors is discussed in the literature. It is a rare entity and I have only seen it once. Direct trauma to the median eminence is a possibility. When a firm tumor is encountered, in perhaps 5% of these cases, resection is not often very

successful from below. This is the time to stop and reoperate from above in a different fashion.

It is important to remember, when dealing with very large pituitary tumors, that despite the size of the tumors or the secretory symptoms, it is necessary to consider many different routes and different adjunctive therapies. Using the transsphenoidal approach, it is possible to accomplish a significant amount from below, despite the impingement and change in the diencephalic area.

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17

SURGICAL MANAGEMENT OF CRANIOPHARYNGIOMAS

Comparison of Results by Different Operative Approaches

Takanori Fukushima and Kenta Yamakawa

INTRODUCTION

Craniopharyngiomas are benign, slowly growing tumors in the area of the hypothalamopituitary axis. According to data from the Japanese Brain Tumor Registry,[1] in the 10-year period between 1969 and 1978 these tumors constituted 5.8% of all primary intracranial neoplasms (15,839 cases) (Fig. 1). They are seen fairly evenly at all ages, with some preponderance between the ages of 5 and 10 years (Fig. 2). Despite the advent of sophisticated microsurgical techniques, surgical management of craniopharyngiomas remains one of the most difficult and challenging subjects in neurosurgery. Although a wide variety of operative methods have been described, the optimum surgical approach continues to be a controversial issue. This report deals with our recent experience with the microsurgical treatment of 21 craniopharyngioma cases, and discussion will focus upon the comparison of our operative results by different surgical approaches and on the radicality of tumor resection.

CLINICAL MATERIAL

Over a period of 7 years, from March 1980 to May 1987, a consecutive series of 21 patients with craniopharyngiomas were treated surgically at the Mitsui Memorial Hospital. There were 14 males and seven females in the series. Their ages ranged from 5 to 69 years, with the mean age being 32 years (Table 1). Six patients were of pediatric age—under 15 years—and 15 patients were adults. The average period of

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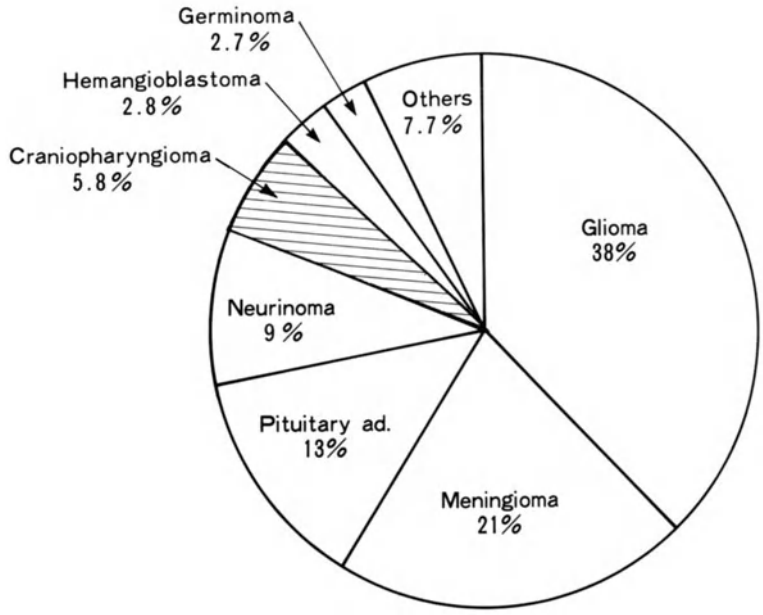

Figure 1. Incidence of craniopharyngioma. Data is taken from 15,839 patients registered in the Japanese Brain Tumor Registry during the 10-year period between 1969 and 1978.[1]

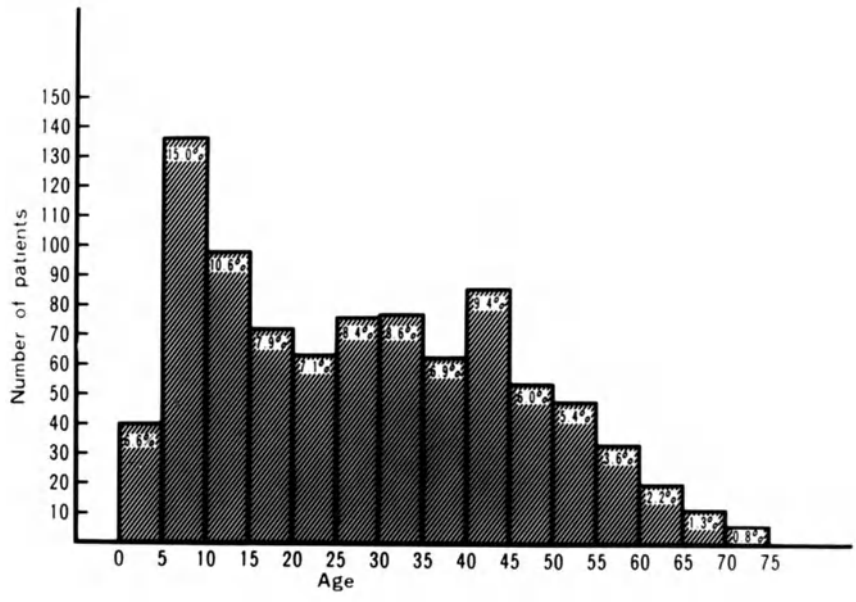

Figure 2. Age distribution in 912 patients with craniopharyngioma. Data from the Japanese Brain Tumor Registry.[1]

Table 1
Breakdown of Cases Involving Different Approaches to Craniopharyngioma Surgery[a]

Surgical approach	Number of cases	Ratio of male : female patients	Age range of patients (mean)
Transsphenoidal	10	7 : 3	13–58 (31)
Interhemispheric	6	3 : 3	7–69 (27)
Pterional	5	4 : 1	5–66 (41)
TOTAL	21	14 : 7	5–69 (32)

[a]A summary of cases treated at the Mitsui Memorial Hospital between March 1980 and May 1987.

postoperative follow-up was 33 months. All cases were operated upon by the senior author (T.F.) and verified histologically.

Symptomatology

The most common presenting symptoms were visual disturbances such as failing vision and field defects (17 out of 21 cases, or 81%). The second major symptom was headache and vomiting indicating some degree of intracranial hypertension (15 cases, 71%). In our series, only three patients presented with diabetes insipidus (DI). Signs of hypopituitarism, such as loss of libido, growth impairment, amenorrhea, hypogonadism, and obesity, were seen in six patients (29%). Two patients were admitted with mental confusion or obtundation.

Radiological Findings

Plain skull films were still very important for the diagnosis of craniopharyngioma, and to some extent for the determination of operative approaches. Enlargement of the sella turcica was noted in 11 cases (52%). Suprasellar calcification was observed in 11 patients (52%). Calcification was common in pediatric cases and in larger tumors. High-resolution reformat CT and newer MRI films were of particular value in delineating the size and the extent of the tumor. Half of the cases were visualized as a mixed mass, with cystic and solid components. Eight cases showed a mainly cystic mass and two cases had solid tumor. Hydrocephalus was seen in 38% of the cases. Based upon the findings on CT and MRI, we have classified the tumors into four types (Fig. 3): Type I indicates an intrasellar mass with enlarged sella; Type II means a sellar mass with a moderate amount of suprasellar extension; Type III is a suprasellar tumor with small sella turcica; and Type IV indicates a large mass extending high up into the third ventricle. There were 10 patients categorized as Type I or II, who were operated via a transsphenoidal route. There were five cases of Type III who had pterional craniotomy.

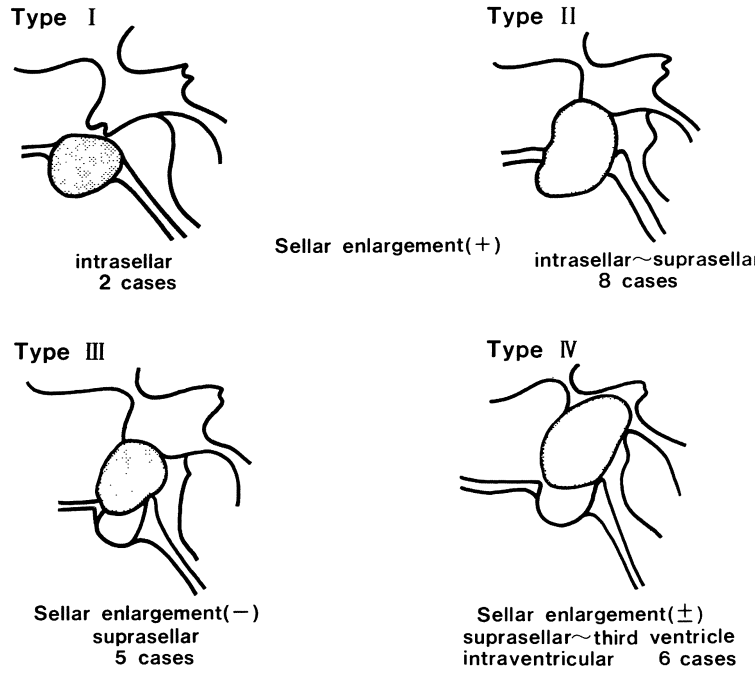

Figure 3. Classification of craniopharyngiomas by size, location, and extension of the mass and sellar enlargement.

Six cases had a large tumor classified as a Type IV mass, and were operated on through an interhemispheric approach (see Table 1).

OPERATIVE TECHNIQUE

A variety of operative approaches for removal of craniopharyngiomas have been described. It is essential at this time (during which the finest microsurgical techniques are available) to obtain all information available from CT scans and MRI pictures. We prefer to use a Contraves Zeiss microscope, which provides the best resolution, with high illumination through a very small opening. We could not find any other microscopes, Japanese or foreign, better than the Contraves. We tried lasers and ultrasonic aspirators for craniopharyngiomas, but they did not contribute much in our experience; rather, we felt that their use was relatively more dangerous at such a depth and in the vicinity of the vital neural structures. We prefer to use conventional, precise, *fine microsurgical instruments* (bipolar forceps, suckers, microscissors, and dissectors), because they achieve better results than machines.

In general, there are five major operative approaches in the surgery of craniopharyngiomas: (1) the subnasal transsphenoidal approach; (2) the subfrontal translamina terminalis or trans-tuberculum sellae approach; (3) the pterional trans-Sylvian

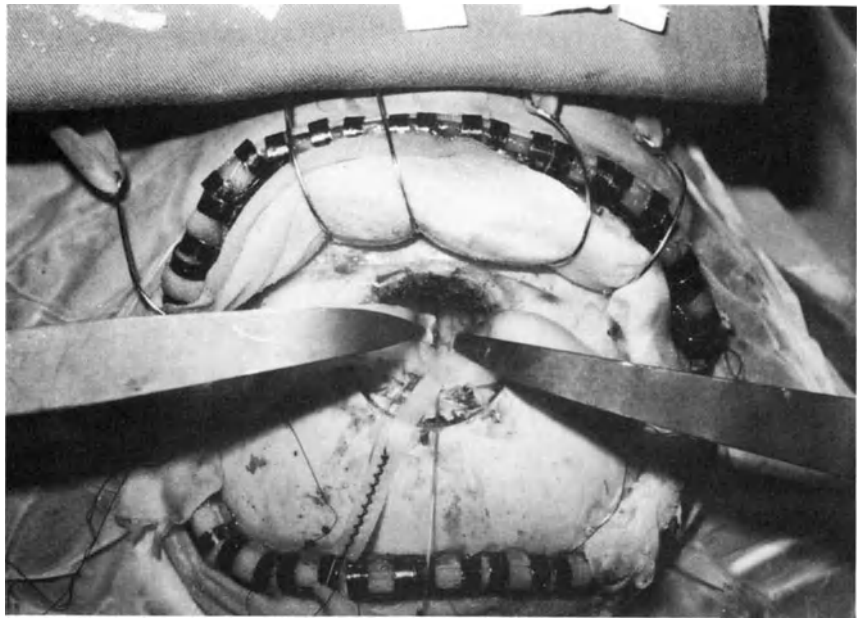

Figure 4. A 3.5-cm trephine interhemispheric approach for Type IV suprasellar–third ventricular tumors. A pair of 2-mm or 4-mm tapered brain retractors are used to expose the corpus callosum.

approach; (4) the subtemporal approach, and (5) the interhemispheric transcallosal or trans-lamina terminalis approach. The appropriate operative approach should be selected case by case in regard to the size and extension of the tumor. For Type I and II tumors with an enlarged sella, we performed transsphenoidal surgery. For Type III suprasellar masses, pterional craniotomy with the combined subfrontal and trans-Sylvian approaches was used. For Type IV third ventricular masses, interhemispheric approaches were adopted. There were 10 cases operated by the transsphenoidal approach, five cases by the pterional, and six cases by the interhemispheric approach (see Table 1, Fig. 3). We did not use a subtemporal or transtemporal approach.

For the transsphenoidal procedure, we use our modified unilateral rhinoseptoplastic technique.[2] For the pterional procedure, a small frontotemporal flap is turned and the approach is directed via subfrontal route or via trans-Sylvian laterobasal route. For the interhemispheric procedure, a small coronal scalp incision is made and a 3–4-cm trephine opening is made, in the same way as we would approach anterior communicating aneurysms[3] (Fig. 4). Either the transcallosal or the trans-lamina terminalis approach is selected, according to the extent of tumor growth. Extreme care was taken in our cases to preserve the underlying neural structures and the fine perforating vessels. In particular, the inferior capsule is often firmly adherent to the hypothalamus and the pituitary stalk; the separation of this portion must be carried out most cautiously, so as not to damage the fragile vital structures. The most important aspect of craniopharyngioma surgery is deciding during operation whether or not to remove the last bit of tumor capsule from the hypothalamus.

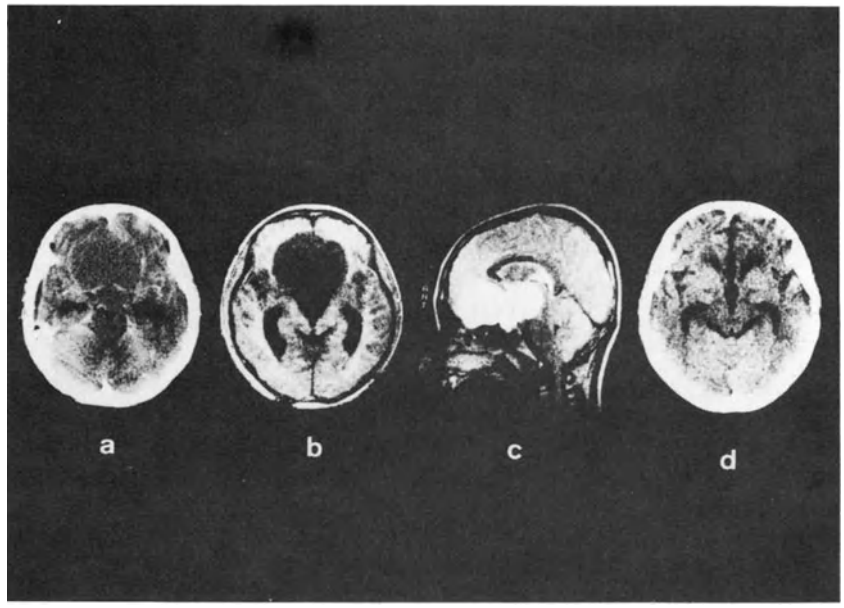

Figure 5. A 13-year-old boy with a huge suprasellar–subfrontal craniopharyngioma. Preoperative CT (a) and MRI (b,c) demonstrated a large cystic mass. After radical subtotal resection of the tumor via the transsphenoidal approach, this patient returned to his normal life, with a normal CT scan (d).

CASE STUDIES

Case Study 1. N.K. is a 13-year-old boy who presented with a 3-month history of headache and occasional vomiting. He complained of some decrease of visual acuity, but no definite field defect was observed. CT scan demonstrated a large subfrontal mass (Fig. 5A) and MRI revealed this huge mass to be cystic (Fig. 5B,C). This tumor was approached via the transsphenoidal method and the large amount of brownish-yellowish cyst fluid was evacuated. The solid part of the tumor could be successfully resected through a transsphenoidal route from the pituitary stalk. Although the sella and the sphenoid sinus were packed with muscle, the patient developed CSF leak and meningitis after surgery; these were well managed by conservative treatment. The patient returned to his normal school life. A postoperative CT scan shows almost total removal of the tumor, with a normal ventricular system after collapse of the huge cyst (Fig. 5D).

Case Study 2. K.T. is a 4-year-old boy who presented with symptoms of acute hydrocephalus. He had received an emergency V–P shunt at the local hospital and was transferred to our hospital. CT films demonstrated a solid calcified suprasellar mass (Fig. 6). This tumor was totally resected through a pterional trans-Sylvian approach. Postoperative CT showed complete removal of the tumor, and the patient is now leading a normal life using Desmopressin nasal drops for his DI (Fig. 6).

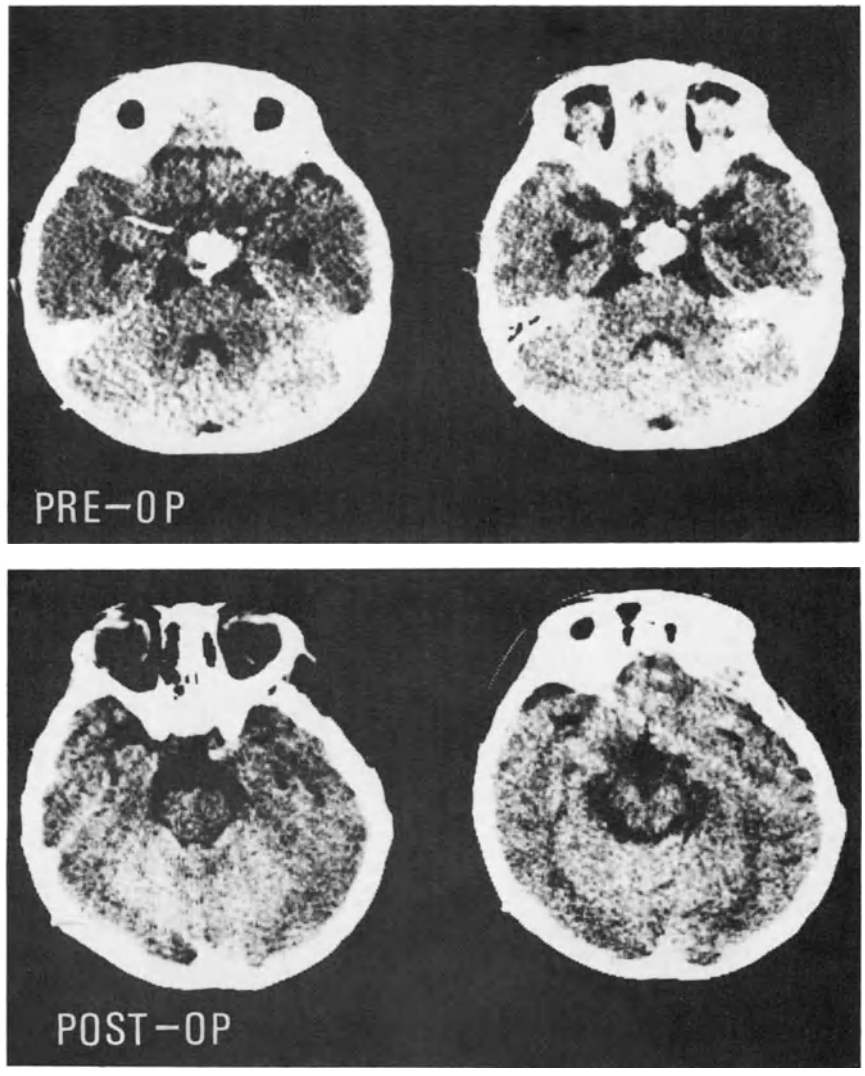

Figure 6. CT scans of a 4-year-old boy with a suprasellar calcified mass. The tumor was resected completely via the pterional approach.

Case Study 3. O.Y. is a 7-year-old girl who presented with headache and vomiting. She was treated initially with a V–P shunt and referred to our clinic for further investigation. Her CT scan showed a large suprasellar and third ventricular mass with some cystic component (Fig. 7). The tumor was approached through an interhemispheric trans-lamina terminalis approach. After division of the anterior communicating artery, the lamina terminalis was opened and the tumor could be widely exposed. This calcified, partly cystic mass was radically resected and the postoperative CT demonstrates excellent removal. The patient receives daily hormonal replacement and DI care, but is leading a normal school life.

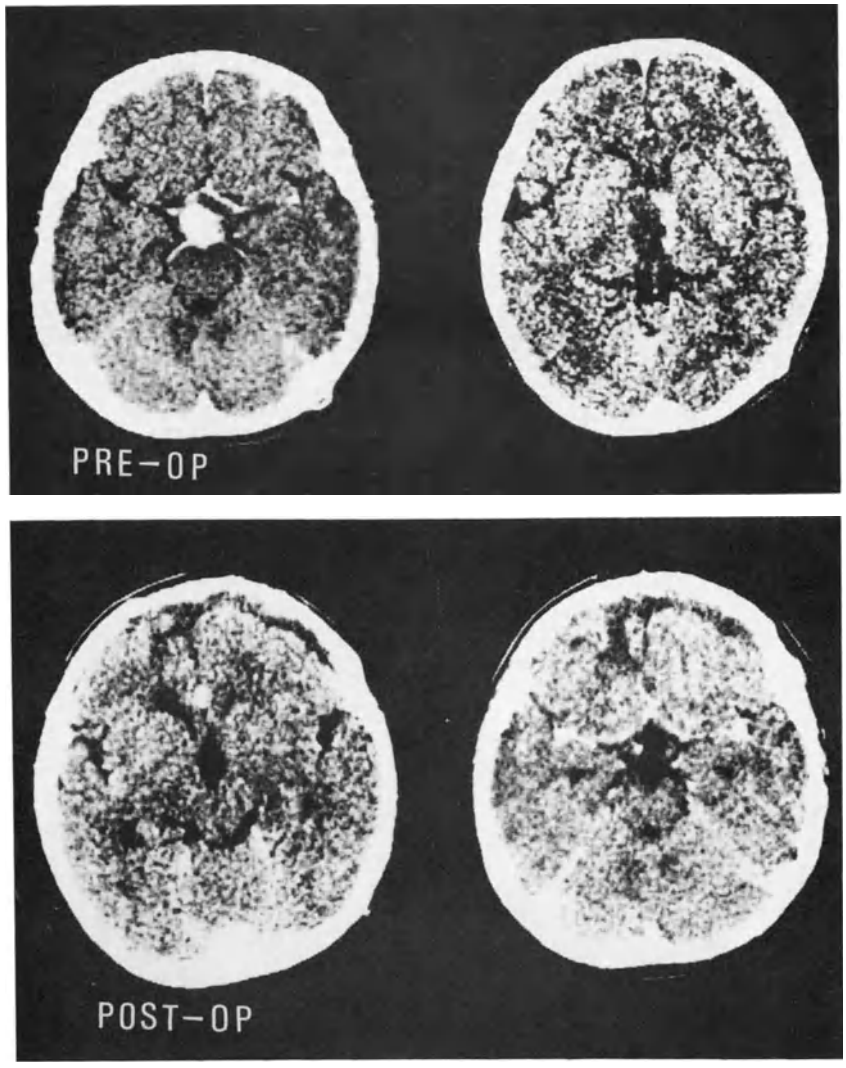

Figure 7. CT scans of a 7-year-old girl with a large suprasellar–third ventricular mass. Preoperative CT showed a cystic and calcified mass, which was radically resected through an interhemispheric trans-lamina terminalis approach.

SUMMARY OF OPERATIVE RESULTS

Among 10 patients who were operated via a TSP approach, radical total resection was achieved in five cases, nearly total removal was done in two, and subtotal removal in two, and partial removal was performed in a 58-year-old, poor-risk patient. Among the interhemispheric cases, radical total resection was achieved in only one patient. A small

Table 2
Correlation between Surgical Approach and Postoperative Life Quality and Late Death[a]

Postoperative condition of patient		Surgical approach		
		Transsphenoidal	Interhemispheric	Pterional
Excellent (normal functioning)	Independent	7 (70%)	3 (60%)	4 (80%)
Good (able to function well despite some deficiency)	Independent	3 (30%)	1 (20%)†	1 (20%)†
Fair (able to function)	Dependent	0	1 (20%)†	
Poor (nonfunctional)	Dependent	0		

[a]Follow-up results were best among the transsphenoidal group and worst among the interhemispheric group. Long-term follow-up outcome was poor among those undergoing radical total resection and better among those undergoing nearly total or subtotal resection. Notation † indicates late death of patient.

portion of tumor capsule was left in three patients, and these were not visible even with high-resolution CT after surgery (i.e., nearly total removal was achieved). Subtotal removal was performed in two cases in the interhemispheric group. In the pterional group, three cases had radical resection and two received nearly total resection. At postoperative evaluation, 16 patients (76%) had had either radical total or nearly total resection. The remaining five patients had subtotal or partial resection, and these five cases received postoperative radiotherapy.

On follow-up evaluation, 14 patients (seven of the transsphenoidal group, three of the interhemispheric group, and four of the pterional group) were leading normal lives (Table 2). Three cases were in good condition; however, another three patients were dead upon follow-up inquiry (two of the interhemispheric group and one of the pterional group): One patient died of leg phlegmone and sepsis 6 months after surgery; another case, a 69-year-old woman who had had interhemispheric radical total resection, developed hemiparesis and panhypopituitarism after surgery and died of pneumonia and sepsis after 1 year in a nursing home; the third case, a 50-year-old man who had had pterional radical resection, died of unknown cause 3 years after surgery. There were no poor results or deaths among the transsphenoidal group.

OPERATIVE COMPLICATIONS

The most frequent postoperative complication was DI. It was seen in 70% of the transsphenoidal group and in all cases among the interhemispheric and pterional groups. Of the DI cases, ten cases had only transient DI and seven cases (33%) had persistent DI. Postoperative drowsiness or mental confusion were seen only in the interhemispheric group (five out of six cases). Temporary meningitis was noted in four patients. The neurological complication of hemiparesis occurred in only one patient who had received radical total removal via the interhemispheric approach. There was one operative mortality—a 9-year-old boy with a large third ventricular mass who was operated through an interhemispheric trans-lamina terminalis approach. Despite clean radical

total resection, this boy developed uncontrollable seizure disorder 4 hr postoperatively and died a few days later. The exact cause of his death was unknown.

CONCLUSION

A wide variety of operative approaches have been reported in the literature. Some have advocated a subfrontal approach[4–6] and others have stressed the transsphenoidal approach.[7,8] Craniopharyngiomas vary significantly in size and extension of the mass, and the growth rate also appears to be quite different from one case to another. Any one operative approach will not cover all types of a tumor. As the present series demonstrates, the most suitable surgical approach should be selected in accordance with the nature, type, size, configuration, and extension of the tumor mass. In principle, craniopharyngiomas are benign tumors and therefore they may be totally resectable and curable. However, the tumor often grows to a large size before it is detected clinically and becomes very adherent to the hypothalamopituitary tissue. During the past two decades, the optimum surgical approach and operative radicality have been issues of major neurosurgical controversy. Matson[9] reported his excellent operative results in 44 cases and stressed the importance of radical surgical resection. However, later reports by Kramer,[10] Kahn,[11] and Sharma[12] advocated a conservative resection followed by radiotherapy. In recent years, with advances in microsurgical techniques, a more radical attitude has been directed to the treatment of this tumor.[4–6,13–15] The present series demonstrates that radical total resection is feasible through any of the transsphenoidal, pterional, or interhemispheric techniques. However, radical removal may result in permanent DI, endocrine imbalance, or more hazardous hypothalamic disturbances. Although the immediate operative mortality was low in our study, the follow-up analysis has revealed that radical resection, particularly in cases of suprasellar masses or third ventricular masses, resulted in a substantial mortality rate. As the previous literature has described,[6,9] more conservative partial removal or subtotal resection will result in a high recurrence rate. With modern microsurgical procedures, the tumor may be safely removed in a radical subtotal fashion. However, the surgeon must recognize during surgery the resectability of the inferior capsule that is adherent to the vital neural structures. If the least bit of capsule does not separate easily from the hypothalamus or from the perforating arteries, radical total resection should not be attempted. Hoffman described that a fleck or chunk of calcium visualized on postoperative CT does not represent the risk of future recurrence.[13] Although many reports have supported the efficacy of radiotherapy after surgery to prevent tumor recurrence,[6,10,16] it may not be needed in cases of radical subtotal resection or nearly total removal. In our series, only five patients received postoperative irradiation.

Charles Wilson stated in his recent paper that radical subtotal removal followed by radiotherapy is an acceptable treatment for craniopharyngiomas.[17] He reported that complete total resection could be achieved in only 10% of his cases. In light of his data and our present results, we conclude that careful microsurgical nearly total or radical subtotal resection, leaving a thin rim or small portion of inferior capsule with the

hypothalamopituitary tissue, would be the optimum operative method in a majority of craniopharyngiomas.

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18

SURGICAL MANAGEMENT OF CRANIOPHARYNGIOMAS

Reoperation in the Management of Recurrent Craniopharyngioma

Peter W. Carmel

INTRODUCTION

Although craniopharyngiomas are commonly regarded as benign tumors, their critical location, capacity for cyst formation, and almost inevitable further growth frequently cause them to be lethal tumors. Management of recurrent or residual craniopharyngioma is often a problem of life or death for the child involved.[1–4]

Subtotal removal of craniopharyngiomas allows recurrence and leads to decreased survival. If surgery has failed to remove the tumor and no further adjuvant therapy is given, half of these children will die within a 10-year period.[5] More than 80% of subtotally removed craniopharyngiomas will recur within 5 years and over 90% will have recurred within 10 years.[6]

It is widely believed that craniopharyngiomas are slow-growing tumors, and that a subtotally removed craniopharyngioma is likely to recur only at the end of many years, or may never recur during the life of the patient.[3,7] However, the majority of recurrences of craniopharyngiomas occur in the first several years after surgery, and there are relatively few patients whose tumors recur only after long periods of time (Fig. 1).

Radiation is valuable adjunctive therapy when the craniopharyngioma has been subtotally removed.[4,8,9] Both the survival rate and the relapse-free rate in children are much better following radiation therapy than after subtotal surgical removal of tumor alone. The use of radiation therapy must be carefully planned. In our experience, recurrences may occur with tumor doses of 4000 rads or less. Only those children who had 6000 rads or more seemed to be fully protected against recurrence of the tumor.[5] However, that level of radiation is potentially damaging to the immature brain. Our current practice is to restrict tumor dosage to approximately 4500 rads.

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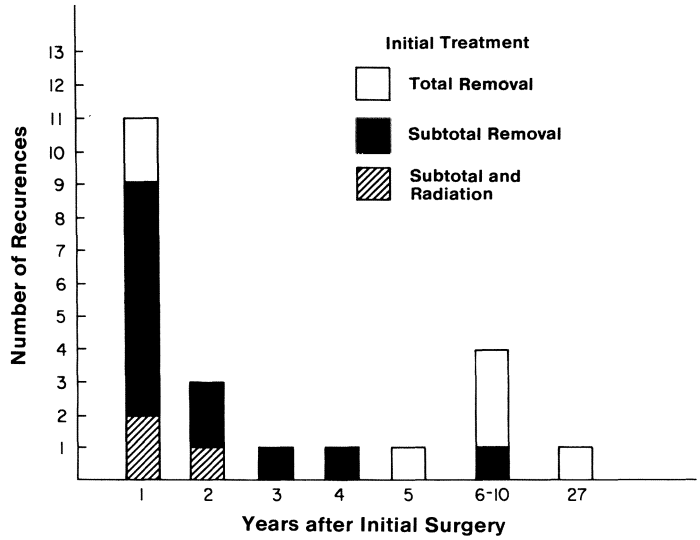


Figure 1. Time of relapse of subtotally removed craniopharyngiomas. Note that the great majority of recurrences occur within the first few years after initial operation. Cases with very long relapse times, such as the final case above (more than 25 years), usually occur in tumors that are radically removed.

There is increasing awareness of the deleterious effects that radiation can exert on the child's brain, and radiation therapy may have higher complication rates than previously thought.[1,4,10,11] Case Study 1, below, is an illustration of this point. Proponents of the use of x-ray therapy have maintained that forceful operative efforts to radically remove all tumors will cause increased neurological or learning deficits,[2,8,12,13] and that subtotal removal and radiation is better therapy. Other authors feel that total removal of craniopharyngioma is the best hope for permanent cure,[11,14] and that contemporary techniques permit removal of these masses with minimal morbidity and mortality.[5,10,14] This paper presents further information on the feasibility of reoperation in the management of craniopharyngioma.

We have previously published data indicating that irradiation improves survival following subtotal tumor removal.[6,10] The following case indicates that the increased longevity may be accompanied by adverse side-effects.

Case Study 1. J.Z. was initially seen in 1971 at 4 years of age. At that time his parents noticed rather rapid visual loss. Examination showed marked visual field impairment bitemporally, more marked on the right than on the left. Workup with arteriography and pneumoencephalography showed a large calcified mass in the suprasellar region. At operation the tumor was largely removed, leaving only a small calcified fragment of tumor that seemed too densely adherent to surrounding structures to be safely removed from the suprasellar region. Postoperatively the patient was treated with x-ray therapy; a dose of 4500 rads was administered over a 6-week period. The child was followed over the intervening years, and when CT scans became available a scan was carried out approximately every 18 months.

Scans taken 14 years postoperatively show changes typical of patients following radiation in childhood for craniopharyngioma (Fig. 2). The residual areas of tumor are densely calcified, and there are calcifications bilaterally in the basal ganglia. There is evidence of radiation atrophy of the cerebral cortex, particularly in cortical areas that were at the radiation ports.

At the age of 20 (2 years following the apparently negative scan shown in Fig. 2), the patient developed headaches, increased seizure frequency, word-finding difficulty, and moderate right hemiparesis. New scans were obtained that showed a large meningioma arising from the sphenoid wing (Fig. 3). Despite the large size and rapid growth of this tumor, it proved to be a benign meningioma, without sign of malignancy. The tumor was totally removed.

Other reported complications of radiation therapy in children with craniopharyngioma include induction of malignant tumors, severe endocrinopathy, learning deficits, and seizure disorders.[4,15–17] These problems have been well reviewed elsewhere,[1,10] but their significant incidence has forced a reconsideration of the use of radiation therapy for residual or recurrent craniopharyngioma.

Case Material

Forty-seven children with craniopharyngiomas were operated at the Neurological Institute of New York from 1978 to mid-1987. Ten were initially operated at other institutions, while 37 had their first operation at the Neurological Institute. Of the 37 children operated at our institution initially, radical removal was thought to have been obtained in 29 cases. However, three of the "radically removed" cases had postoperative CT findings indicative of residual tumor. Radical removal was, therefore, initially achieved in 26 of 37 cases (70%). The most frequent cause of failure to radically remove the tumor was adherence of pieces of calcified tissue to a major blood vessel, or (less often) to the undersurface of the visual apparatus or hypothalamus. Calcified adherent tumor tissue accounted for failure in 5 of 11 cases.

The operative findings in the case shown in Figure 4 were typical of tumors with dense calcific adherence. This 7-year-old boy initially presented with bitemporal hemianopia; left eye visual acuity was 20/40, while right eye acuity was 20/200. CT scan revealed a calcified tumor that was partially cystic (Fig. 4A,B). At operation the cystic portion of the tumor was readily emptied, but the calcific rim of the tumor was found to be densely adherent to the undersurface of the right optic nerve. The nerve on top of this calcified rim was paper thin, and it was felt that the tumor could not be removed without loss of the remaining vision in this eye (Fig. 4C). The postoperative residual tumor is shown in Fig. 4D. This tumor was electively irradiated almost a year following this operation.

In two further cases, operation was only palliative. Both of these children had had prior operations followed by radiation therapy. In both, the tumor regrew and pressure signs developed. Operation in these cases was designed to remove the bulk of the tumor and reduce compression of surrounding structures, without a serious attempt at radical removal.

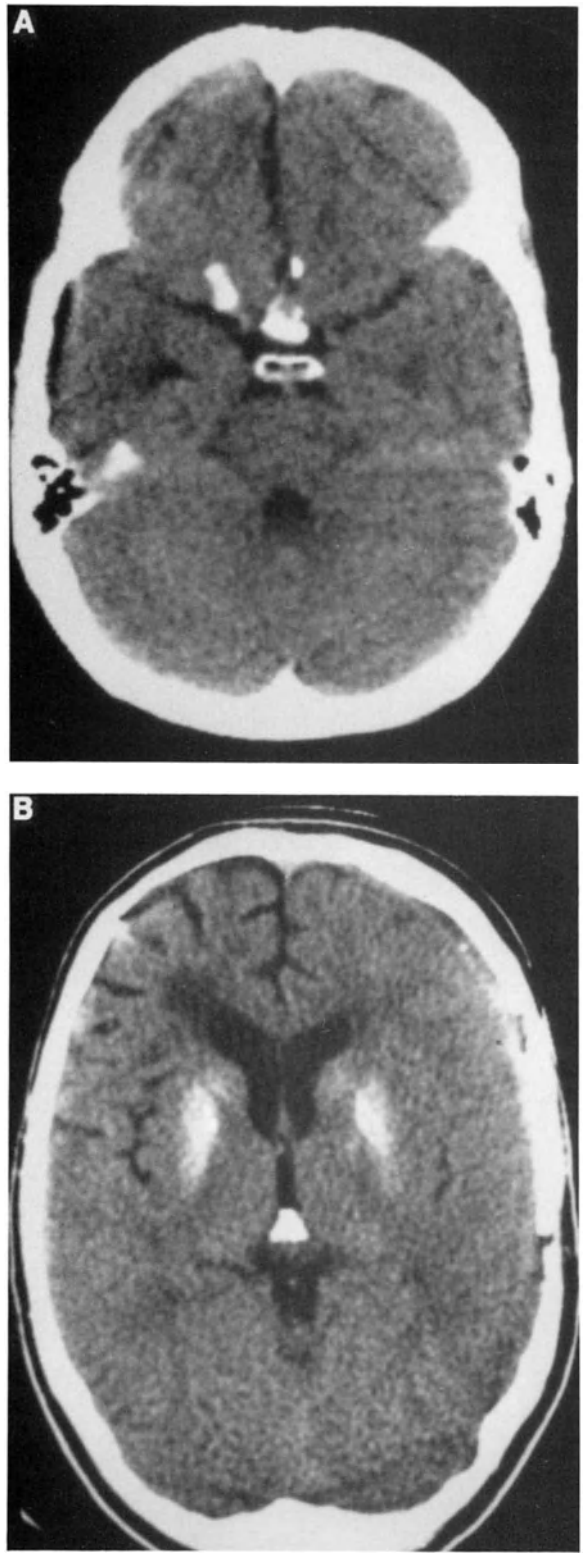


Figure 2. (A) Scan taken 14 years after subtotal removal of tumor and radiation. The tumor remnants have calcified. There was no apparent change in these fragments in almost a decade of CT follow-up. (B) Section through the ventricular level in the same study as in (A). Calcification in the basal ganglia and a degree of cortical atrophy are seen bilaterally, and are typical of patients irradiated in childhood. This boy is somewhat obese, and short, and requires pituitary endocrine replacement.

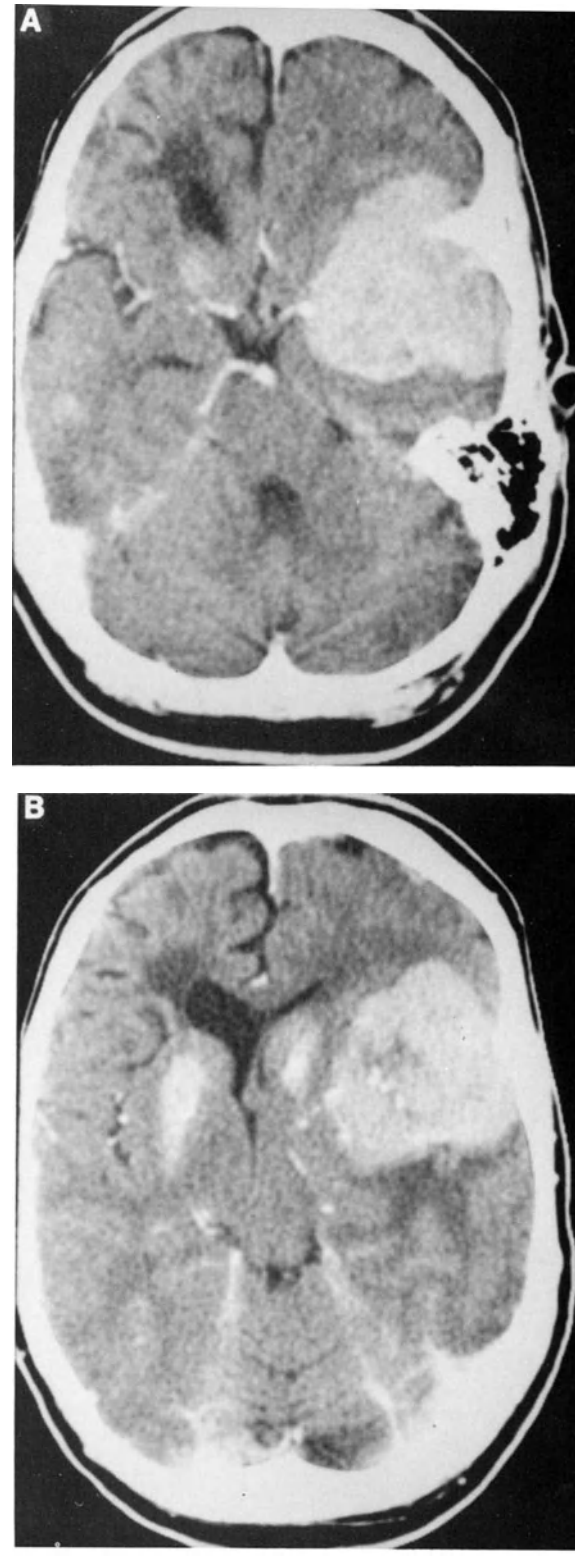


Figure 3. (A) Enhanced CT scan of the same patient shown in Fig. 2, taken 2 years later (16 years after original operation and irradiation therapy). The patient had signs and symptoms of increased intracranial pressure and an increase in seizure frequency. This large tumor originated at the sphenoid wing. (B) Contrast-enhanced scan of the same patient shown in (B). Despite the rapid appearance and growth of this tumor (less than 2 years), there were no histologically malignant features found in this benign meningioma. The symptoms abated when the tumor was totally removed.

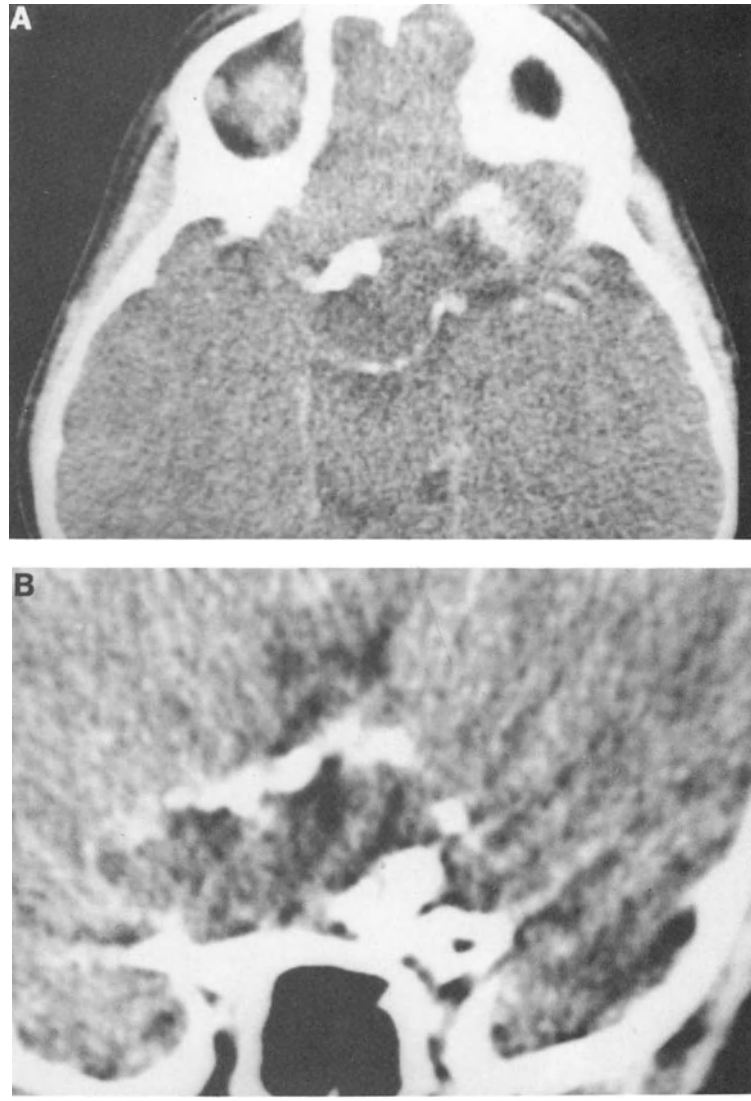
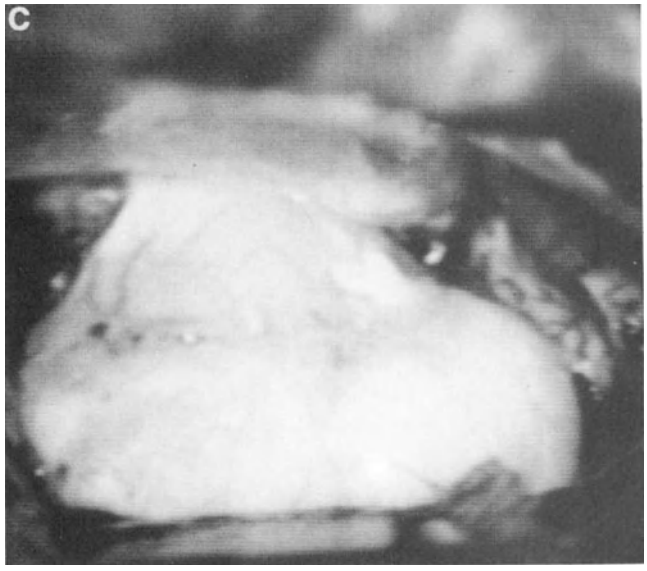


Figure 4. (A) Axial CT scan of a 7-year-old boy with bitemporal hemianopia and failing acuity. The tumor is largely cystic, with a projection toward the right eye. Calcium was deposited circumferentially around the cyst wall. (B) Coronal CT scan of the same patient. The circular calcification at the right optic nerve is well defined. (C) Operative photograph showing the right optic nerve stretched over the calcific tumor, which extended to the undersurface of the chiasm. It was felt that this calcified rim could not be removed without serious damage to the visual pathways. (D) Postoperative axial CT scan showing tumor fragments that were not removed at operation. Vision in the left eye returned to normal, and useful vision remained on the right.



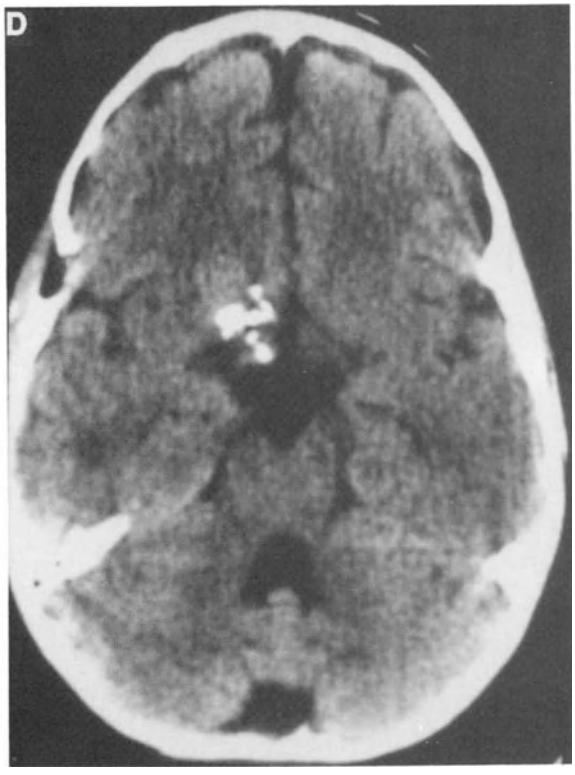


Figure 4. (*Continued*)

REOPERATION FOR CRANIOPHARYNGIOMA

Seventeen children in our study were reoperated for recurrent or residual tumor. Ten children were referred with residual tumor after operation elsewhere, and seven children were initially operated at our institution (described above). These 17 children had gone through a total of 22 prior operations on their tumors, exclusive of shunting procedures required to control hydrocephalus. Eight of these also had undergone tumor irradiation, utilizing dosages ranging from 3500 to 5000 rads.

Reoperation via the Initial Operative Approach

In most cases the initial operation was carried out through a right subfrontal approach. If this approach failed to achieve a radical removal initially, should it be employed for reoperation? In those cases in which a fragment of tissue was *knowingly* left behind, there is little question that the initial operative approach will again expose this tumor fragment. In those cases in which a fragment of tumor remains *inadvertently* (usually discovered by scan), it is frequently necessary to modify the initial subfrontal operative approach somewhat. Case 3 is typical of this operative strategy.

> *Case Study 3.* This little girl, A.M., was initially seen at age 7 years. At that time she had rapidly failing vision, and was quite short. Scan evaluation revealed a large, partially cystic tumor that filled the third ventricle and had a calcified portion at the base of the tumor.
>
> At operation the tumor was thought to have been entirely removed, but the initial postoperative scan showed a small calcification located at the junction of the posterior communicating and posterior cerebral arteries on the left side (Fig. 5A). This fragment was calcified and no additional soft tissue portion was seen after contrast enhancement. Although this sort of fragment typically has low potential for recurrence, a scan taken 14 months following operation showed a clear recurrence of the tumor. There was enlargement of the calcified fragment and development of a cyst that had pushed into the floor of the third ventricle (Fig. 5B). Reoperation was elected. At the second operation the tumor was not seen via the routine right subfrontal approach and was visualized only by opening the lamina terminalis. The cyst was then readily visualized as it pushed up into the floor of the third ventricle, covered by a thin ependymal layer. The ependyma was opened and the cyst emptied. The cyst wall was followed downward to the solid piece, which was gently dissected free from the vessels of the Circle of Willis. The postoperative scans showed no remaining tumor (Fig. 5C).

Tumors Reoperated via a Second Operative Approach

After initial subfrontal craniotomy, it may be necessary to use an entirely different approach for tumor recurrence. This is particularly true for those fragments that were inadvertently left behind at initial approach. For example, fragments that are lodged in the third ventricle may have to be approached via a transcallosal route, or those that are within the sella may be reached by the transsphenoidal route. Case 4 is an example of this latter group of operations.

Case Study 4. This little girl, M.M., was initially seen at age 12 at another institution. She presented with visual loss, delay in sexual maturation, and growth failure. Scans showed a partially cystic, calcified suprasellar mass. She was operated by a right subfrontal approach and the surgeon felt that the entire tumor had been removed. However, the postoperative CT showed a small tumor residual, which dramatically enlarged within 1 year. This recurrence was partially within the sella, and again a right subfrontal approach was used to approach the tumor. Unfortunately, the postoperative CT scan was again positive for residual tumor, and within 2 years there was considerable tumor growth of the residual tumor. At this point the tumor was largely within the sella, with a calcified portion adherent to the diaphragm sellae and slight suprasellar extension (Fig. 6A,B). Both the initial failures to remove the tumor subfrontally and the intrasellar location of the mass suggested a new approach, utilizing a transsphenoidal route. Fortunately, this was a child with a well-pneumatized sphenoid sinus, facilitating the transsphenoidal approach. Reoperation was carried out and the tumor removed. Fat was installed in the sella to prevent chiasmatic prolapse and CSF leak. The postoperative scan failed to show residual tumor.

Reoperation Following Prior Operation and Radiation Therapy

Eight children had undergone prior operation followed by radiation therapy. While radiation therapy may often inhibit tumor growth, some craniopharyngiomas seem little affected by irradiation. In all eight of these cases the tumor was demonstrated on serial scanning to have grown, and in all but one case it had done so within 3 years of the initial operation.

Radiation therapy has been thought to make reoperation more difficult because of the arachnoidal thickening and proliferation induced in the target region.[4,18] However, in these cases there were no unusual operative difficulties that could be ascribed to irradiation. The technical problems encountered following both prior operation and irradiation seemed no greater than those seen in patients with prior operation alone. Morbidity in the irradiated group was indistinguishable from that in other groups. Case 5 is illustrative of this group of children.

Case Study 5. This 6-year-old little girl, A.S., was operated on at another hospital because of progressive severe loss of vision in both eyes. Postoperatively she had no vision in her right eye and 20/400 vision in her left. One year later she had a cystic recurrence of the tumor and a second craniotomy was undertaken. At this operation, the cyst wall was partially resected and a silastic catheter was inserted into the cyst cavity and connected to a subgaleal Ommaya reservoir. A small calcified piece of tumor was adherent to the undersurface of the left optic nerve (the remaining sighted eye) that the surgeon was reluctant to remove. Following this operation a course of x-ray therapy (4500 rads) was given.

One year later the patient noted progressive loss of vision and a shrinking visual field in her good eye. MRI and CT scanning revealed recurrence of the tumor (Fig. 7A,B), and she was referred to our institution. Attempts at aspiration of the reservoir failed to yield fluid or reduce the cyst. Right frontal craniotomy was chosen despite two previous attempts by this route, as it offered good visualization of the undersurface of the left optic nerve. There was extensive scarring of the pia-

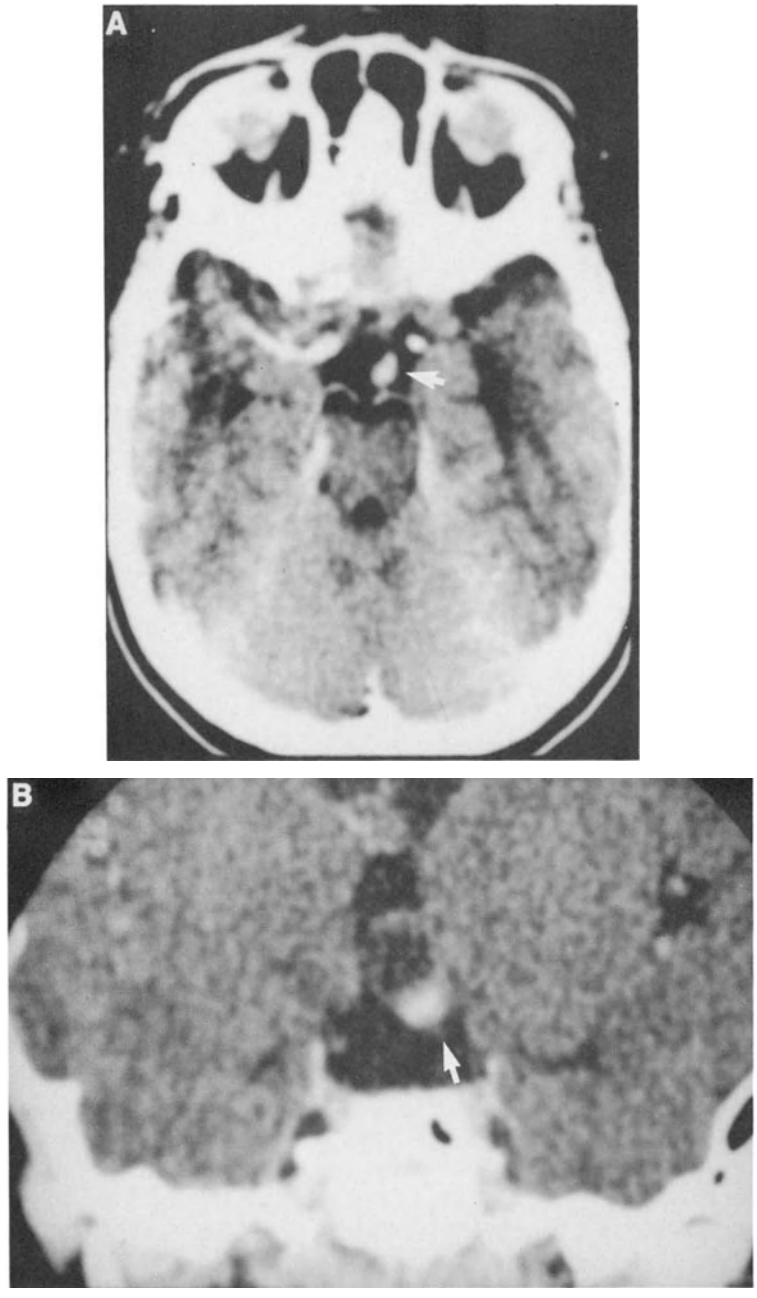
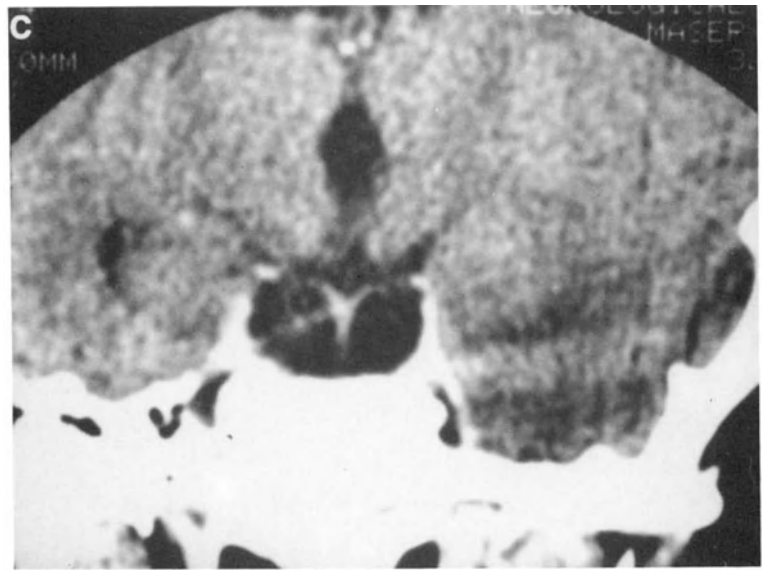


Figure 5. (A) Postoperative axial CT scan of a patient following removal of craniopharyngioma. This tumor fragment, adherent to the left posterior cerebral artery at the junction with the posterior communicating artery, was not recognized at operation. (B) Coronal CT scan taken 14 months after scan in (A). The calcified fragment is larger, and a cyst has developed. The cyst has pushed up into the third ventricle, nearly filling it. (C) Coronal-enhanced CT scan taken after reoperation. The tumor could not be visualized by the



right subfrontal approach, but was seen pushing up into the ventricle when the lamina terminalis was opened. The cyst fills the sella and bulges the diaphragm sellae upward. The portion of the capsule adjacent to the diaphragm is partially calcified. Two prior operations by the subfrontal approach failed to remove the intrasellar tumor. For reoperation at this point, a new route was indicated.

arachnoid of the convexity and subfrontal region, and the cisternal arachnoid was markedly thickened. However, the suprasellar cisterns and the visual apparatus were not unusually scarred. The cyst catheter had been excluded from the regrowing cyst and was adherent to the upper surface of the tumor capsule. The tip of the catheter was actually indenting the undersurface of the left optic nerve at its junction with the chiasm. Tumor removal was not restricted by arachnoiditis, and the tumor was dissected from the left optic nerve. Postoperative MRI scan demonstrated no residual tumor (Fig. 7C).

Proton-Beam Irradiation

A final case of unusual interest is included in this report although the patient is not a child. In this instance, proton-beam irradiation failed to control the patient's craniopharyngioma, and the tumor was subsequently operated upon.

Case Study 6. This 28-year-old woman, S.S., appeared at another institution with signs and symptoms of increased intracranial pressure of several weeks' duration. She had no visual complaints and no overt endocrinopathy other than chronic oligomenorrhea. Scans showed hydrocephalus caused by a calcified, cystic tumor (Fig. 8A). A shunting procedure was carried out, with total relief of headache and papilledema. The patient and her husband refused direct operative approach to the tumor. Six months later she underwent proton-beam irradiation. In a subsequent MRI scan the tumor appears to be only slightly changed in size, but the patient had

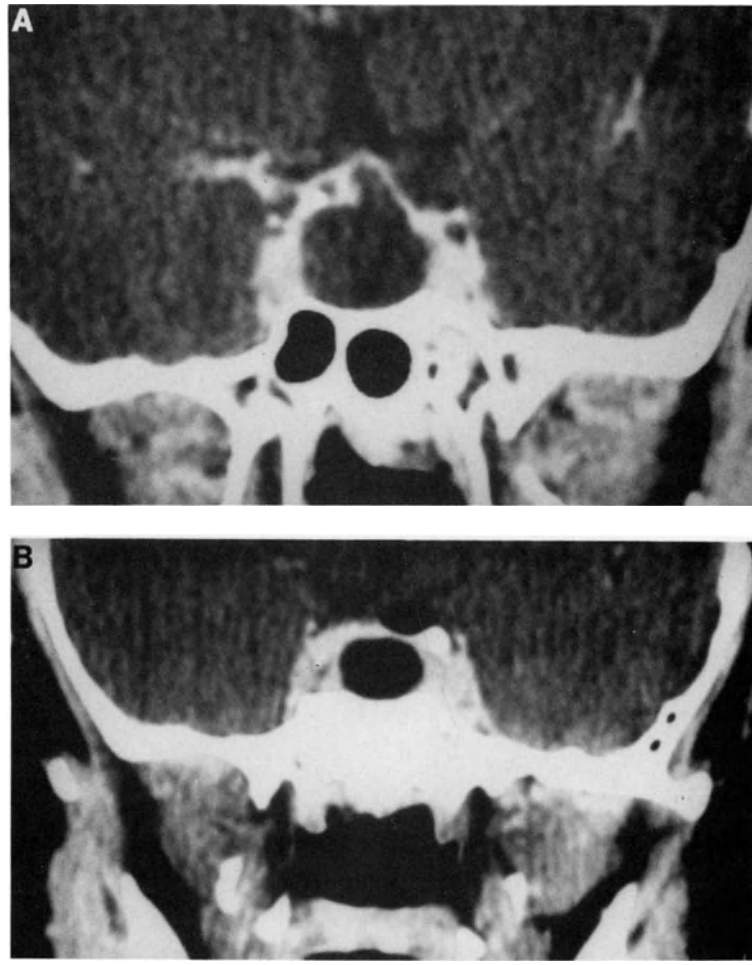


Figure 6. (A and B) Recurrent cystic craniopharyngioma seen in coronal CT scans. The cyst fills the sella and bulges the diaphragm sellae upward. The portion of the capsule adjacent to the diaphragm is partially calcified. Two prior operations by the subfrontal approach failed to remove the intrasellar tumor. For reoperation at this point, a new route was indicated.

become amenorrheic (Fig. 8B). Seven months after the scan shown in Fig. 8B, the patient developed severe headaches, with rapidly progressing visual loss. MRI scan demonstrated dramatic enlargement of the cystic portion of the tumor (Fig. 8C,D).

Operation was carried out subfrontally. The proton-beam irradiation left the CSF cisterns and arachnoid in normal condition. However, the arachnoid applied directly to the tumor surface was very tough and adherent to the tumor capsule. The tumor was radically removed, but postoperative CT scan shows a calcific remnant (Fig. 8E).

RESULTS

Reoperation was elected as therapy for recurrent craniopharyngioma in 17 children. Radical removal of tumor, confirmed by negative postoperative CT scan, was achieved by reoperation in nine cases (53%). There was no operative, perioperative, or subsequent mortality in these cases. Two children had decreased visual field in the right eye postoperatively, and this improved slowly to preoperative level in one child. The remaining children who had visual impairment prior to reoperation (11 children), had either unchanged or improved visual fields or acuity.

Sixteen of these children had diabetes insipidus postoperatively, and all were treated with either aqueous pitressin and desmopressin (DDAVP) or DDAVP alone. Children who required maintenance DDAVP as a result of their first operation usually had increased requirements following reoperation. In at least seven children the need for DDAVP was time limited, with no medication required beyond periods ranging from 4 months to 3 years. Fourteen children required other endocrine supplements, usually cortisone, thyroid, or combinations of replacement.

CONCLUSIONS

Three conclusions may be drawn from our experience: neither prior operation nor irradiation, or even both, will preclude the subsequent successful removal of a craniopharyngioma; reoperation can be undertaken without significant mortality or morbidity; and reoperation is a useful management technique for subtotally removed craniopharyngiomas, either instead of irradiation or until radiation therapy is more suitable.

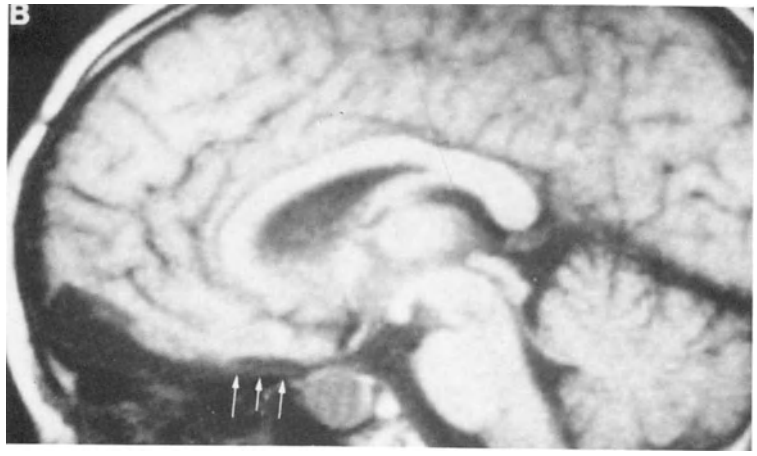
DISCUSSION

THE MRI APPEARANCE OF CRANIOPHARYNGIOMAS IN CHILDREN AND A NOTE ON THEIR RECURRENCE

Edwards contends that cystic craniopharyngiomas in children are often "dense" on MRI. This is so, he informs us, if they have blood or a high iron content. He refers back to a study recently completed at the University of California at San Francisco: In 70 MRI scans performed in a similar manner with thin sections, the site of a pituitary microadenoma could be identified in about 70%. They always had a low-intensity signal. The three craniopharyngiomas all had a high-intensity signal on T_1-weighted imaging. Therefore, if a child has endocrine dysfunction such as diabetes insipidus and a high-intensity signal on T_1-weighted imaging, the intrasellar lesion is more likely to be a craniopharyngioma than a primary pituitary adenoma.

Figure 9, however, represents the MRI scans of a 13-year-old who had undergone two prior resections at age 4 and 8 years and was followed with sequential scans. The latest scan suggests recurrence, but contrary to Edwards' statement, it is hypointense. This child was normal, his visual acuities were normal, and we requested an intrathecal metrizimide examination, which


A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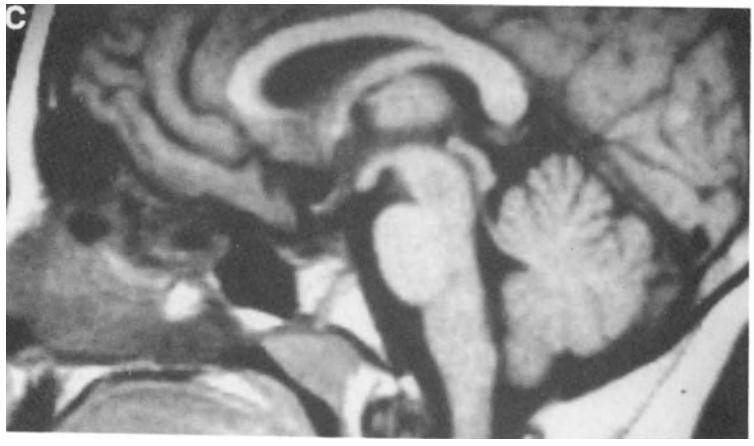
C

confirmed the fact that there was no recurrent tumor (Fig. 9B). The clue was the degree of health of the patient and the absence of calcification. When craniopharyngiomas recur in children their radiographic appearance is similar to that on initial presentation and includes calcification.

STAGING OF CRANIOPHARYNGIOMA REMOVAL

Apuzzo asks what prompts the need to stage the removal of a given craniopharyngioma, in the experience of our team.

Staging is often involved in "above" and "below" types of tumors—that usually implies a large intrasellar component and a suprasellar portion that is exophytic toward the temporal lobe, the clivus, or even the anterior fossa. We would deal with the intracranial part first and then go transsphenoidally at a second operation.

Another instance of staging is exemplified by a patient with a suprasellar tumor that filled the third ventricle, split the choroid fissure of the temporal lobe, and filled the entire ventricle on the right (Fig. 10). We approached this tumor subfrontally at first and then, after a period of time, reoperated transtemporally for the intraventricular portion.

Staged approaches in my experience have been planned staged approaches. I don't include inadvertent reoperations for residual tumor in my statistics for staged approaches.

THE ROLE OF RADIATION IN SUBTOTAL REMOVAL OF CRANIOPHARYNGIOMAS

Leeds states that the cases presented in this volume indicate that radiation in adults over 35 years of age has more harmful side effects than it does in children. These complications include dementia, vasculitis and vascular occlusion, and new tumor formation, including meningiomas and sarcomas of the base of the skull.

I agree with Leeds regarding radiation therapy for craniopharyngiomas. We must recall where the benchmark is at present. At the University of California at San Francisco, Baskin and Wilson[8] published their experience with 74 patients—not all children—treated with subtotal removal (except for a few patients in whom total removal was achieved) and irradiation, with complications.

Edwards adds that radiation in long-term survivors has complications, but other important factors determine the ultimate outcome—specifically, how impaired is their endocrine dysfunction?

Patterson offers that with the lower doses of radiation that were used 3 years ago (3500 to 4500 rads), a surgeon had a chance at reoperation, but in his own experience, in the case of patients—especially adults—who have been treated with 5500–6500 rads, the operation turns into a nightmare of scar formation. It appears to Patterson and his colleagues that the chance of achieving total removal after 6000 rads, when the tumor recurs, is very small.

However, of the eight patients in my own study who received radiation therapy, two received 5700 rads: One of these tumors was totally removed and the other was not. The scar

Figure 7. (A) Coronal CT scan in a 6-year-old girl who had undergone two prior craniotomies and x-ray therapy. The radio-opaque tip of a catheter that had been implanted in an attempt to drain the cyst fluid is seen at the upper border of the capsule. (B) Sagittal MRI scan showing the same tumor as in (A). The tumor is largely cystic. Arrows indicate the course of the catheter. At operation the catheter had been excluded from the growing tumor, and its tip indented the undersurface of the left optic nerve. (C) Postoperative sagittal MRI, with no apparent residual tumor. The tumor was knowingly left behind at the prior operation and was very likely to be seen, even if the same approach was used.

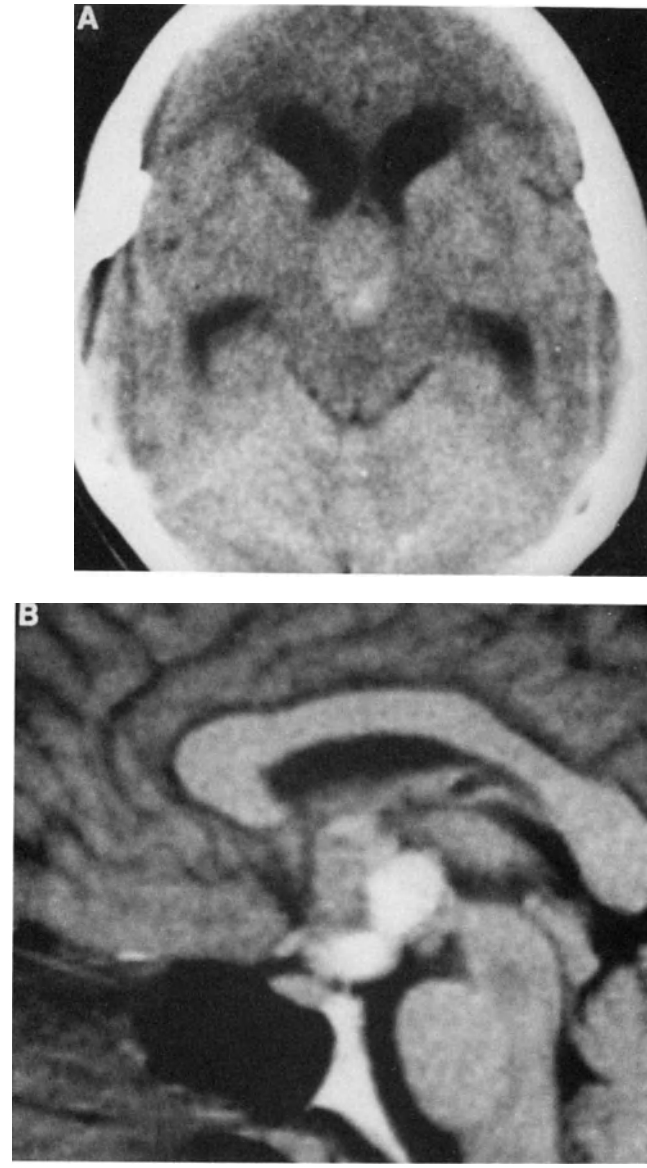

Figure 8. (A) Axial CT in a 28-year-old woman with signs and symptoms of increased intracranial pressure. A cystic, partially calcified tumor is seen obstructing the third ventricle. (B) Sagittal MRI in the same patient. The hydrocephalus has been controlled by shunting, and the tumor has been treated by proton-beam irradiation. (C and D) MRI scans taken 7 months after that shown in (B). The cystic portion of the tumor has dramatically increased. (E) Axial CT scan after craniotomy and tumor removal. Although it was felt that the entire tumor had been excised, scan shows a suspicious fragment near the right posterior communicating artery (arrow). This fragment will be watched on serial follow-up scans.

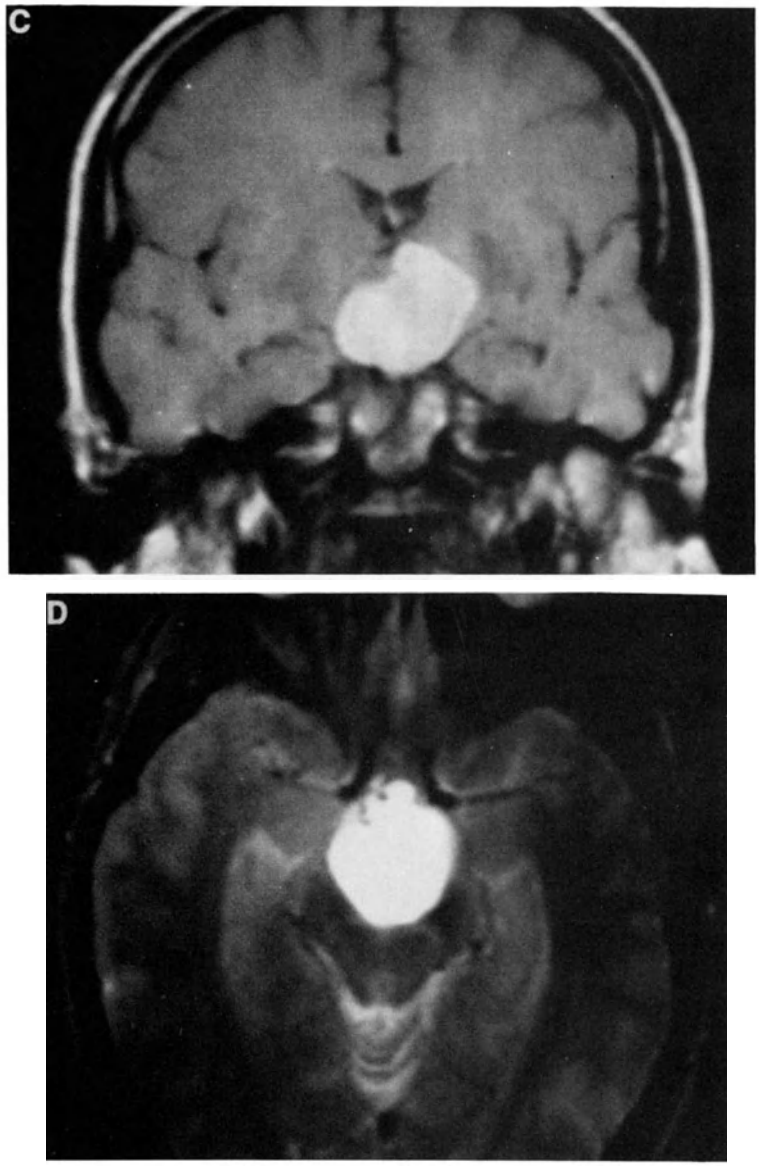

Figure 8. (*Continued*)

formation postradiotherapy was not an insurmountable element in these children. The dosages for the entire group ranged from 4000 to 5700 rads.

Edwards states that we must be careful when we compare radiation therapy of the present to that of the past. We must look at the portals. In the past, most patients received full bitemporal fields. Now radiotherapists use rotational arcs, which give only one rad per degree to normal brain tissue. Pituitary region tumors are now treated with a rotational beam. Edwards personally

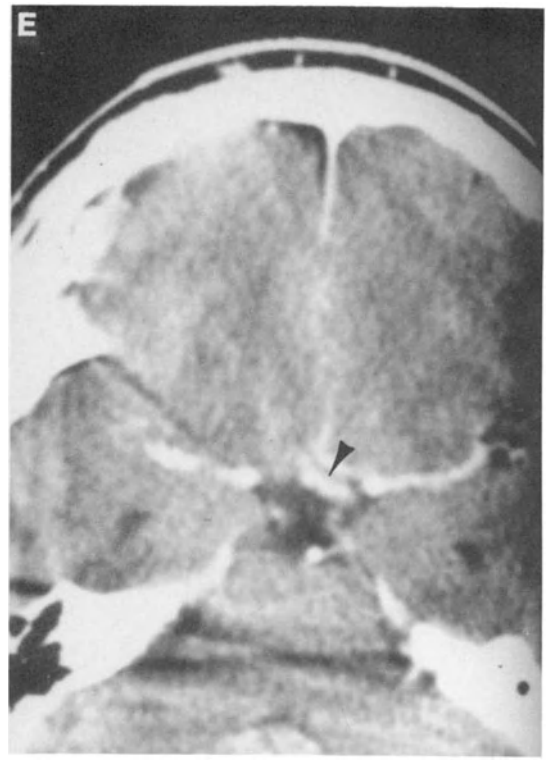

Figure 8. (*Continued*)

doesn't know whether this will reduce the risk factors and complications, but feels it should affect the bilateral temporal lobe damage and subsequent calcification.

Tew presents a subject that has not yet been discussed—the role of intracavitary P^{32}-beta emitters in the treatment of cystic lesions.

This role is still under evaluation. The largest series in Europe—namely, that of Eric Backlund (unpublished observations)—remains unpublished. There is a series from Tokyo of P^{32} colloid instilled in craniopharyngiomas, although Fukushima does not believe that there is an extensive series of such implantation going on in Japan at the present time. He states that most people are interested in radical surgical removal.

THE TERM "RADICAL OPERATION" AND ITS MEANING

Fukushima asks what our teams mean by the words "radical operation": Does it mean complete and total removal, or is it akin to Charles Wilson's term "radical subtotal removal," which Fukushima himself calls "nearly total removal"?

I consider "radical removal" a case where, under microscopic visualization with micromirrors, I find no remaining tumor. In addition, the fourth-generation CT scanner with axial and coronal views must be negative for tumor.

Fukushima wonders what we would call the operation if, during surgery, a thin fragment of the inferior tumor capsule is left adherent to the hypothalamus.

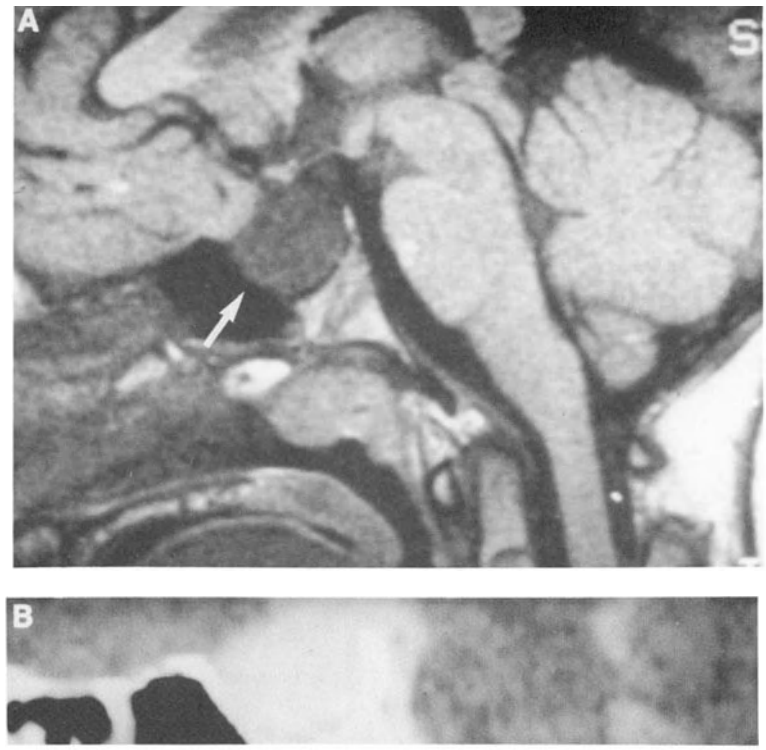

Figure 9. (A) Sagittal MRI take 5 years after total excision of recurrent tumor. The sella is filled with an apparent round cystic mass, raising the possibility of tumor recurrence. (B) Sagittal reconstruction of cisternal metrizamide CT scan. Cerebrospinal fluid freely enters the sella, and there is no evidence of tumor.

I would call this a radical subtotal removal. A subtotal removal is not a radical removal. I believe there is a radical removal, a radical subtotal removal, and a subtotal removal.

PRESERVATION OF THE PITUITARY STALK AND ENDOCRINE FUNCTION

Tew asks if one can do a radical total removal without creating a hypopituitary patient with diabetes insipidus.

I believe it is possible to preserve the pituitary stalk in about one half of the cases of total removal, and on the initial surgery I believe one is able to totally remove about 70%. In those with the pituitary stalk left intact, diabetes insipidus appears transiently in all. It is usually short lived, lasting for as brief a period as 72 hr to 2–6 months. Then there is a long period of time, from 6–14 months, where none of the children with diabetes insipidus change, and then a late group, occurring after 14 months, in which a few individuals will become DDAVP-independent.

Regarding growth hormone, 40% of the children undergoing total removal without an intact pituitary stalk will grow, and I believe that this is due to the viability of the median eminence. It becomes revascularized and some growth hormone is produced. The figure of 40% is seen in a number of series. With the stalk intact, I believe the number increases to about 75%. In children with the stalk intact, we have been able to avoid growth hormone replacement in a number of instances. The question remains whether that growth is adequate: One of the children whom I

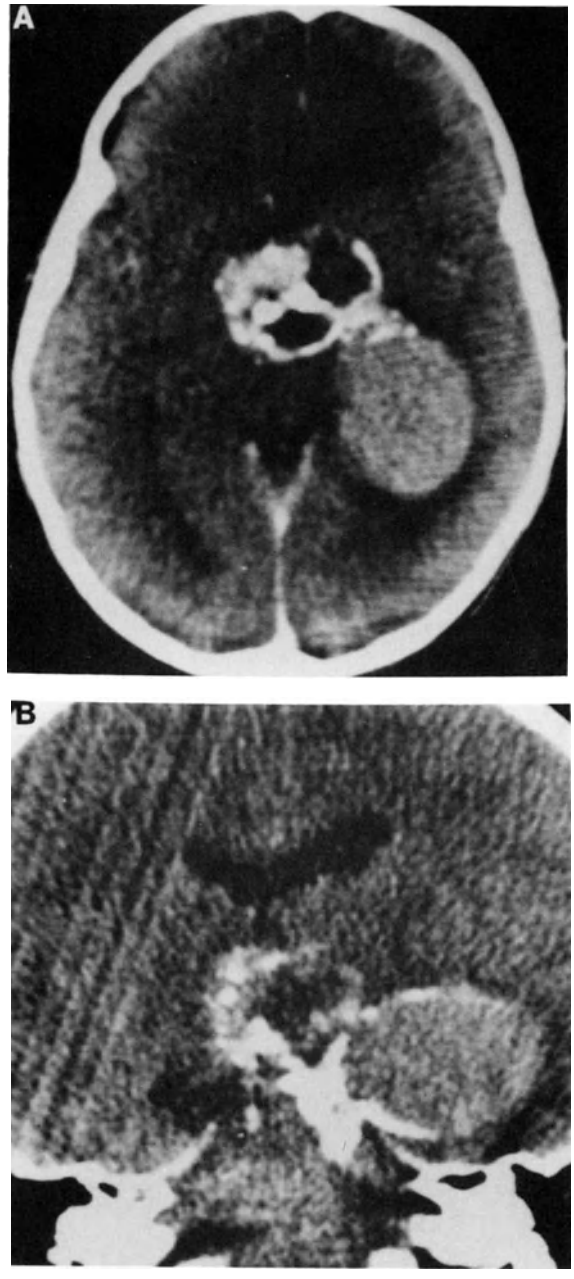

Figure 10. (A and B) Axial and coronal CT scans of a 10-year-old with large, complex tumor. The suprasellar component was partially cystic, but had large calcified pieces. The tumor had entered the choroidal fissure of the right temporal lobe and distended the temporal horn. This portion was largely cystic, with milky-white fluid.

considered to have adequate growth was not considered to be growing adequately by his parents. With the wider availability of growth hormone, he qualified for it under the federal program and is now receiving it.

On the other hand, at least one quarter of the children with intact stalks behave anatomically in the postoperative period as though there was no stalk present. There is no explanation for this at present.

Edwards adds that the only patients who have had really dramatic improvements have been those with intrasellar craniopharyngiomas that were attacked via a transsphenoidal route. The concept put forth by Wilson of transsphenoidal cyst aspiration followed by radiotherapy is no longer recommended at Edwards' institution, in view of the number of recurrences over a 20-year period.

SURGICAL TECHNIQUES IN CRANIOPHARYNGIOMA REMOVAL

In general, extra-axial approaches are preferred to transaxial approaches. Most use the right subfrontal approach. This subfrontal route leads into the traditional approach between the optic nerves that Patterson has elaborated upon (Chapter 8, this volume), with tuberculum sellae resection and entry through the sphenoid sinus combined with lamina terminalis entry. Lateral approaches via pterional craniotomy are also utilized.

The first step after identifying the tumor is aspiration of the cystic contents. Subsequent identification of the tumor (not cisternal) arachnoidal planes permits identification of all vital structures, including the pituitary stalk. With gentle retraction on the tumor capsule this may be delineated from the optic nerves. Opening the lamina terminalis may be helpful. Drilling firm pieces of calcium may allow their removal between or lateral to the optic nerves. At the back of the tumor the whole capsule moves up in one's sucker. The Cavitron is not useful in view of its size. Perhaps when a 3-mm tip becomes available it will begin to play a role. Micromirrors are used to assess residual tumor.

There are problems with opening the lamina terminalis. The most vital concept here is to open the lamina terminalis in its midline portion. This can sometimes be identified by a tiny artery that in teleost fishes fed the organum vasculosum lamina terminalis. The artery has no apparent function in humans, but most people have it. The lamina terminalis can be so tight that one doesn't distinguish it, particularly if there is a big tumor behind it. Frequently in our cases, it has been possible to identify this artery and subsequently open it in the midline. In addition, the lamina terminalis may be distinguished from the back of the optic chiasm and tracts by its different color.

We open the lamina terminalis just alongside the artery with a stroke of the microball dissector and look directly into the third ventricle. Occasionally, tumor material will be adherent to the posterior cerebral artery, requiring meticulous dissection.

Finally, the major point is to preserve the pituitary stalk. In this regard it is important to re-emphasize the necessity of distinguishing between the cisternal arachnoid and the tumor arachnoid. It is very easy to do the dissection in the cistern, but one doesn't want to be in the layer between the cisternal arachnoid and the tumor arachnoid: one wants to be in the layer between the tumor arachnoid and the tumor capsule. It is necessary to identify the cisternal arachnoid in order to save the pituitary stalk, because the cisternal arachnoid is going to reflect up onto the stalk; the surgeon should pick up the cisternal arachnoid up front, right at the planum sphenoidale, and peel it off the diaphragm, and then locate the stalk.

First we enter the cyst and aspirate its contents, being careful not to let the cyst fluid—which is high in cholesterin—seep into the subarachnoid space, as this increases the postoper-

ative risk of aseptic meningitis. Then we can begin cauterizing the cyst wall. As material comes down from the floor of the third ventricle and the lesion is decompressed, one can elevate the cisternal arachnoid from the diaphragma sellae and identify the pituitary stalk. The stalk has a striate appearance, with its accompanying portal vessels. Now one can roll the tumor capsule off the stalk, dissecting in the plane between tumor capsule and tumor arachnoid. Subsequently, it is necessary to dissect between the redundant hypothalamus and the remaining capsule. Little bridging vessels may be cauterized. Slight traction on the capsule with a microcup forceps allows the tumor to be delivered as the floor of the hypothalamus is gently teased apart from the tumor.

Alternative Approaches to Craniopharyngioma Removal

Dolenc offers a slightly different approach. He maintains that he was not always successful with tumor removals using a prechiasmatic approach and drilling into the sphenoid sinus; he had some postoperative CSF leaks. This led him to consider an alternative approach. He reminds us that in 1956 Dawson described arteries running medially from the carotid artery to the optic nerve, chiasm, and pituitary stalk. Dolenc believes that diabetes insipidus results from injury to these arteries, and for that among other reasons he began to approach craniopharyngiomas from the lateral aspect of the carotid artery. In actuality, he was looking for a better approach to the basilar tip aneurysm. He began to drill off the anterior clinoid, opened the optic canal, and entered the first part of the cavernous sinus. Then he could visualize the loop of carotid artery on the lateral aspect of the sella turcica. Then, following the lateral border of the IIIrd nerve he came down to the posterior clinoid and drilled off the posterior clinoid. With the diamond drill one can achieve a space of from 8 mm to 1 cm from the base of the anterior clinoid, and one can approach craniopharyngiomas without retraction.

I believe the artery Dolenc speaks of is part of the anastomotic ring around the median eminence. The cisternal arachnoid that comes up is outside of that. The cistern is usually below it, and usually posteriorly, according to Dolenc. If one keeps the arachnoid intact and brings it up high enough, one can save that anastomotic ring.

Dolenc continues that he was never satisfied with this approach: When one retracts the optic nerve and the carotid artery, then one stretches those arteries and perforators backwards, too. In addition, he had done 400 or 500 aneurysms, and over 300 were in an acute stage. He always performs the Scarff operation, or so-called "cisternostomy." The Swedish group from the Karolinska Institute were critical of this approach and claimed that it led to the destruction of functionally significant brain tissue, but Dolenc claims to have never encountered problems with the lamina terminalis approach. I myself believe their troubles may have stemmed from not being accurately in the midline.

Dolenc continues that the idea of this approach, including drilling of the posterior clinoid, was not original. Kemp Clark of Dallas mentioned it more than 10 years ago. Dolenc's team was aware of this possibility, but initially considered it too dangerous.

Patterson debates whether this approach is necessary. He claims to have had patients with basilar artery aneurysms that some said couldn't be approached via a pterional route. It was his experience that if he split the Sylvian fissure far enough and wide enough, he could get around the back of the posterior clinoid and need not drill it off.

Dolenc questions whether one should be sacrificing the Sylvian fissure veins. Peng Huang, from Mount Sinai Hospital, described the veins draining from the basal structures. In Dolenc's approach, he intentionally does not cut the arachnoid in the front and in the Sylvian fissure, just to preserve those veins. In perhaps 80% of cases, those veins are not prominent, but in some cases they are very large so he preserves them.

LASER MANAGEMENT OF CALCIFIED PORTIONS OF TUMOR

Long asks if Edwards has had any experience with the microwatt laser in the removal of craniopharyngiomas.

Edwards responds that he has not. However, there is a new unit that is less unwieldy. It has a spot that can be focused to 50 microns and can vaporize tiny pieces of tissue.

To the question of whether, when the laser is directed at calcified tissue, it heats the tissue to a dangerous level, Edwards responds that it may. If one leaves the laser beam on the calcified tissue for the length of time required to vaporize it, the tissue will heat up. To avoid this one must use a high-powered short-duration pulse, and then vaporization occurs without significant tissue heating.

Tew adds that in his experience, anything one can see one can safely vaporize. The heat will spread, but it is less of a problem on a vascular structure than on a nerve. In this regard, one has to be more careful if one is working on the pituitary stalk or adjacent to a nerve. It is necessary to stop frequently and use the super-pulse mode, which has a built-in interruption in the current density.

Edwards concurs that lateral heat spread is prevented when one uses high-peak pulses on a 1-mm piece of calcified tissue. The tissue will vaporize without transmission of heat to the neural tissue. However, to the question of how long it would take.to vaporize an 8-mm × 12-mm lump of calcium, Edwards responds that this laser will not function satisfactorily on large pieces of calcium.

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