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Preface

As an addition to the European postgraduate training system for young neurosurgeons we began to publish in 1974 this series devoted to Advances and Technical Standards in Neurosurgery which was later sponsored by the European Association of Neurosurgical Societies.

The fact that the English language is well on the way to becoming the international medium at European scientific conferences is a great asset in terms of mutual understanding. Therefore we have decided to publish all contributions in English, regardless of the native language of the authors.

All contributions are submitted to the entire editorial board before publication of any volume.

Our series is not intended to compete with the publications of original scientific papers in other neurosurgical journals. Our intention is, rather, to present fields of neurosurgery and related areas in which important recent advances have been made. The contributions are written by specialists in the given fields and constitute the first part of each volume.

In the second part of each volume, we publish detailed descriptions of standard operative procedures, furnished by experienced clinicians; in these articles the authors describe the techniques they employ and explain the advantages, difficulties and risks involved in the various procedures. This part is intended primarily to assist young neurosurgeons in their postgraduate training. However, we are convinced that it will also be useful to experienced, fully trained neurosurgeons.

The descriptions of standard operative procedures are a novel feature of our series. We intend that this section should make available the findings of European neurosurgeons, published perhaps in less familiar languages, to neurosurgeons beyond the boundaries of the authors countries and of Europe. We will however from time to time bring to the notice of our European colleagues, operative procedures from colleagues in the United States and Japan, who have developed techniques which may now be regarded as standard. Our aim throughout is to promote contacts among neurosurgeons in Europe and throughout the world neurosurgical community in general.

We hope therefore that surgeons not only in Europe, but throughout the world will profit by this series of Advances and Technical Standards in Neurosurgery.

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A. Advances

Regeneration in the Central Nervous System: Concepts and Facts*

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* Dedicated to Professor Paolo Crepax (1920–1974).

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1. Introduction

In many years, based on Cajal's statement "... nerve paths are fixed, ended, immutable. Everything may die, nothing may be regenerated ..." (Ramon y Cajal 1928) it has been assumed that the central nervous system (CNS) is unable to regenerate a lesioned pathway. Current opinion is in many instances the opposite (Liu and Chambers 1958; Fuxe *et al.* 1974; Cotman 1978; Björklund and Stenevi 1979). There is now a general belief in possible regeneration in the CNS, even if clearcut results remain scarce (Finger and Almli 1985; Berry 1985). In fact, in some cases, functional recovery after a CNS lesion has been observed and correlated with a morphological readjustment of the neural circuitry. However, a cause-effect link between morphological and functional recovery has not yet been provided, at least not beyond any doubt (Finger and Almli 1985). Since, as a general rule, for both invertebrates and vertebrates, there is little or no further generation of nerve cells in the mature brain, the morphological recovery observed after a lesion must rely on the ability of neurons to form new processes and new contacts (Raisman and Field 1973; Goldberg 1980; Veraa and Grafstein 1981). In fact, neuronal connections are in a dynamic state (morphological plasticity), since also in physiological conditions in the mature brain they are subjected to continuous remodelling (Björklund and Stenevi 1979; Cotman *et al.* 1981; Cotman and Nieto-Sampedro 1984). These observations support the assumption that morphological recovery may mediate behavioural recovery of specific brain function after a focal brain lesion. Functional recovery could also depend on changes in the efficacy in preexisting synaptic contacts or, more generally, on modulation of the activity of entire neural networks (functional plasticity). Thus, regeneration should be evaluated considering both morphological and functional plasticity. Therefore, this phenomenon is in some aspects linked to the problem

of forming suitable connections during development as well as probably to the problem of the formation of at least some types of engrams.

Studies on developmental growth and regeneration after lesion have been carried out especially on monoamine neurons (see e.g., Olson and Malmfors 1970; Nygren *et al.* 1971; Jonsson and Sachs 1972; Olson and Seiger 1972; Jonsson *et al.* 1973; Seiger and Olson 1973; Jonsson *et al.* 1974) in view of the vast knowledge of these systems which has been gathered by means of the Falck-Hillarp technique (Dahlström and Fuxe 1964; Dahlström and Fuxe 1965). One aim of the present paper is to clarify some conceptual features of this issue. Thus, morphological and functional plasticity will be discussed in the frame of the special function of the CNS: the handling of information. We will deal mainly with the regenerative features of the central monoamine neurons, underlining the relevance of a common mechanism which is activated in the CNS and in other tissues in response to a lesion: the polyamine biosynthesis (Agnati *et al.* 1985 b). In fact, the morphofunctional remodelling of the CNS network after injury depends on trophic factors like gangliosides and nerve growth factor (NGF), which may exert at least part of their actions via the polyamines (Lewis *et al.* 1978; Zini *et al.* 1986).

2. Lesions and Degeneration of the Central Nerve Cells

The term lesion should be distinguished from the term degeneration. Degeneration can be defined as a set of morphological and biochemical changes which result in a decreased capacity of the neurons to survive and which, eventually, may lead to cell death.

Degeneration can be the outcome of a lesion, but it can also be observed in situation in which a "cellular insult" is not apparent, as in aging. A CNS lesion can be acute or chronic and it can be in principle of three types: mechanical, chemical or metabolic. A mechanical lesion is observed after head injury or surgery. A chemical lesion can be due to various agents: endogenous and exogenous neurotoxins; alteration in trophic agent concentration in the microenvironment; alteration in humoral agents which can modify the survival capability of the neurons (e.g., glucocorticoids) (Sapolski 1985). A metabolic lesion is observed when the metabolic support (such as glucose and O_2) to the brain fails or when there is an increase in metabolic waste products (such as CO_2 and lactic acid).

The basis for the heterogeneous sensitivity of the CNS to the lesioning agents is only partly known. In fact, the lesioning agents act at the CNS level on a highly heterogeneous cell population, since not only are there different classes of glial and nerve cells, but also the cell chemistry, connectivity and local environment can result in a peculiar sensitivity of each cell to a certain type of lesioning agent (Jacob 1963; Kogure *et al.* 1985).

A basic biological difference between glial cells and neurons is that only glial cells retain the mitotic capability, which is lost for neurons already during neonatal life. The glial cell response to a mechanical lesion consists of well known stages. At the site of trauma, the axon and myelin sheath undergo rapid local degeneration (1st–3rd day). Not only glial cells (astrocytes and microglia) proliferate and act as phagocytes on the axonal debris, but also, through the lesioned blood vessels, macrophages can enter the area of the lesion and act as scavengers (2nd–4th day). The proliferation of fibrous astrocytes (3rd–5th day) leads to the formation of a "scar" (gliosis, 1–6 weeks), which has been considered one of the elements preventing the proper rerouting of the regenerating axon to its target (Windle 1956; Clemente 1964; Bernstein and Bernstein 1973). The glial cell response can therefore be seen, at least in mammals, as a tissue response with no clear link to the special functions of CNS, that is the transmission and elaboration of information. The neuronal response to a lesion is an apparently more complex event, and some characteristics of this response are linked to aspects of neuronal function which are highly dependent on the organization of the neural networks.

3. Survival, Regrowth, and Regeneration

After a lesion of an axon there are very likely some chemical signals which inform the soma that an injury has occured. The neuron now faces the problem to survive, to repair the damage and then possibly to regrow, and to remake the prelesion connections. As we will discuss the survival of a neuron can be, in some way, related to restoration of its connections (i.e., regrowth). After a lesion there is an alteration of gene expression, which is reflected in metabolic changes. It is important to underline that very likely there are more qualitative than quantitative metabolic changes. Thus, protein synthesis is increased, but not as markedly as should be expected. Biosynthetic enzymes for transmitters are sometimes increased (Agnati *et al.* 1984 b), sometimes reduced, but never completely turned off. Cytoskeletal proteins are increased in some systems but not in others. In conclusion, as Austin (1985) underlines, it seems as if there is a "fine tuning" of protein synthesis to suit the needs of the individual neurons.

Besides anterograde and retrograde intraneuronal degeneration, i.e., the degenerative processes affecting, respectively, the part of axon and associated structures which has been detached from the parent cell and the dendritic tree and the parent cell body which are proximal to the lesion (see e.g., Williams and Warwick 1980), it is also possible to observe anterograde and retrograde transneuronal, or transsynaptic, degeneration (see Fig. 1 a). Thus, a lesion hitting a neuron may lead to degeneration of the

neuron receiving inputs from the lesioned one (anterograde transneuronal degeneration), as well as of the neuron impinging on the lesioned one (retrograde transneuronal degeneration). This evidence underlines the view that even if, in principle, a neuron is a functional and trophic unit (Ramon y Cajal 1908), the neuronal network is the arrangement within which each neuron can show the entire range of its survival capabilities, and thus, probably, the state to which a lesioned neuron will attempt to return. In fact, this tendency of neurons to create connections has been observed also for neuronal cells in culture and can be considered as an intrinsic property of the nerve cells (for review see Purves and Lichtmann 1985).

After lesion a neuronal cell can give out a set of "pre-programmed" responses, which can be considered as stereotyped attempts to reconstruct

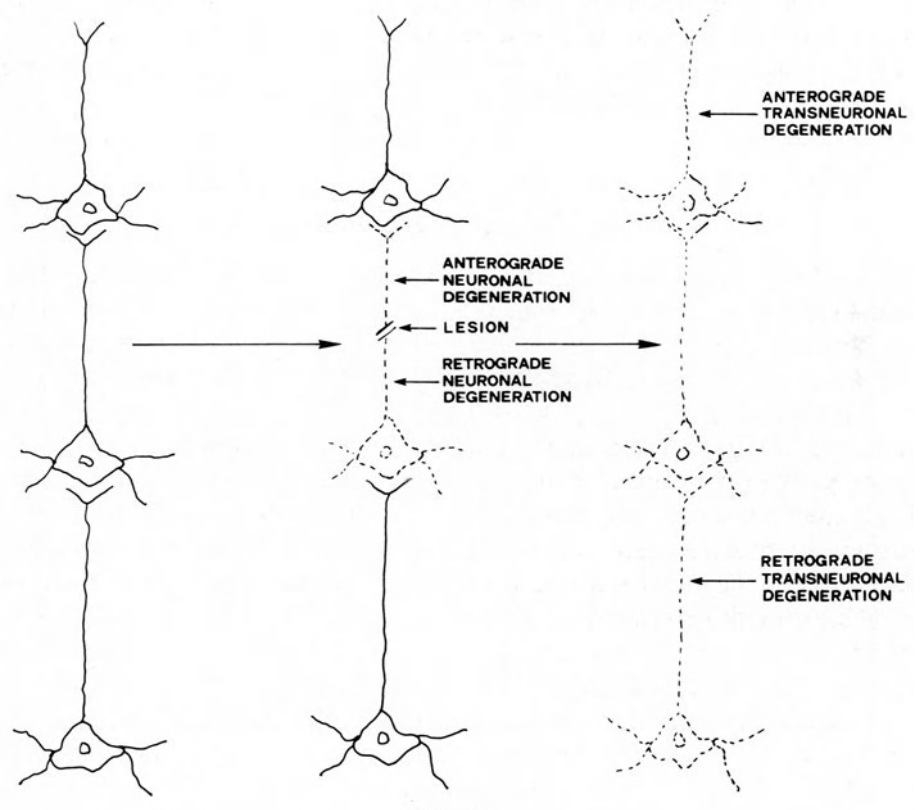


Fig. 1a

Fig. 1. Schematic representation of the possible morphological responses of neurons after differently localized lesions. a) Morphological responses of a neuronal chain to a lesion. b) Responses of a neuronal pathway to different type of lesions

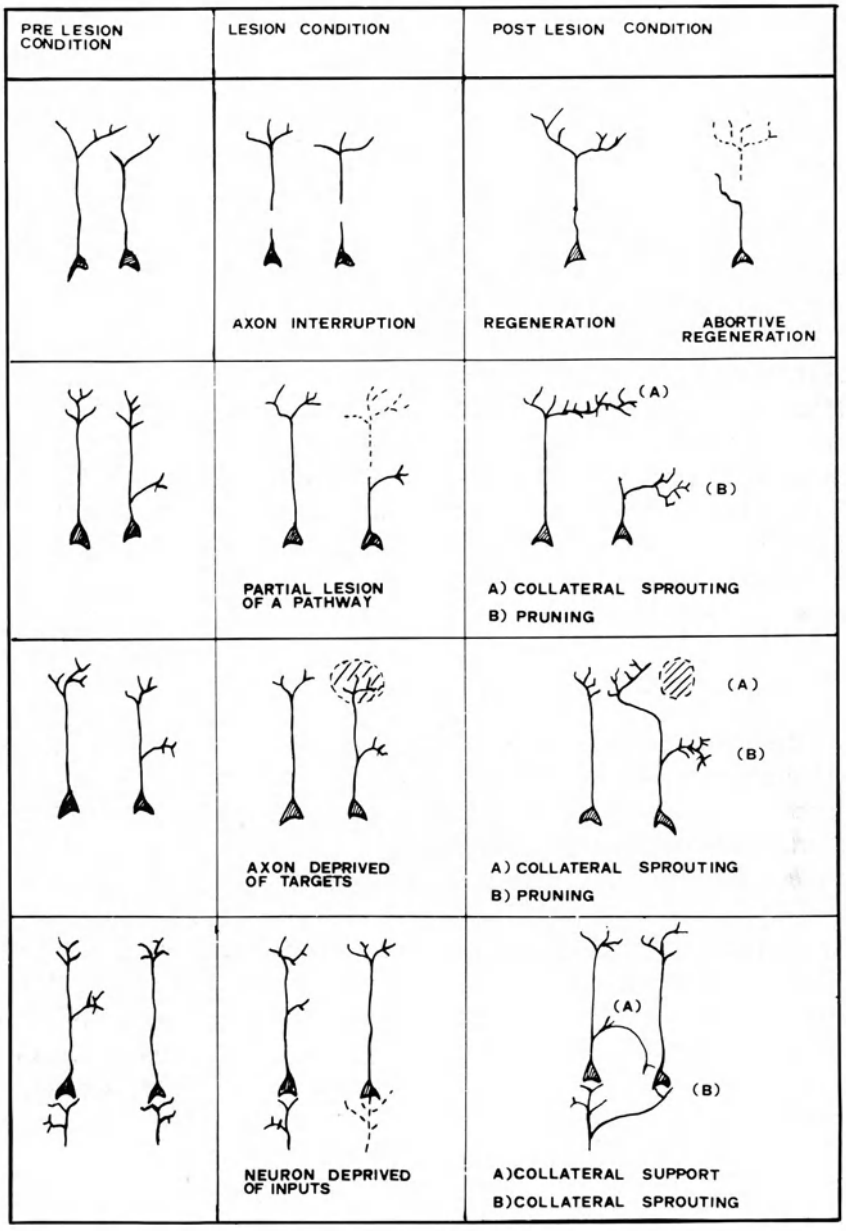


Fig. 1b

the network's milieu, where the survival capabilities of the neuron are maximized. A schematic representation of these responses in different conditions following a CNS lesion is summarized in Fig. 1 b.

A. Survival

The principle according to which the neuronal tissue works in a first phase after injury is probably to save the maximal number of nerve cells, and thus attempts to reconstruct the connections may represent a trophic phenomenon and not an event to improve information handling. In agreement with this view we have put also forward the hypothesis (Janson *et al.* 1988) that during this period it is of basic importance for the neuron to be freed from the tasks of the electrochemical elaboration of the information and thus to spare energy for the more urgent survival tasks. In fact, in a neuron which fulfils its electrochemical tasks, about 60% of the total energy expense is used for the maintenance of the membrane potential (ATPase activity) (Alberts *et al.* 1983). Experimental support for this hypothesis derives from studies on the decreased sensitivity to hypoxic damage of cultured neurons, whose activity was blocked by tetrodotoxin (Rothman 1983) and on the protective action of thiopental during cerebral hypoxia (Michenfelder and Theye 1973). The neurotoxicity of excitatory aminoacids and the protective action of inhibitory aminoacids (Saji and Reis 1987) can also be interpreted according to the present hypothesis.

B. Regrowth versus Regeneration

After the new circuitry, which tends to maximize neuronal survival, is established the CNS faces the problem of integration of this circuitry in the preexisting pattern and to use it to recover the lost function. In fact, regrowth should be clearly distinguished from regeneration. Regrowth can be an abortive phenomenon or, as assessed above, it can be a process aimed only at restoring the trophic link between the axon-lesioned neurons and other neurons to form a network without any electrochemical integrative capability, i.e., without any capacity for information handling. Instead regeneration is a process of regrowth leading to reconstruction of the original network or of a similar network which can subserve tasks for information handling as performed before the lesion. Thus, regeneration has to be considered as a true morphofunctional recovery.

C. Aspects of CNS Development

Regeneration in the CNS shows many similarities with CNS development. In mammals (Kandel 1985) the total genetic information is about 10^5 genes, and, as such, is insufficient to specify the total number of neuronal interconnections, which probably are in the order of 10^{15}. Thus, CNS organization relies upon not only genetic, but also upon epigenetic information. Epigenetic processes can sequentially activate and modulate specific portions of the genetic code within the developing CNS cells. Epigenetic in-

fluences arise not only within the CNS milieu but also from the external environment. There is a continuous reinforcing interplay within the CNS and between the CNS and the environment during maturation. The increasing number of new connections formed probably progressively increase the number of internal cue signals as well as allowing for a progressively improving ability to filter and integrate inputs from the environment. The final result is a maximization of the fitness of the CNS to the environment within the frame work of the genetic patrimony of the subject. Kandel (1985) recognizes five mechanisms underlying the early matching and the later fine tuning of the neurons during CNS development:

– chemical coding of pre- and postsynaptic cells. Both the outgrowing cells and their targets are chemically marked according to their position

– path finding by reading substrate cues. Outgrowing axons are guided to their targets by following cues along the pathway

– selective chemical recognition of the targets by the outgrowing axons

– adjustment in the size of the population by means of cell death and synapse elimination

– fine tuning of connections through activity, competition and other interactive processes

D. Relationship of Regrowth Processes to Developmental Processes

Regrowth phenomena after brain injury share some common features not only with the forementioned developmental growth processes, but also with mechanisms active in the adult brain. In fact, it has been suggested that spontaneous synaptic modification and turnover may take place not only in developing but also in mature nervous system (Cotman *et al.* 1981; Cotman and Nieto-Sampedro 1984). However, injury introduces a profound alteration of morphological and biochemical characteristics of nervous tissue, which may prevent the full accomplishment of activated repair processes. Thus, it is possible that in regeneration there are too few substrate cues or that the capability of the outgrowing axon to read them is reduced. It is also possible that the capability of chemical recognition is reduced. Furthermore, an important regulatory mechanism active during development is represented by cell death (Cowan *et al.* 1984; Purves and Lichtman 1985): during embryonic life a redundancy is observed in cell and connection generation, which allows the loss in some cases of as much as 75% of the original cell population (see Jacobson 1978). On the contrary, since during the regeneration process the size of the nerve cell population is already fixed and hence the survival of the neurons is a primary aim, circuitry adjustments cannot take place, at least not to a great extent, through cell death. Therefore, the newly formed circuitry might not be capable of useful

(i.e., integrated with other circuits) electrochemical handling of information. The possibility should also be considered that the fine activity tuning of this circuitry devoid of capabilities for electrochemical handling of information is difficult. The functional meaning of such a circuitry may be doubtful (Finger and Almli 1985). However, it may well be that such a circuitry is important not only for the survival of the lesioned neurons, which are again interconnected, but also for more general aims. In fact, these surviving neurons could give trophic support to neurons of other circuitries (Varon 1985) and could help to maintain the topological relations among different networks in the region, i.e., in this way avoiding excessive glial cell proliferation (see above section on scar formation) and changes in the geometrical and electrochemical features of the extracellular fluid (see below the discussion on volume transmission) (Agnati *et al.* 1986 a, 1986 b).

E. Mechanisms of Regeneration

Regeneration is therefore a difficult goal for the mature CNS in mammals, due not to any intrinsic incapability of the nerve cell, but rather to the complex organization of the CNS and also to the special biochemical characteristics of the environment, in which the lesioned central neurons have to regenerate. This view is supported by circumstantial evidence. After axotomy peripheral axons in mammals can as a rule reinnervate the proper targets and reestablish functional integrity (Gutman and Young 1944; Bessou *et al.* 1965; Sanes *et al.* 1980); in contrast, axons in the CNS usually show only abortive regeneration (Clark 1943; Clemente 1964). Thus, as Cajal (Ramon y Cajal 1928) demonstrated, after an early phase, in which a damaged axon in the CNS starts to elongate from the proximal stump, the axonal regrowth stops after about 2 weeks and the newly-grown axon begins to fragment and disappears within 1–2 months. The reasons for this arrest of growth and subsequent degeneration are not understood. One of the many hypotheses maintains that the glia-collagen scar, formed in CNS wounds, represents a "barrier" to axonal rerouting (Bernstein and Bernstein 1967, 1971; Kiernan 1979). In favour of this hypothesis, successful regeneration in the CNS of young animals is correlated with paucity of scar formation (Hess 1956; Reinis 1965; Gearhart *et al.* 1983). Thus, when pyramidal tracts were cut in infant hamsters, normal connections were reformed, but this did not occur in mature animals (Kalil and Reh 1979; Reh and Kalil 1981). It is well established that neonatal or embryonic tissue has a higher capability of reconstructing connections. Grafting of this type of tissue in suitably denervated regions has lead to functional reinnervation (Björklund and Stenevi 1984). For example, grafts of the rat embryonic ventral mesencephalon, which contain dopamine (DA) cells have been placed in contact with a previously 6-hydroxy-dopamine (6 OHDA) de-

nervated striatum. After 6 months, DA axons entered the host striatum to form a plexus of DA containing terminals reaching about 1/3 of the nucleus caudate-putamen. DA levels and turnover were restored to normal in the reinnervated regions. Also a certain functional recovery was observed as evaluated by means of contralateral apomorphine-induced rotational behaviour (Björklund *et al.* 1980; Dunnett *et al.* 1981). Similar results were observed when a suspension of embryonic nigral cells was injected into the 6 OHDA denervated striatum, but using this approach the functional recovery was more prompt, since it was already present after 3–6 weeks (Schmidt *et al.* 1981, 1982; Herrera-Marschitz *et al.* 1984).

All non-myelinated central neurons possess some regenerative capacity (Björklund and Stenevi 1979; Austin 1985), while this does not hold true for the myelinated central neurons, even if the regrowth is not inhibited by myelin per se (Berry 1985). In fact, when a segment of autologous rat optic nerve was inserted between the cut ends of a severed peroneal nerve and with the grafts maintained up to 28 months, it was found that the regenerating fibers penetrated the optic nerve graft (Aguayo *et al.* 1978; Weinberg and Spencer 1979).

F. Inhibitory Role of Neuroglia in Axonal Regrowth

A peculiar phenomenon is the capability of central neurons to grow axons into peripheral nerves, while the opposite does not take place. In fact, if the distal end of a severed peripheral nerve is embedded into the CNS, peripheral axons either do not penetrate in the CNS or penetrate only for a short distance (Clark 1943). On the contrary, central axons enter the stump and elongate within it for long distances becoming myelinated by Schwann cells (Aguayo *et al.* 1979). Thus, as Varon states "it appears that peripheral nervous system (PNS) terrain favours, and CNS terrain opposes, the regrowth of both PNS and CNS axons" (Varon and Manthorpe 1985).

A bridge has also been built between the medulla and the spinal cord after focal CNS injury, using peripheral nerve segments. The axons were found to grow out from both centers to a distance of about 30 mm. The regeneration potential seemed to be expressed when the glial environment changed from that of the CNS to that of the PNS (David and Aguayo 1981). Kiernan suggests that, in this case, the triggering to express regeneration potential is due to plasma or extracellular factors (Kiernan 1979). Thus, it seems as if central neurons are still capable of regeneration in adult life. However to achieve this goal it is necessary to provide them with the correct environment, which should contain suitable cues for the directed growth and triggering factors to have them express their regenerative capability. In fact, adult mammalian CNS has a reduced plasticity, which

can only induce short range changes in the geometry and connectivity of neural processes; this may depend on inhibitory factors (Skaper *et al.* 1983; Davis *et al.* 1984) present in the CNS environment. As Aguayo suggests (Aguayo 1985) "it seems possible that one of the roles of the central neuroglia of the uninjured mature brain is to dampen wider fluctuations in neural connectivity and thus ensure the permanence of the "wiring" arrangements determined during development by a multitude of well timed events".

4. Regrowth versus Morphological and Functional Recovery

A. Morphological Recovery Linked to Functional Recovery

As evaluated on the basis of their abilities to grow into a peripheral autonomic target tissue (which has been grafted by insertion into a vascularized cavity in the CNS of the rat) the following rank order of regrowth capability has been established for some transmitter-identified neurons: noradrenaline > acetylcholine > dopamine > serotonin > γ-aminobutyric acid (Björklund and Stenevi 1979).

Neuropeptide systems may also be able to regrow. β-endorphin-like neurons in the hypothalamus have been observed to respond to a metabolic lesion (carotid lesion and cortical infarction) with increased synthesis of β-endorphin material (Hosobuchi *et al.* 1982). Vasopressin neurons, microdissected from fetal brain, can be grafted into the III ventricle of Brattleboro strain rats, overcoming the genetic syndrome which affects this strain of rats (Gash and Sladek 1980). In this case regrowth of fetal vasopressin neurons is associated with morphofunctional recovery, since functional synaptic contacts between host and graft cells have been described. Thus, there are examples of morphological recovery, probably linked to a functional recovery, with causes other than the survival of the lesioned neurons. There are also cases in which regrowth can worsen the effects of a lesion and prevent what functional recovery has been obtained by vicarious networks (Finger and Almli 1985).

The demand for morphological recovery provides a series of problems since after most CNS lesions it is not possible to reconstruct a network exactly as it was in the prelesioned state. Thus, even in the most favourable cases, only a similar set of connections with respect to the original ones are formed. Therefore, even if we observe more than a simple regrowth phenomenon we have not a complete morphological recovery (for a review see Steward 1982). In this case it is important to consider the main characteristics of the wiring of the system. In fact, in a network neurons are connected according to topological, chemical and also trophic specificity criteria. Alterations in the original pattern as evaluated by means of these criteria

lead to losses or abnormalities in the function which seldom can be foreseen (Schneider and Jhavary 1974; So and Schneider 1976). In this frame we can fully understand Aguayo's statement (see above) that the glia function in the CNS acts to reduce the plasticity of connections.

B. The Role of Volume Transmission in Functional Recovery Without Morphological Recovery

The potential of a functional recovery that is not based on a morphological recovery is underlined by the "diaschisis" phenomenon: When one part of the brain is damaged, other parts will also suffer a temporary disruption or suspension of normal functioning (Finger and Almli 1985). With time, there will be a certain recovery which is not dependent on a morphological recovery. On this positive phenomenon a regrowth process may be superimposed with negative effects for functional recovery, due to the formation of abnormal networks. This regrowth may prevent either the vicarious action of other networks or may exaggerate an imbalance between different elements of a system (e.g., spinal reflex spasticity after spinal cord transection).

It is our opinion that functional recovery without morphological recovery may also depend on the reacquisition and potentiation after lesion of the "volume transmission" type of information handling by the CNS (Agnati *et al.* 1986 a, b). In fact, we have introduced the hypothesis that the CNS is endowed with the capability of handling information, not only via the topological organization of its elements and the patterns of impulse flow along the neural networks ("wiring transmission": WT) but also via the electrotonic currents and the spreading of humoral signals in the extracellular fluid ("volume transmission": VT).

The concepts are summarized in Table 1 and 2. The VT is a humoral type of chemical transmission. However, it does not only consist of humoral signals, diffusing in the extracellular fluid to reach the appropriate receptors (see e.g., Vizi 1984), but also of electrotonic signals, which also operate in the extracellular fluid. In fact, the extracellular space of the brain constitutes a restricted microenvironment. Thus, ion fluxes across cellular membranes can induce substantial changes in the ion composition. These ionic fluctuations in the extracellular fluid and the ionic fluxes from sources to sinks may represent signals for communication between neural groups (Nicholson 1980). In Table 1 the possible role of glia and neurons in the WT and VT is summarized. In VT the glial cells control the extracellular fluid ion composition and the shaping of extracellular fluid pathways (i.e., the communication channels between neuronal groups) for signal diffusion as well as the release, uptake and metabolism of humoral signals. With regard to the function of neurons in VT they represent the location of sources and sinks for electrotonic signals and the sites of release and recognition of

Table 1. *Role of Neurons and Glia Cells in Wiring and Volume Transmission*

		GLIA FUNCTIONS		NEURON FUNCTIONS	
		PHYSICAL	BIOCHEMICAL	PHYSICAL	BIOCHEMICAL
WIRING TRANSMISSION	ELECTRICAL SYNAPSE	SYNAPSE SEGREGATION	MODULATION OF COUPLING VIA ECF	LOCATION OF SYNAPSE	MODULATION OF COUPLING VIA ICF
	CHEMICAL SYNAPSE	SYNAPSE SEGREGATION	MODULATION OF SYNAPTIC CLEFT MICROENVIRONMENT	LOCATION OF SYNAPSE	CONTROL OF THE EFFICACY OF TRANSMISSION LINES AND THEIR INTERPLAY
VOLUME TRANSMISSION	ELECTROTONIC SIGNALS	SHAPING OF ECF PATHWAYS FOR SIGNAL DIFFUSION	CONTROL OF ECF ION COMPOSITION	LOCATION OF SOURCES AND SINKS FOR SIGNALS	CONTROL OF SOURCES AND SINKS FOR SIGNALS
	HUMORAL SIGNALS	SHAPING OF ECF PATHWAYS FOR SIGNAL DIFFUSION	RELEASE , UPTAKE AND METABOLISM OF SIGNALS	LOCATION OF SOURCES AND SINKS FOR SIGNALS	RELEASE , UPTAKE AND METABOLISM OF SIGNALS

Table 2. *Summary of the Main Informational Features of Wiring and Volume Transmisson in the Central Nervous System*

	Speed of transmission	Degree of divergence	Segregation ("safety" of the transmission)	Plasticity	Preferential information processing
"Wiring transmission" neuron linked electro-chemical transmission	high	low to moderate	high	low to moderate	elementary elaboration short term action
"Volume transmission" humoral ("open") electro-chemical transmission	low	high to very high	low	high to very high	holistic elaboration long term action

humoral signals. From a biochemical standpoint the neurons control the sources and sinks of electrotonic signals and are involved in the uptake, release and metabolism of humoral signals. When we are focussing our attention on chemical signals in WT and VT it is possible to recognize some main differential features. Thus, as seen in Table 2, VT is characterized by a low speed and a long term action, a high degree of divergence and a low safety of the transmission process. WT is the classical type of electrochemical transmission which is neuron linked and operates with a high speed and safety, and short term actions, the divergency and plasticity being relatively low. It seems clear that the integrative capability of the CNS is increased by the presence of VT, which is not submitted to neuroanatomical constraints and which may affect the computing characteristics of the neuronal networks.

The VT can recover after lesion when:

– the membrane potentials are restored as well as the genesis of membrane potential fluctuations and hence of electrotonic currents in the extracellular fluids

– the release, recognition and decoding mechanisms of chemical signals are returned to normal

A potentiation of the VT can rely upon:

– increased density of sites for the release of chemical signals (could this be a positive effect of collateral sprouting?) or increased amount of chemical signals released by each terminal

– increased density of recognition sites or increased gain of the decoding mechanism for chemical signals (could this be a positive effect of denervation supersensitivity?)

– widening of the extracellular fluid pathways connecting the region of release with the target area

According to this view it can be also surmised that the functional recovery of diffuse systems, like central monoamine systems, which are mainly connected via non-synaptic transmission (Vizi 1984) with the respective targets relies upon mechanisms of this type. In fact, as mentioned above, noradrenaline, dopamine and serotonin systems can recover rather effectively after lesion (Nygren *et al.* 1971; Fuxe *et al.* 1974) and above all the transplantation of embryonic dopamine neurons outside but in contact with a denervated striatum can reduce the functional deficit (Björklund and Stenevi 1984; Olson 1985).

5. Trophic Agents

A. Concepts in Trophic Mechanisms

The trophism of the brain is for some aspects similar to the ones demonstrated for peripheral tissues, but it shows also unique peculiarities.

It can be surmised that in the nervous tissue different trophic organizations are possible:

– trophic interactions between neurons in a network, which may take place via synaptic contacts or non-specialized connections

– trophic interactions between glial cells and neurons

– trophic signals released in the extracellular and cerebrospinal fluids by specialized neural and glial cells which can reach distant target neurons and glial cells

– trophic signals reaching the CNS from peripheral organs

Hence, the trophism of the CNS is, to a certain extent, linked to its specific function, the handling of information which is carried out by means of electrochemical signals. It seems as if the survival of neurons and the neurite growth, as well as the establishment of connections, depends on electrochemical signals. While there is clear evidence that electrical activity can be of paramount importance for neuron survival and for maintenance and shaping of synaptic contacts (Benoit and Changeux 1978; Thompson 1983; Jackson 1983), the chemical signals involved in these processes are still largely unknown. However, it is now clear that the study of molecular mechanisms guiding the neuronal development and/or regeneration after injury requires the identification of "trophic agents" able to selectively promote or inhibit the survival or growth of different neuronal subpopulations (Levi-Montalcini and Calissano 1986; Berg 1984; Varon and Adler 1981).

Trophic agents are endogenous molecules which have an informational role in triggering on biosynthetic mechanisms important for neuronal survival and/or growth. Usually they are active at very low concentrations.

According to Varon (Varon *et al.* 1984), the terms "trophic agents" and "neurite-promoting agents" should be used to indicate substances (regardless of their nature and size) which allow nerve cell survival and stimulate neuronal growth respectively. The term "factor" should be reserved to describe agents that are proteins and exert their trophic influences by interacting with neuronal receptors. Several trophic agents have been purified and some of them are listed in Table 3.

B. Nerve Growth Factor and Other Trophic Factors

The best characterized is the Nerve Growth Factor (NGF), which was discovered by Levi-Montalcini in 1951 (Levi-Montalcini and Hamburger 1951, 1953). This factor stimulates growth and increases survival of sympathetic and dorsal root sensory neurons in development or after injury (for recent reviews see: Levi-Montalcini 1982; Purves and Lichtmann 1985; Levi-Montalcini and Calissano 1986). NGF-like immunoreactivity was demonstrated

in several tissues, such as brain, in cultures of ganglionic glial cells, in submaxillary gland of mouse, in iris, in fibroblast and cultured muscle cells. It is not yet clear whether NGF is synthesized by neuronal or non-neuronal cells of the brain. However, it has been demonstrated that in vitro astrocytes can produce NGF (Lindsay 1979). From the submaxillary gland of mouse was extracted a multi-component protein (7 S) which contains a biologically active β subunit and two non active subunits, α and γ (Thoenen and Barde 1980). It has been found that NGF is present in the targets of sympathetic ganglion cells in amounts proportional to the density of the innervation (Korshing and Thoenen 1983). Recently, it has been shown that NGF mRNA, identified by means of blot hybridization assay, is present in rat CNS areas at different levels. NGF mRNA accumulation begins at birth, with adult levels reached three weeks postnatally (Whittemore *et al.* 1986). The highest concentration was found in cortex and hippocampus, the lowest in cerebellum (Shelton and Reichard 1986). Also NGF immunocytochemistry has been performed which permitted the visualization of widespread distribution of NGF-like immunoreactivity in the adult brain, preferentially in major fiber tracts. However, also finer fiber-like structures were observed for example in the cerebral cortex (Whittemore *et al.* 1986). Some evidence suggests that NGF produced by the target cells is taken up at the synaptic level of growing neurons and retrogradely transported to the neuronal cell bodies (Thoenen and Barde 1980), affecting neuronal metabolism (Yankner and Shooter 1982). There is evidence for a role of NGF in the trophism of magnocellular cholinergic neurons in basal forebrain (Seiler and Schwab 1984; for review see Korsching 1986). These cholinergic neurons are located in the medial septum, the nucleus of the diagonal band of Broca and in the nucleus basalis of Meynert and innervate the neocortex, the hippocampus and the olfactory bulb. In these areas an increase of the enzyme choline acetyltransferase (CAT) was observed in neonatal rats after repeated intraventricular NGF injections (Gnahn *et al.* 1983; Mobely *et al.* 1986). Furthermore, in adult rats, NGF can partially prevent the death of septal cholinergic neurons after lesion of septo-hippocampal pathway (Hefti 1986). Relatively high levels of NGF were found in septum (see Korsching 1986), while in the same area NGF mRNA is absent (Shelton and Reichardt 1986). These results indicate that NGF is not synthesized in the septal cholinergic cell bodies, but accumulates there following retrograde axonal transport from the target areas. One could speculate that the nonavailability of NGF (or some trophic factors) for the magnocellular cholinergic neurons could contribute to the morphofunctional degeneration of the cholinergic neurons in Alzheimer's dementia (Hefti 1986; Korsching 1986).

A second trophic factor, the Ciliary Neuronotrophic Factor (CNTF) has been obtained from the chick embryo eye (Barbin *et al.* 1984). This

Table 3. *Summary of the Main Features of Some Trophic Agents that Were Shown to Possess Trophic Activity for Mammalian CNS.* ANS = autonomic nervous system; 5-HT = serotonin; NA = noradrenaline; POMC = proopiomelanocortin. References are indicated by numbers as follows: (1) Hefti 1986; (2) Björklund and Stenevi 1984; (3) Korshing and Thoenen 1983; (4) Whittemore et al. 1986; (5) Korshing et al. 1986; (6) Levi-Montalcini and Angeletti 1968; (7) Nieto-Sampedro et al. 1982; (8) Manthorpe et al. 1983b; (9) Needels et al. 1986; (10) Toffano et al. 1983; (11) Agnati et al. 1983; (12) Kojima et al. 1984; (13) Sabel et al. 1984; (14) Cuello et al. 1985; (15) Oderfeld-Novak et al. 1984; (16) Hilbig et al. 1983/84; (17) Schwartz and Spirman 1982; (18) Gnahn et al. 1983; (19) Edwards et al. 1984; (20) Schwartzberg and Nakane 1982; (21) Bijlsma et al. 1984; (22) Agnati et al. 1985d; (23) Agnati et al. 1985e; (24) Agnati et al. 1986b; (25) Shaw 1979; (26) Jonsson et al. 1984; (27) Watson et al. 1978

Trophic agents	Experimental models	Basal levels in the brain	Increased levels during development	Increased levels after lesion	Effects of trophic agent (in vivo admin.)		Effects of the specific antagonism of the trophic agent	
					survival	growth	survival	growth
NGF	fimbria lesion (1) ANS cell transplantation in hippocampus (2)	detectable (3)	yes (4)	yes (5)	increased (1, 2)	increased (1)	reduced (6, 18)	reduced (6, 18)
NPF*	ablation of the entorhinal cortex (7, 8, 9)	detectable (8, 9)	yes (8, 9)	yes (8, 9)	not tested	not tested	not tested	not tested

GM 1	mesodiencephalic hemitransection (10, 11) lesion of 5-HT spinal system (26) mediofrontal cortex aspiration (13) unilateral devascularizing lesion of the cortex (14) chemical denervation of NA cortical terminals (12) partial deafferentation of hippocampus (15)	detectable (16)	yes (16)	not	increased (10, 11, 14)	increased (12, 15, 26)	not tested	reduced (17)
POMC-derivated peptides	parafascicular area lesion (21)	detectable (27)	yes (20)	yes	increased (21, 19)	increased (21, 19)	not tested	not tested
Polyamines	mesodiencephalic hemitransection (22,23,24)	detectable (25, 22)	yes (25)	yes	not tested	not tested	reduced (22)	not tested

* Chemical structure not yet characterized.

factor is active on sensory neurons of the dorsal root, increasing their survival in vitro (Skaper and Varon 1986).

A third trophic factor is the Brain Derived Growth Factor (BDGF), purified from extracts of pig brain and active in vitro only on sensory neurons of the dorsal root (Barde *et al.* 1982).

C. Neurite Promoting Factors, Anabolic Hormones, Polyamines and Pyruvate

A second group of trophic factors are the neurite-promoting factors. Neurite promoting factors are proteins that stimulate neuritic outgrowth, such as the factor purified from bovine brain which elicits neurite extension from cultured chick embryo cortical neurons (Kligman 1982). In vitro neurite extension assays have revealed a class of proteins that stimulate neurite growth by adsorbing to the culture substratum. Collagen, laminin and fibronectin are some of the most studied neurite-promoting factors (Rogers *et al.* 1983; Manthorpe *et al.* 1983). Trophic agents or agents capable of enhancing the effects of trophic agents on ganglion neurons have been found in tissue extracts and conditioned media from several cell sources, but their molecular characteristics have not yet been established (for review see Manthorpe and Varon 1986 in press). Unknown neuronotrophic agents are present in serum, which has been used to supplement the neuronal culture media. However, a set of "permissive" agents has been identified. Recently, replacement of serum with the so called mixture N 1 has been proven to be succesful in various nerve cell cultures (Selak *et al.* 1983). Some of the N 1 components (insulin, progesterone) are anabolic hormones. Among the others (putrescine, selenite and transferrine), putrescine has been recently studied after experimental brain lesions (see next paragraph).

However, central and peripheral neurons may not survive in a glucose-containing medium even when supplemented with N 1 ingredients and trophic factors, unless pyruvate is supplied (Selak *et al.* 1985). Pyruvate secreted by astroglial cells in culture has been shown to support CNS neuron survival (Selak *et al.* 1985). Signals from neurons may in turn reach the glial cells. Magistretti and collaborators (1983) demonstrated that neurotransmitters released from neurons, such as vasoactive intestinal peptide, noradrenaline and DA containing neurons, produce a rapid gluconeogenesis and thus mobilization of energy substrates such as pyruvate, in cultured astrocytes. These findings support the existence of reciprocal metabolic cooperation between glial cells and neurons (Noble *et al.* 1984).

D. Epidermal and Fibroblast Growth Factors

Other compounds, generally indicated as polypeptide growth factors because of their mitogen activity in peripheral tissues, have been described in the brain (Herschman 1986).

Epidermal Growth Factor (EGF), a polypeptide genetically related to NGF, was first isolated from mouse salivary gland. The primary structure of EGF has been determined by Savage and colleagues (1972). EGF, which initiates increased DNA synthesis and cell division (Carpenter and Cohen 1978) has been found in the nervous system. In fact, analysis of EGF histofluorescence in brain slices of colchicine-treated rats suggested that the peptide is present in nervous tissue but is not synthesized by neurons (Fallon *et al.* 1984). EGF exerts a definite mitogenic influence on astrocytes which is both dose and time dependent. EGF also produces absolute increases in ornithine decarboxylase (ODC) activity as observed at 2 and 4 hour time intervals after administration. Thus, EGF may stimulate ODC mediated trophic responses (Huff and Schreier 1985). Fibroblast Growth Factor and Platelet-Derived Growth Factor (see below) have also been found within the nervous system and these two factors appear capable of reducing the mitogenic actions of EGF. It, therefore, seems possible that growth factor interactions may lead to an inhibition of the proliferative signals to the astrocytes, at least with regard to the EGF signal.

Fibroblast Growth Factor (FGF) is a brain extracted polypeptide able to stimulate DNA synthesis and cell division in quiescent 3T3 cells (Gospodarowich *et al.* 1984). Cultured glial cells from rodent brain proliferate when FGF is added (Morrison and deVellis 1981).

Platelet-Derived Growth Factor (PDGF), a polypeptide derived after extensive purification from human platelets (Doolittle *et al.* 1983; Waterfield *et al.* 1983), has been found to be homologous to the oncogene "v-sis" of the simian sarcoma virus. Specific receptors for PDGF were characterized in various tissue, but not yet in CNS.

E. Insulin, Insulin Growth Factors, Trophic Neuropeptides and Gangliosides

Insulin, a well known trophic hormone, has been shown to be produced within the brain (Raizada 1983) and specific receptors for insulin as well as for Insulin Growth Factor I (IGF-I) and II (IGF-II) were found on neurons (Sara *et al.* 1983; van Schravendijk 1984). The IGFs are a family of polypeptides that can cause insulin-like responses in target cells, but are not immunologically cross-reactive with anti-insulin antisera. In particular, IGF-I immunoreactivity increased during nerve sciatic regeneration after surgical transection in rats, indicating a possible trophic role of IGF-I on neurons (Hansson *et al.* 1986). Like the EGF receptor, the insulin receptor

and the PDGF receptor, the IGF-I receptor is a ligand-dependent protein tyrosine kinase (Ushiro and Cohen 1980; Ek *et al.* 1982).

However, according to the present knowledge, most of these factors appear not to be directly involved in neuronal survival or growth. An indirect effect through the modulation of astrocyte synthesis of agents which promote neuronal survival or neurite elongation may not be excluded (Varon 1985).

Recently, several neuropeptides which serve as neurotransmitters in the CNS, such as bombesin, vasopressin, substance P and substance K, have been also shown to act as mitogens, by stimulating DNA synthesis (Rosengurt and Sinnet-Smith 1983; Nilsson *et al.* 1985).

Peptides derived from pro-opio-melano-cortine molecule (POMC), such as ACTH, α- and γ-MSH or their synthetic analog (e.g., ORG 2766) distributed in various areas of CNS, have been shown to be effective in facilitating the regeneration of peripheral nerves (Bijlsma *et al.* 1982) and to reverse behavioural impairement induced by parafascicular area lesions (Nyakas *et al.* 1985) after chronic administration. These effects do not appear to be related to increased synthesis of actin or tubulin during regeneration, but probably to their ability of mimicking the actions of endogenous peptides formed in degenerating nerve stumps (Edwards *et al.* 1984, 1985).

Among the enhancing agents, gangliosides, a class of membrane bound glycolipids, have been found to stimulate in vitro and in vivo neurite outgrowth (Rapport and Gorio 1981; Oderfeld-Novak *et al.* 1981; Agnati *et al.* 1983, 1984 b, 1985 c, and next paragraph; Toffano *et al.* 1983; Skaper *et al.* 1985).

Recently, a neurotrophic protein purified from human blood cells has been turned out to be a catalase (Walicke *et al.*, in preparation), an enzyme which degrades peroxides. According to the fact that free radical poisoning may be prevented by inclusion of catalase, "protective" factors may be also considered in the frame-work of nerve regeneration after a brain injury.

F. Trophic Activity After CNS Lesions

Astrocytes have been described producing neurotrophic factors such as NGF and CNTF in culture according to extrinsic modulation, and thus may participate directly in the process of nerve regeneration. In fact, in vivo-in vitro combined approaches provide evidence that the highest in vitro trophic activity, obtained after a brain injury, resides within the tissue surrounding the lesion, a region rich of gliotic reactions (Nieto-Sampedro *et al.* 1982). This trophic activity induced by a CNS lesion increases steadily over one week. Implantation of neurons from rat embryo corpus striatum in the wound cavity at the 4th–6th day after the lesion greatly improved

the survival of grafted cells and the innervation of the host took place. The neuronotrophic agents appeared to be proteins immunologically distinct from NGF (Manthorpe *et al.* 1983 b). A recent study suggests a possible human counterpart of the observations gathered with rodents. Longo *et al.* (1984) found that human cerebrospinal fluid collected by spinal tap in head injured patients contained detectable trophic activity for cultured E 8 chick telencephalic and E 18 rat hippocampal neurons. Therefore, CNS lesions may induce both survival and neurite promoting agent synthesis in the areas surrounding the lesion. In fact, the presence of two agents capable of increasing the rate of neurite elongation in cultured neurons extracted from normal rat hippocampus was reported by Crutcher and Collins (1982). Deafferentation of hippocampus by entorhinal cortex lesion produced a several fold increase in neurite promoting activity (Needels *et al.* 1986). Gel filtration indicated that the apparent molecular weight of the active substance present in extracts of uninjured brain was 9–17 Kdaltons, whereas the extracts from injured brain showed peaks at 30, 70 and 200 Kdaltons. Therefore, one or more proteins different from NGF are involved in lesion-induced brain neurite promoting activity.

G. Interplay of Various Trophic Agents and Growth Inhibitory Substances in Regeneration

Production of survival or growth promoting substances in denervated target cells or reactive astrocytes do only partially explain the heterogeneity of the regenerative features in the CNS. The existence of growth inhibitory substances has been proposed in order to explain regenerative failure in mammals and birds after a brain lesion. Inhibiting growth factors may be released by proteolysis from injured myelin or oligodendroglia (Berry 1982). Neurite inhibiting agents have been also found in serum (Skaper *et al.* 1983). Successful regeneration may therefore depend upon the availability of permissive agents, the continuous uptake and transport of trophic agents and the presence of growth-inhibiting and promoting agents in optimal concentrations.

It is very difficult to find guidelines in this wide and probably still largely incomplete spectrum of trophic agents. Sometimes it is also difficult to assess the real relevance of some of them, in view of the different experimental models in which their activity has been proven. In a first attempt to classify these agents (see Table 3) it could be useful to distinguish those present in physiological conditions from those activated or even synthesized after a lesion. A further step could be to distinguish those involved in survival from those involved in regrowth, and from those involved in both survival and regrowth. Furthermore, in aech of these classes it could be possible to distinguish permissive agents (blockade of their basal levels or

of their increase after a lesion prevent survival, regrowth or both, respectively) from modulating agents (blockade of their basal levels or of their increase after a lesion reduce modulation of the survival, of the regrowth or of both, respectively).

It could also be important to observe if there are criteria from the field of chemical neuroanatomy to characterize these trophic agents as diffuse (present both in glial cells and in neurons) or selective (present only in glial cells or in neurons or only in limited populations of neurons and glial cells). Possibly clusters of trophic agent-identified cells (neurons or glial cells) will also be detected. In this context it could be important to observe if some transmitter-identified neurons costore a specific trophic agent.

This approach is still at its beginning. However, it is already possible to hypothesize that there are set of neurons specialized in producing agents which have a basic trophic meaning for a large population of neurons or glial cells.

This view is supported by the recently gained evidence of ODC-positive neurons in the CNS (Cintra *et al.* 1987). ODC is the biosynthetic enzyme of the polyamines. On the basis of immunocytochemical results it is not possible to assess whether ODC-immunoreactivity corresponds to ODC enzyme activity. However, in agreement with biochemical data (Scalabrino and Ferioli 1984) showing a decrease of ODC activity in the aged rat, we have observed a reduced ODC-immunoreactivity in old rats (data not published). Besides trophic activity, other functions of polyamines in the CNS have been proposed, like involvement in neurotransmission (Shaw 1979).

6. Ganglioside-Polyamine Interactions

The results reported in this section have been obtained in collaboration with: A. Corti (Department of Biochemistry, University of Modena), P. Davalli (Department of Biochemistry, University of Parma) and M. A. Desiderio (Department of General Pathology, University of Milano).

A. Gangliosides

Gangliosides are a family of acid complex lipids composed by a hydrophobic moiety and a hydrophilic moiety. The hydrophobic moiety is represented by ceramide, while the hydrophilic moiety contains one or more sugar molecules in glycosidic linkage, plus one or more neuraminic acid residues linked to galactose or to another neuroaminic acid (for review see Ledeen 1985). Mammalian brains (especially the cerebral cortex) contain a very high concentration of gangliosides. About 70% of this content is represented by four molecular species: GM 1, GD 1 a, GD 1 b, GT 1 b. In

particular gangliosides are most abundant in the plasma membrane of neurons, where they constitute about 7% of the total lipid mass.

Their function is still largely unknown. It has been observed that GM 1 can act as a cell-surface receptor for cholera-toxin (O'Keefe and Cuatrecasas 1977) and possibly also for nerve growth factors. In vitro, antibodies against gangliosides block neurite outgrowth in CNS and PNS explants (Schwartz and Spirman 1982). Antibodies against GM 1 administered neonatally at a critical period of dendritic development, induce subtle behavioural dysfunctions in the adult, associated with morphological alterations in dendritic arborization (Karsarskis *et al.* 1981), whereas early chronic administration accelerates functional development in the rat (Karpiak 1983). Thus, gangliosides (see Rapport and Gorio 1981) and especially GM 1 have been employed to study neurite outgrowth in tissue culture (Leon *et al.* 1984), and regeneration after lesion in peripheral and central neurons.

B. Effects of Gangliosides in Mechanically Lesioned Rats. Studies on the Mesostriatal Dopamine Pathway

An animal model involving a mechanical brain lesion has been mainly used in our studies on the GM 1 effects on the degenerative and regenerative features of the ascending DA nigrostriatal neurons. Thus, an unilateral partial hemitransection at the mesodiencephalic junction was performed, inducing a preferential lesion of the lateral component of the nigrostriatal pathway. This lesion is not selective for the nigrostriatal pathway, involving, at least in part, the strio-nigral pathway.

Following the mechanical lesion of a monoaminergic pathway a local sprouting, called shunting (Björklund and Stenevi 1979) is observed, while growth to the original target is modest or absent (see also Fig. 1 b). In our model, the DA neurons show a local regenerative reaction at nigral level and a sprouting at target level, leading to a partial reinnervation of striatum within 3 months after the lesion. The functional recovery of the pathway can be followed by analyzing the imbalance between the two sides, by means of studies on apomorphine-induced rotational behaviour, which is maximal 14–21 days after the lesion (induction of DA receptor supersensitivity) and which subsequently decreases (functional recovery).

In this model of mechanical lesion the effects of chronic treatment with ganglioside GM 1 (10 mg/kg/day, i.p.) on the morphofunctional features of the nigrostriatal pathway have been analyzed. A possible effect of GM 1 on the survival of mechanically lesioned neurons was first studied (Agnati *et al.* 1983, 1984 b, 1985 c; Toffano *et al.* 1983). A morphometrical analysis of the cell bodies of the substantia nigra (SN) pars compacta, performed 14, 21 and 56 days after the lesion, demonstrated a protective effect of GM 1 on the lesion-induced degeneration of the tyrosine hydroxylase (TH)-

positive neurons. A rostrocaudal gradient of GM 1-induced cell survival was also noted, GM 1 being more effective on neurons distant from the lesion. The analysis of DA receptor autoradiograms at striatal level showed a decrease of the positive area in the saline-treated group, while GM 1 was able to revert the lesion-induced shrinkage of the striatum. A protective action of GM 1 on the survival of mechanically lesioned striatal cells, on which DA receptors are located, can thus be hypothesized (Fig. 2).

The possible effects of GM 1 on DA cell regeneration were then studied. Morphometrical analysis of TH-positive profiles in SN pars reticulata showed an increased density and length of dendrites in the GM 1 treated rats (Fig. 3). At striatal level an increased density of TH-positive terminals

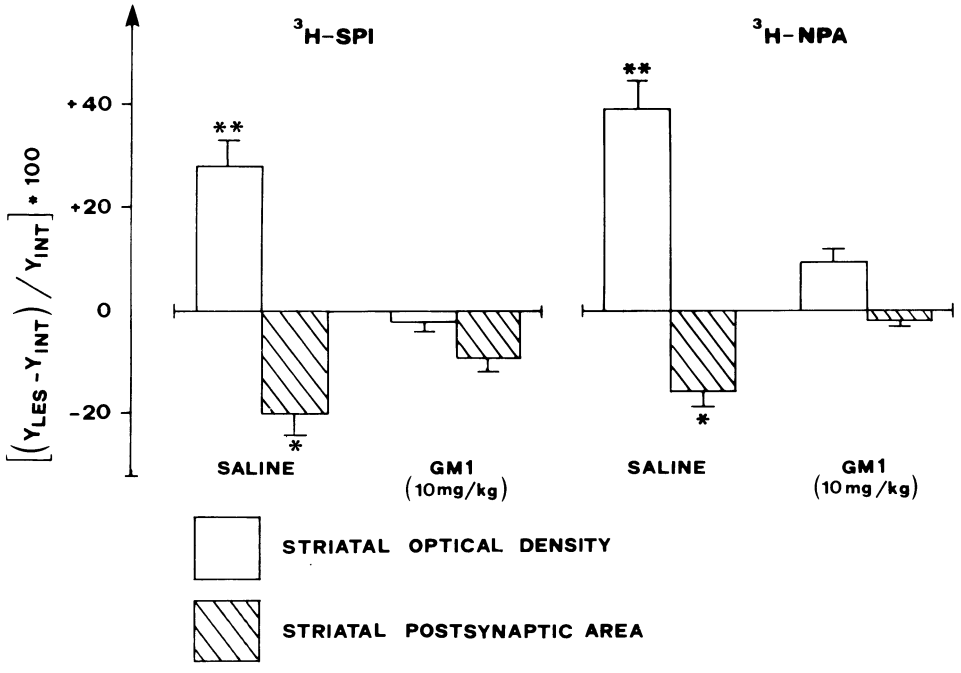


Fig. 2. Effects of GM 1 treatment (10 mg/kg/day, i.p., 45 days) on ^{3}H-spiperone (^{3}H-SPI) and ^{3}H-N-propylnorapomorphine (^{3}H-NPA) binding sites at striatal level of partially hemitransected rats, evaluated by means of quantitative receptor autoradiography. The optical density values as well as the postsynaptic areas have been measured. The optical density gives an evaluation of the degree of blackening of the tritium-sensitive film, thus of the degree of binding in that region. The striatal area labelled by the radioactive ligand gives an evaluation of the postsynaptic area. The mean values (n = 6) are expressed as percent ratios [lesioned side value (Yles) minus intact side value (Yint) in percent of the Yint]. The statistical analysis was carried out by means of Mann-Whitney U-test; asterisks mark mean values significantly different from the zero value (no difference between intact and lesioned side); * = $p < 0.05$, ** = $p < 0.01$

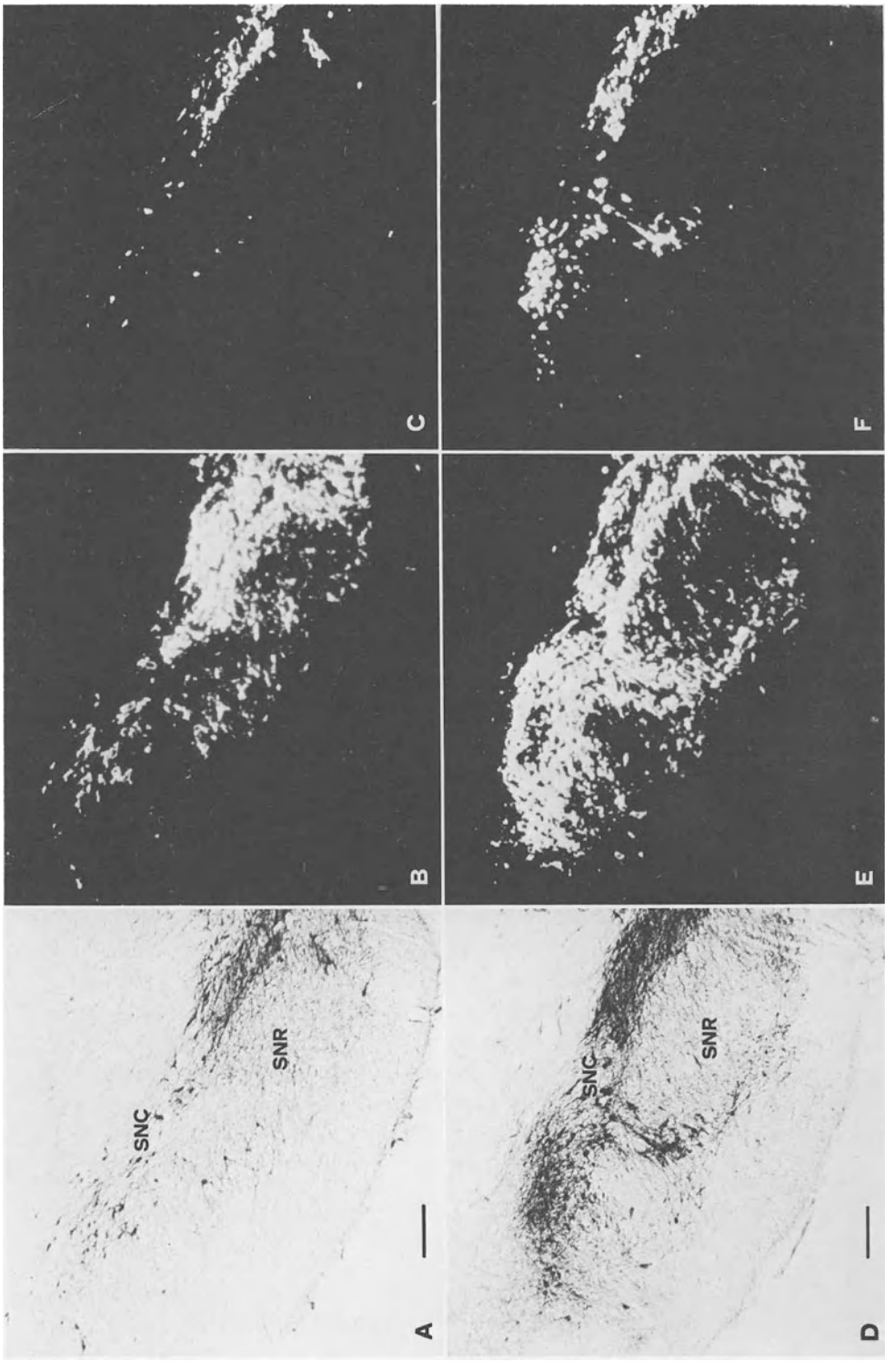
was also observed. Microdensitometrical analysis of TH-immunoreactivity showed increased contents in striatal terminals, and in nigral cell bodies, where a rostrocaudal gradient, opposite to the one previously described for the GM 1 induced cell survival, was observed. Thus, it seems that GM 1 has differential effects on the less damaged cells, whose survival is increased, and on the most damage cells, in which the metabolic response is stimulated.

The present data (Fig. 4) suggest that the administration of GM 1 can potentiate the regrowth of mechanically lesioned nigral cells, possibly by inducing the formation of an alternative route for DA transmission, through increased local contacts at nigral level and collateral sprouting at striatal level. The hypothesis of a new informational circuit in the lesioned pathway favoured by GM 1 treatment (see Fig. 5) could link together the evidence of a regrowth of the lesioned nigrostriatal pathway with that of an increased functional recovery in the GM 1-treated rats (Agnati *et al.* 1983; Zini *et al.* 1986). In fact, the lesion-induced DA supersensitivity at the striatal level was reduced by GM 1 treatment as well as the apomorphine-induced rotational behaviour. GM 1 treatment was also effective in reducing the lesion-induced decrease in food/water intake and the alteration in sensory-motor bias (Fig. 6).

Similar results have been obtained in other laboratories by using different lesion models (Cuello *et al.* 1985; Jonsson *et al.* 1984; Sabel *et al.* 1984). Thus, after a mechanical lesion, GM 1 is able to reconduct altered parameters of the lesioned side towards a normalization. Besides this type of actions, GM 1 is also able to reduce lesion-induced unbalances by a preferential action on the unlesioned side. The importance of balancing processes in the lesioned CNS must be underlined. In fact, to attain global functional recovery, together with morphofunctional recovery of the lesioned neuronal system, rearrangements in the metabolism and activity of the functionally related, unlesioned neuronal systems must also occur. One of the main functional rearrangements following an unilateral lesion is the recovery of the imbalance between the two sides. This can be obtained by means of both an enhancement of the activity on the lesioned side and a decrease of the activity in the intact side. A balancing effect of GM 1 was observed on lesion-induced alterations of local glucose utilization (evaluated by the 2-deoxy-glucose method), on regional blood flow (evaluated by the antipyrine method) and on Ca^{2+} and cAMP-induced protein phosphorylation (Fig. 7) (see Agnati *et al.* 1985 a).

C. Involvement of Polyamines in Trophic Mechanisms Operating in Mechanically Lesioned Rats

The model of mechanical lesion was further characterized, investigating the possible involvement of polyamines (putrescine, spermidine and sper-


A
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mine) in the regrowth of the lesioned nigrostriatal and strionigral pathways. Polyamines constitute a trophic system in the peripheral nervous system (Gilad and Gilad 1983) and in other organs [i.e., kidney, liver (Bachrach 1973; Cohen 1971)]. From a chemical standpoint putrescine, spermidine and spermine are ubiquitous organic cations which are present at different concentrations in different brain areas (see Seiler 1981). These compounds can be released in the extracellular liquid and also actively taken up by nerve cells; furthermore they can also diffuse from the CNS into the cerebrospinal fluid (Marton *et al.* 1976).

Although the physiological function of the polyamines is not yet assessed, it is clear that their concentration inside the eukaryotic cells is highly regulated and that polyamines play an essential role in cell growth and differentiation. In particular polyamines can control the synthesis of some messenger RNAs and thus the synthesis of special classes of proteins (Seiler and Lamberty 1975).

The biosynthesis and catabolism of these substances in mammalian CNS has been reviewed elsewhere (Cohen 1971; Shaw 1979).

We have evaluated ODC and diamine oxidase (DAO) activity as well as polyamine levels in our model of mechanical lesion, in order to assess whether this trophic system is activated in the lesioned CNS and whether this response is in some way related to the GM 1 action (Agnati *et al.* 1985 b, d, e; Zini *et al.* 1986).

After hemitransection, a huge increase in ODC activity was observed at nigral (up to 8 times the basal values) as well as at striatal (up to 80 times the basal values) levels. The effect was present 4 hours after the lesion and lasted 10 days. This increase was paralleled by an increase in putrescine content in the same regions (maximal 48 hours after the lesion), that lasted more than 21 days. A slight increase in spermidine (7–14 days) and no

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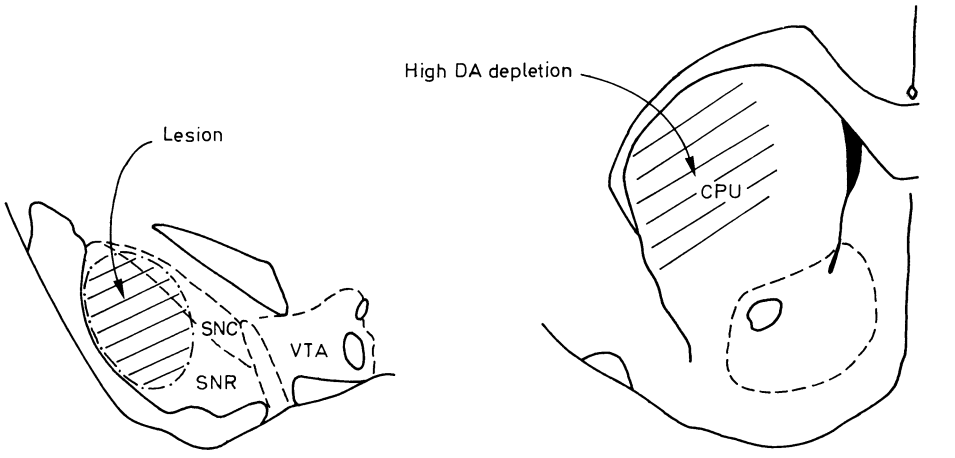
Fig. 3. Effects of GM 1 treatment (10 mg/kg/day, i.p., 21 days) on TH-positive structures at nigral level. PAP procedure; TH antibody dilution 1 : 1000. On the left panels the original images A) Saline treated animal, D) GM 1 treated animal are shown. Calibration bar = 250 μm; level A 1950 μm according to König and Klippel atlas (König and Klippel 1963); *SNC* substantia nigra pars compacta, *SNR* substantia nigra pars reticulata. On the central and right panels the fields A) and D) after discrimination procedure, performed on IBAS (Zeiss Kontron) image analyzer, are shown. This procedure allows the selective visualization of gray tones darker than a fixed discrimination level. The discrimination level chosen in B) and E) allowed the separation of the specifically stained profiles from the background. The discrimination level chosen in C) and F) allowed the visualization only of profiles containing the darkest gray tones (i.e., cell bodies and big dendrites) (for technical details see Agnati *et al.* 1984 a, b)



SUBSTANTIA NIGRA

	Saline	GM1 (10 mg/kg)
N° of TH-positive cell bodies	↓↓	↓
Density of TH-positive dendrites	↓	↑
Optical density of TH-IR	≃	↑
Substantia nigra hypoplasia	++	±

STRIATUM

	Saline	GM1 (10 mg/kg)
Density of TH-positive terminals	↓↓	≃
DA receptor sensitivity	↑	≃
DA receptor area	↓	≃

Fig. 4. Summary of the effects of GM 1 chronic treatment on the morphometrical and microdensitometrical features of the nigrostriatal DA pathway in partially hemitransected rats. The schematic drawing on the left shows the lesioned substantia nigra at a rostral level; the corresponding table reports the changes observed at nigral level in some morphometrical and microdensitometrical parameters in hemitransected saline-treated and hemitransected GM 1-treated rats. The schematic drawing on the right shows the lesioned striatum at an intermediate level; the corresponding table reports the changes observed at striatal level in some morphometrical and microdensitometrical parameters in hemitransected saline-treated and hemitransected GM 1-treated rats. The comparisons have always been performed with respect to the unlesioned saline-treated rats

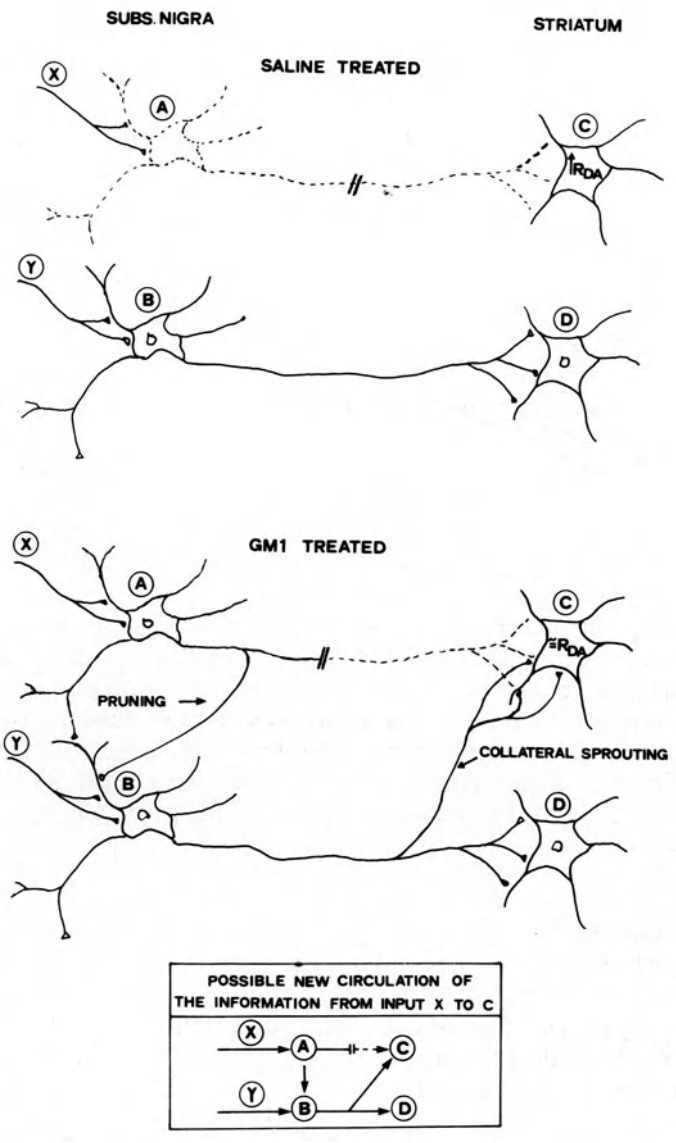


Fig. 5. Schematic representation of the possible actions of GM 1 chronic treatment on the mechanically lesioned nigrostriatal pathway, possibly leading to the reconstruction of an alternative path for the DA transmission. Structural plasticity responses (pruning and collateral sprouting) are reported. The normalization of the dopamine receptor population (*RDA*) is also shown. In the lower panel a scheme of the newly formed route, through which the input × can again reach the target C, is shown

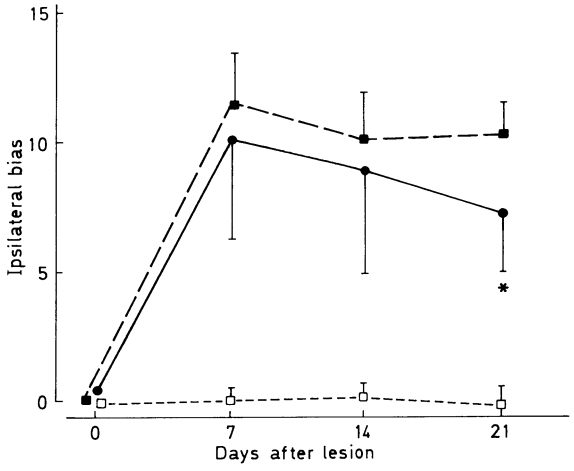


Fig. 6. Effects of GM 1 treatment (10 mg/kg/day, i.p.) on a sensorimotor test battery in partially hemitransected rats. The animals were tested for ipsilateral bias and coordinated limb use according to a sensorimotor test battery modified from that described by Björklund *et al.* (1980). The tests were carried out 7, 14 and 21 days after the lesion. The following tests were performed: general posture; spontaneous rotation; six site pin pricks; whisker touch; forelimb suspension; mouth probe; climbing grid. The response of each test was rated on a 3 point scale: 0 (absent), 1 (weak), 2 (strong). An index was derived from the sum of the test scores on the two sides of the body and the difference between the indices of the two sides calculated (ipsilateral bias). The statistical analysis was carried out by means of Dunn test (n = 10); GM 1-treated versus saline treated group; * = $p < 0.05$

significant change in spermine contents were observed. Also an increase in the activity of the polyamine catabolic enzyme DAO was present in both regions: the peak level was observed at 48 hours after the lesion (3 times the basal values) and 7 days after the lesion the basal value was again reached. The polyamine system was also investigated in a model of chemical lesion of the nigrostriatal pathway, using local administration of the DA neurotoxin 6 OHDA (Zini *et al.* 1986). In this model no spontaneous regrowth is observed. The analysis of ODC activity showed only a slight increase within the first day after the lesion, while no change of putrescine levels was observed at 7 days (Agnati *et al.* 1985 b, d).

The relevance of the involvement of polyamines in the regrowth of lesioned DA neurons was demonstrated by the administration of an irreversible ODC inhibitor, D,L-α-difluoromethyl-ornithine (α-DFMO). The administration of α-DFMO after hemitransection prevented the spontaneous local regrowth of the lesioned DA neurons, measured by the entity of the TH-positive area in the substantia nigra (Agnati *et al.* 1985 d).

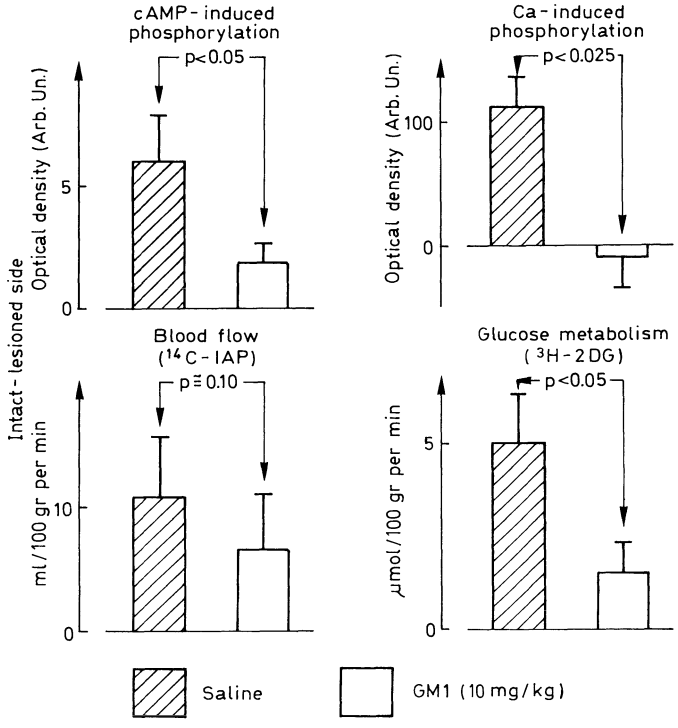


Fig. 7. Effects of GM 1 treatment (10 mg/kg/day, i.p., 14 days) on biochemical (cAMP-induced and calcium-induced protein phosphorylation) and metabolic (local cerebral blood flow and glucose utilization) indexes at striatal level after partial hemitransection. The values are expressed as difference between the mean value of the intact side and the mean value of the lesioned side, to give a measure of the unbalance between the two sides for the parameters considered. For details on the methods used see Agnati *et al.* 1985 a. The statistical analysis was carried out by means of Mann-Whitney U-test

Interaction was then investigated between the trophic actions of polyamines and GM 1 (Agnati *et al.* 1985 d, e; Zini *et al.* 1986).

GM 1 was found to have a modulatory action on the polyamine systems in vivo. The administration of GM 1 has a basal stimulatory action on ODC activity in various brain regions (see Fig. 8, Zini *et al.* 1986). This action is similar to the known stimulation of ODC activity by another trophic agent, NGF (Lewis *et al.* 1978). After hemitransection, a complex interaction between GM 1 and polyamines has been observed. In the first stage after the lesion, at nigral level GM 1 was able to anticipate the increase of DAO activity, while no clear-cut effect was observed for ODC activity. At 14 and 21 days from the lesion a balancing effect of GM 1 on polyamine levels became predominant (Fig. 9) (Agnati *et al.* 1985 d).

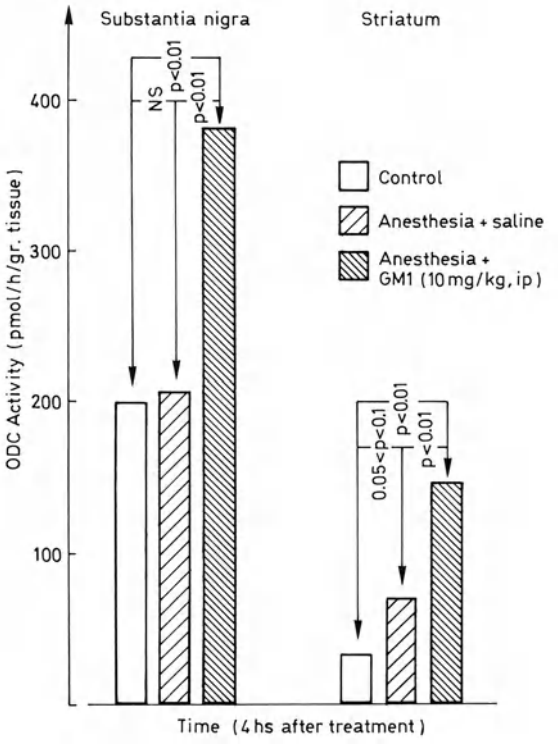


Fig. 8. Effects of GM 1 administration (10 mg/kg, i.p.) on ODC activity in the substantia nigra and striatum of intact rats. GM 1 or saline were administered 4 hours before the killing. The statistical analysis was carried out by means of Dunn test for multiple comparisons (n = 15)

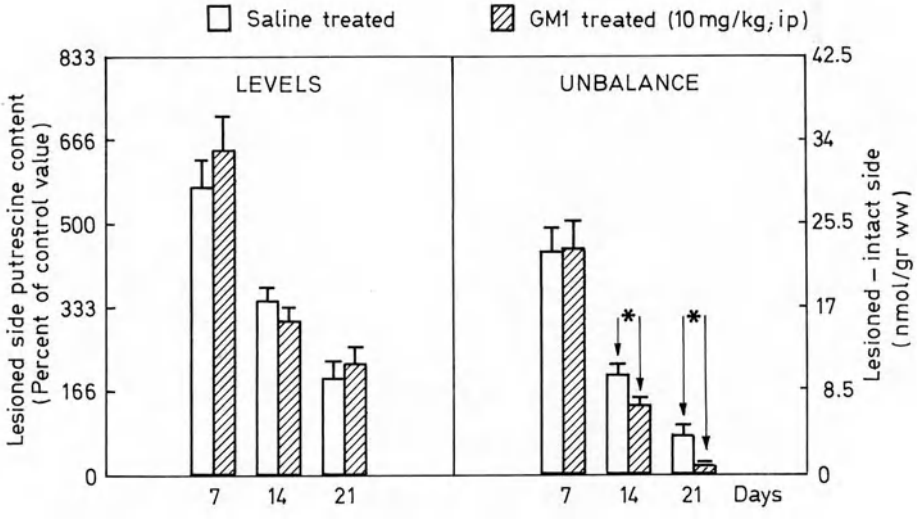


Fig. 9. Effects of GM 1 treatment (10 mg/kg/day, i.p.) on putrescine levels and unbalance at striatal level of partially hemitransected rats. Statistical analysis was carried out by means of Mann-Whitney U-test (n = 15); * = $p < 0.05$. control value: putrescine = 5.41 ± 0.40 nmoles/gr ww

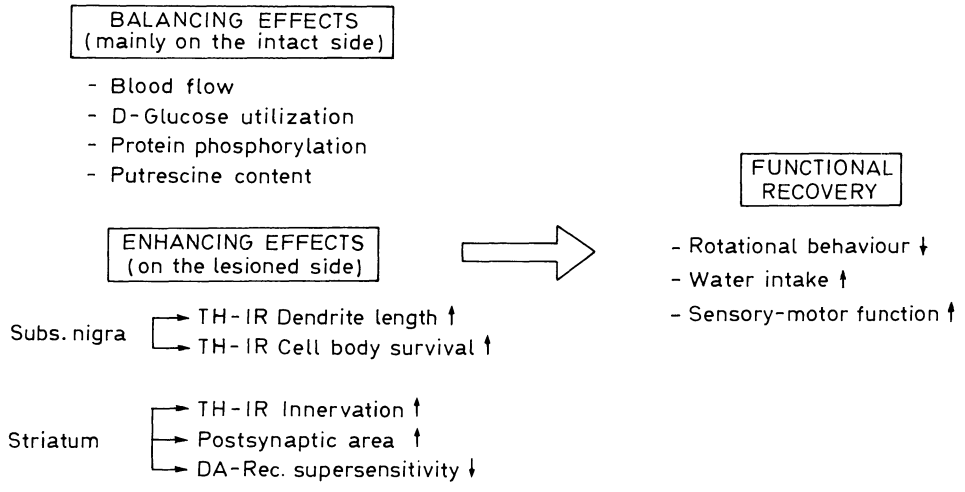


Fig. 10. Summary of GM 1 effects on morphofunctional recovery after partial hemitransection

In addition to a complex modulatory action of GM 1 on the polyamine system, a permissive role of putrescine on GM 1-induced regrowth was demonstrated. Administration of α-DFMO, in a dose effective in preventing the lesion-induced increase in putrescine, not only blocked spontaneous regrowth (see above) but also GM 1-induced enhancement of regrowth (Agnati *et al.* 1985 d).

This study of the GM 1-induced effects on degenerative and regenerative features of a transmitter-identified neuronal system (the DA ascending nigrostriatal pathway) may serve to highlight the multifacet action of trophic agents and their interplay. In fact (see Fig. 10), GM 1 has "balancing effects", which take place mainly on the intact side. These effects are probably important to help the CNS to escape from the diaschisis and to orient the metabolism of the neurons and glial cells towards the reparative responses.

However, GM 1 has also "enhancing effects", which take place on the lesioned side and are more strictly correlated with morphofunctional recovery. It should also be underlined that in order to favour the morphofunctional recovery of the lesioned DA pathway, GM 1 requires intact polyamine biosynthesis. Thus, trophic agents should be thought to work in a cooperative fashion. Hence, regeneration probably is not an "assolo" of a single instrument but very likely is an orchestrated piece, played by many instruments.

7. Conclusions

The trophism of the brain appears to be strictly intermingled with its special function, the handling of electrochemical information.

In principle, isolation of trophic agents supplied to the brain and favouring its recovery after a brain lesion is possible, but very difficult. In fact, by considering how CNS special function relies upon a topological and electrochemical organization of its elements that is largely fixed during the embryonic and neonatal period, the regrowth processes and the formation of new contacts are not "per se" useful phenomena. It would be important to know how to affect and to orientate these responses, possibly by using signals that mimic the epigenetic influences that were active during development.

However, the search of these trophic agents will have certainly a great impact to discover the etiopathogenetic mechanisms of degenerative disorders or of CNS malformations. Thus, some diseases such as Alzheimer dementia, Parkinsonism and Huntington's chorea will be better understood and treated (Goedert *et al.* 1986; Korshing 1986).

Furthermore, the relevance of the VT type of information handling by the CNS should be assessed to evaluate if it is possible to take better advantage of this type of transmission which avoids the need of an exact reconstruction of the wiring of the lesioned network. Since, as discussed in the text, some instances of functional recovery, which are not correlated with the proper morphological recovery (e.g., collateral sprouting, contact formation between transplants and denervated targets), could be explained on the basis of a potentiation of the VT type of information handling by the CNS in the lesioned area.

Finally, deeper knowledge of brain trophism and the possibility of employing suitable general trophic agents (for all neuronal cells) as well as selective trophic agents (for some specific neuronal systems, which are especially vulnerable to aging processes, such as the DA ascending nigrostriatal pathway) may lead to a life-long prolongation of the capabilities of this tissue.

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Editors' Comment

The paper by Professor Agnati and his associates is a valuable overview of some aspects of the complex problem of regeneration in the central nervous system. While it is undoubtedly true that isolated examples of apparent regeneration can be quoted within the central nervous system, and indeed upon these the whole transplant philosophy and the treatment of Parkinsonism depends, the clinical significance of such regenerative phenomena and indeed their very general applicability remains highly speculative. It is clear that the greater part of functional recovery following apparent loss as for example in stroke represents either the reawakening of tissue lying dormant as a result of having crossed the thresholds of function in ischaemia, but not the threshold of tissue viability, or represents re-organisation within the nervous system. The capacity for re-organisation particularly within the child's nervous system doubtless explains many of the astonishing functional persistences after, for example, hemispherectomy.

It is clear, however, that in the next few years increasing knowledge of the capacity of sience to induce regenerative connections within the nervous system will consitute an enormous potential advance in our treatment of disease and no neurosurgeon can afford to be without some basic understanding of the processes involved.

The Intraarterial Route of Drug Delivery in the Chemotherapy of Malignant Brain Tumours

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Contents

Abbreviations

ACNU	3-(4-amino-2-methyl-5-pyrimidinyl)methyl-1-(2-chloroethyl)-3-nitrosourea
AZQ	2,5-diaziridinyl-3,6-biscarboethoxyamino-1,4-bezoquinone
BBB	blood-brain-barrier
BCNU	1,3-bis-(2-chloroethyl)-1-nitrosourea
BTB	blood-tumour-barrier
CCNU	1-(2-chlorethyl)-3-cyclohexyl-1-nitrosourea
CDDP	Cis-diamminedichloroplatinum
DW	distilled water
5-FU	5-Fluorouracil
i.a.	intraarterial
i.c.	intracarotid
ICA	internal carotid artery
i.v.	intravenous
MCA	middle cerebral artery
Me-CCNU	1-(2-chloroethyl)-3-(trans-4-methylcyclohexyl)-1-nitrosourea
MST	median survival time
MTP	median time to tumour progression
MTX	methotrexate
MW	molecular weight
P	octanol/water partition coefficient
PCNU	1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea
QAR	quantitative autoradiography

Rd	ratio of drug delivery by arterial compared to venous infusion
Re	relationship between the ratio of the pharmacological effects by arterial compared to venous infusion
SSEP	somatosensory evoked potentials
TCD	transcranial doppler ultrasound
TIA	transient ischaemic attack
VCR	vincristine
VM-26	teniposide
VP-16	etoposide

I. Summary

This review is based on literature data and own experiences in 79 patients with malignant brain tumours using intraarterial delivery of cytostatic agents as adjuvant therapy. A survey is given of the pharmacological rationale of this therapeutic approach, of the drugs which have been used and of the related experimental and clinical experiences. Advantages and limitations are discussed and clinical conclusion drawn.

Experience so far suggests that in anaplastic astrocytomas and oligodendrogliomas intraarterial ACNU might be as effective as intravenous BCNU against the tumours but causes less systemic side-effects.

II. Introduction

Intraarterial chemotherapy of malignant brain tumours is a controversial method of adjuvant therapy. It is not yet an established treatment. Except for BCNU, which has proved not to be suitable for this route of delivery, up to now only uncontrolled series with other agents have been reported but no phase III trials. Preliminary experiences using ACNU however are encouraging. It is therefore one of the aims of this paper to stimulate further research in this field. To obtain sufficient clinical data within a reasonable time it is necessary that several departments join on a common protocol of a phase III trial of ACNU and eventually also of cisplatin.

Based on literature reports and our own experiences this survey intends

– to outline its pharmacological rationale,

– to review critically the drugs which have been used and the experimental and clinical experiences with this kind of treatment,

– and to give some advice as to the practical handling and the selection of patients.

III. The Pharmacokinetic Rationale of Intraarterial Drug Administration

1. Some Kinetic Properties of Cytostatic Agents Important for Intraarterial Therapy

Rational administration of cytostatic agents, as indeed of all agents, requires pharmacokinetic considerations.

Referring to the intraarterial (i.a.) application the papers of Eckman[8], and of Fenstermacher[9, 10] and coworkers are of special importance. Unfortunately, clinicians are often afraid of the complicated mathematical models used to show the kinetic behaviour of drugs. Using necessarily simplified assumptions the above research groups demonstrated that:

a) *The ratio of drug delivery (Rd) to the tumour cells by arterial compared to venous infusion,* is influenced by the blood flow through the infused artery: the smaller the fraction of the cardiac output received by the artery the bigger the advantage of arterial infusion in that artery. Thus an i.a. delivery of the cytostatic agent by superselective catheterization of the main tumour feeding artery would achieve the best Rd value.

b) *The recirculation integral* (i.e. the time integral due to systemic recirculation of the drug) is an equally important factor: the "first pass" advantage of increased drug delivery obtained by arterial administration will be less significant if the drug continues to recirculate in sufficient concentration for sufficient time.

c) The ratio of drug delivery by arterial compared to venous infusion (Rd) is theoretically uninfluenced by the following factors because they act after arterial as well as after venous infusion: rate of drug infusion, tissue blood flow, capillary permeability within the brain or tumour, partition coefficient of the drug and binding to plasma proteins. These factors however determine the *"trapping" of the drug within the tumour* during the first arterial pass of the cytostatic agent respectively within other parts of the body after i.v. infusion. The greater the amount of drug trapped within the tumour after i.a. delivery the smaller is the further systemic delivery and its side-effects. Conversely the more drug is trapped within other organ systems after i.v. administration before reaching the tumour, the smaller is the specific antitumour effectiveness, but the higher the unwanted systemic side-effects.

d) *The concentration-effect relationship* of the specific drug also influences the relationship between the ratio of the pharmacological effects by arterial compared to venous infusion (Re).

For example:

$Rd = Re$ if the concentration-effect curve of the drug is linear (i.e. linear increase in effect per unit increase in concentration);

$Rd \leqslant Re$ if the concentration-effect curve of the drug is concave (i.e. gradually decreasing effect per unit increase in concentration);

$Rd \geqslant Re$ if the concentration-effect curve of the drug is convex (i.e. gradually increasing effect per unit increase in concentration).

This last relationship would be the most favourable for i.a. drug delivery: Unfortunately, the concentration effect curves for most drugs which have been evaluated are either linear or concave[37].

2. Experimental Models

Based on these pharmacokinetic data, experimental models were developed in order to assess and to quantify possible advantages of i.a. administration of cytostatic agents.

Levin and coworkers[36] showed in squirrel monkeys that the delivery of 14C-BCNU via the internal carotid artery (ICA) achieved 190 to 280% higher brain nucleic acid bound drug levels in the infused hemisphere (averaging frontal, temporal and parietal regions) than using the intravenous (i.v.) route. The temporo-parietal region subserved by the MCA had bound drug levels four- to fivefold greater than those found following i.v. administration. The drug levels in the non-infused hemisphere of i.a. treated animals were similar to those found after i.v. application. Harper *et al.*[21] illustrated the i.a. delivery advantage following intracarotid (i.c.) administration of two different radiolabeled 2-deoxy-D-glucose isotopes in rats. The i.a. first pass delivery advantage equaled 19, decreased to 13 after 2 minutes and to 5 afterwards. Hiesiger *et al.*[23] measured entry of 14C-MTX in rats C6 glioma comparing intracarotid (i.c.) versus i.v. delivery. Both the mean concentration of 14C-MTX and the drug exposure (concentration × time; C × T) of the tumour over 90 minutes were determined. I.c. delivery of the 14 C-MTX increased the C × T over i.v. delivery for cortex, tumour and brain adjacent to tumour (BAT) by 70, 141 and 99% respectively. Bullard *et al.*[5] demonstrated that the i.v. administration of 13,3 mg/kg of BCNU in tumour bearing rats achieved an equal therapeutic response to only one-quarter of this dose i.a. given in a second group. Tyler *et al.*[64] compared in a group of ten patients with recurrent malignant gliomas the pharmacokinetics of i.v. versus superselective i.a. 11 C-BCNU delivery using positron emission tomography (PET). I.a. administration of 11 C-BCNU achieved concentrations of the drug in the tumour that averaged 50 times higher than with a comparable i.v. dose.

IV. Cytostatic Agents Suitable for Intraarterial Treatment

1. General Remarks

Many pharmacological properties of a cytostatic agent like molecular weight (MW), octanol/water partition coefficient (p), ionization, plasma protein binding etc., play an important role as well in i.a. as in i.v. drug delivery. At the same extent the more or less disrupted blood-tumour-barrier (BTB) finally influences the drug exposure of the tumour cells, irrespective of the route of drug administration. The following points however are of basic importance if i.a. drug delivery is taken into consideration:

a) Venous Recirculation and Half Life Time of the Cytostatic Agent

A high venous recirculation integral would reduce the first pass advantage (Rd) of arterial administration for obvious reasons. Systemic toxicity as well as intratumoural drug concentration would become comparable to i.v. administration. Therefore the half life (t 1/2) of the cytostatic agent ought to be short, i.e. a rapid transcapillary diffusion to the tumour cells, a quick chemical change and irreversible binding at the target site are necessary. The nitrosourea compounds BCNU (t 1/2 = 15 min and transcapillary diffusion time of < 1 min)[34, 35] and ACNU (t 1/2 = 26 min) fulfill quite adequately these criteria. Further, a high systemic drug loss would be of advantage.

b) Transcapillary Transport into Tumour and Brain

The transcapillary transport of a cytostatic agent into the tumour and the brain increases as the MW decreases and the lipoid solubility, defined by log p (1 – octanol/water partition coefficient), increases (Table 1).

In recent years, however, new data have given cause to reevaluate the clinical importance of these factors, especially of the lipoid solubility, and to take into account not only the positive but also possible negative aspects of increase in such characteristics. Experimental[7, 47] and clinical[18, 27] observations have shown that the remarkable lipoid solubility of the alkylating agent BCNU is at the same time responsible not only for the rapid transcapillary transport into the tumour, but also into the normal brain tissue, causing severe neurotoxicity. This fact clinically limits the i.a. usefulness of the drug[3, 15, 16, 19, 27, 30, 32, 56, 58].

c) Blood Tumour Barrier (BTB) and Blood Brain Barrier (BBB)

The BBB and even more the BTB play an important role especially in i.a. drug delivery. Recently Stewart *et al.*[60] performed quantitative studies of microvessel ultrastructure in human peritumoural brain tissue and found evidence for a BBB defect even in the brain tissue beyond the visible boundaries of the tumour. Blasberg and coworkers[1] measured in experimental tumours the breakdown of the BTB using quantitative autoradiography (QAR).

Nowadays the same investigations are clinically available[20]: It is possible to quantify the drug entry into the tumour. Consequently, in special cases with impaired BTB and sufficient entry of these drugs into the tumour, it may be of advantage to choose a more hydrophilic compound like ACNU or Cisplatin (CDDP) thus avoiding or minimizing neurotoxic side-effects because they cannot as easily pass the intact BBB as more lipoid soluble drugs like BCNU. This holds true for i.a. delivery because BCNU proved to be especially neurotoxic when infused arterially.

Table 1. *Cytostatic Agents Used in the Chemotherapy of Malignant Brain Tumour*

Compound	Molecular weight (MW)	log p
Nitrosoureas		
ACNU	309	+ 0.92
BCNU	214	+ 1.53
CCNU	234	+ 2.83
Me-CCNU	248	+ 3.30
PCNU	263	+ 0.37
Plant Alkaloids		
Vincristine (VCR)	923	+ 2.5
Epipodophyllotoxin (VM-26)	657	+ 2.8
Etoposide (VP 16)	588	?
Antimetabolites		
5-Fluorouracil (5 FU)	130	—0.95
Methotrexate (MTX)	454	—2.52
Others		
Cisplatin (CDDP)	300	?
Diaziquone (AZQ)	364	+ 0.50

The assumption that the i.a. chemotherapy of anaplastic gliomas may yield better results if the BTB is reversibly opened to cytostatic agents by hyperosmolar (i.e. Mannitol 20%) intracarotid infusions has led to some clinical trials[2, 42, 43]. Experimental research[23, 55, 66, 67], however, shows that after hyperosmolar infusions the main barrier opening concerns the BBB and only to a lesser degree the BTB. As a result the concentration of the cytostatic drug increases mainly in normal brain tissue and not much in the tumour, thus raising the neurotoxicity. The data of Hiesiger and co-workers[23] are especially impressive:

In rats inoculated with C 6 glioma the 14 C-MTX mean concentration was determined in the normal cortex, tumour and brain adjacent to tumour (BAT) after i.v., intracarotid (i.c.) without mannitol and i.c. delivery following i.a. hyperosmolar mannitol infusion. I.c. delivery of 14 C-MTX compared to i.v. administration increased the concentration of cortex, tumour and BAT by 70, 141 and 99%, respectively. After i.c. hyperosmolar mannitol infusion compared to arterial delivery without mannitol, the MTX concentration increased for cortex by 685%, tumour by 121% and BAT by 216%. In other words, the largest drug increase within the tumour with the smallest increase in brain tissue followed i.c. drug delivery without mannitol.

Up to now therefore there is no justification for the clinical use of intracarotid mannitol infusion prior to i.a. delivery of cytostatic agents. On the contrary, it raises toxicity without any therapeutic advantage.

2. Specific Compounds

Table 2 summarizes the characteristics of the cytostatic agents which already have been applied intraarterially. These are: BCNU, ACNU, CDDP, MTX, AZQ, VP 16.

Intraarterial application of MTX[42], AZQ[17] and VP 16[14] cannot be recommended because of the questionable responses reported in uncontrolled series. BCNU also, albeight its clinical i.a. application has been tried, proved to be not suitable for i.a. treatment. In a randomized phase III trial of the Brain Tumour Cooperative Group (BTCG) it has been shown that its i.a. application was more neurotoxic but not more effective compared to i.v. administration[56].

The clinical efficacy of the quite well tolerated i.a. administration of ACNU or of Cisplatin has to be compared to the combination of i.v. BCNU and radiotherapy, this combination being the benchmark for comparison of all other non-operative treatments.

V. Clinical Experiences

1. Review of Published Intraarterial Chemotherapy Series

Series of single agent and combined i.a. chemotherapy are presented in Table 4 and 5 respectively. Only publications since 1980 have been taken into account, since the WHO classification of brain tumours has only been published in 1979. Since then a better comparison of histological data has become possible.

The series came to partly contradictory results and does not show a real "breakthrough" in spite of the seemingly convincing pharmacokinetic rationale of intraarterial drug delivery. Possible explanations are the small numbers of patients, the sometimes uncontrolled conditions of the series, and the fact that many more factors which affect each other and may change over time, can influence the clinical outcome of chemotherapy. Not all were taken into consideration in the design of most of the studies. Only the factors of patient, tumour, drug and route of delivery were generally considered. Some of these main factors are surveyed in Table 3.

The clinical experience can be summarized as follows: With regard to the single agent i.a. chemotherapy, BCNU is the drug best investigated[3, 16, 18, 25, 26, 27, 54, 56]. The first clinical experiences with this drug soon showed its remarkable neurotoxic side effects, such as visual impairment and leukoencephalopathy. At that time optimistic reports on increased median

Table 2. *Characteristics of Intraarterially Applied Cytostatic Agents*

Compound	Activity	Toxicity		Schedule every ( ) wks
		Neurologic	Systemic	
BCNU	alkylation carbamylation	ophtalmologic leukoence-phalopathy	myelosuppression pulmonary fibrosis	80–240 mg/sqm (6)
ACNU	alkylation carbamylation	similar but milder than BCNU	myelosuppression	80–100 mg/sqm (6)
Cisplatin	inhibition of DNA synthesis	otologic ophtalmologic peripheral neuropathy	renal	60–75 mg/sqm (4)
Not recommended:				
MTX	antimetabolite	encephalopathy	myelosuppression digestive tract interstitial pneumonitis	55 mg/sqm (4)
AZQ	alkylation effect on mitochondria	not known	myelosuppression	5–15 mg/sqm (3)
VP 16	inhibition of tubulin poly-merization	not known	myelosuppression	100 mg/sqm (4)

survival time led investigators to underestimate the worsening of quality of survival caused by toxicity. In 1987 the phase III trial of the BTCG assessed definitely that i.a. BCNU was not more effective than i.v. administration, but only more neurotoxic.

The more hydrophilic nitrosourea compound ACNU seems to be less neurotoxic than BCNU[50, 69, 70]. Reports on uncontrolled series are also favourable with regard to quality and length of survival time, but a phase III trial proving a comparable or even better efficacy than i.v. BCNU is still lacking.

The effectiveness of i.a. Cisplatin has not yet been evaluated by a phase III study in spite of some promising initial reports[11, 22, 61, 62, 46]. It has severe neurological (deafness, peripheral neuropathy) and renal toxic side-effects, but these seemingly can be reduced by administration of no more than 60 mg/sqm. Nevertheless the management remains difficult and we would recommend this cytostatic agents as only one of "second choice".

In a recent series[11], the infraophthalmic delivery of cisplatin was associated with monocular visual loss ipsilateral to the infusion in 15% of the cases. Therefore, therapy with cisplatin requires the catheter placement with its tip above the origin of the ophthalmic artery.

Referring to the reports on combined i.a. chemotherapy[4, 6, 12, 13, 29, 32, 65, 68] it must be stated that this therapeutic approach has not achieved convincingly better results than single agent treatment. On the contrary, toxic side-effects seem to be more severe and evaluation more difficult. As holds true for the arterial delivery of all cytostatic agents except BCNU, combined intraarterial chemotherapy has not yet been evaluated by a controlled study.

2. Personal Experiences

Part of our own material has already been published in 1987[48]. We shall not deal with details related to i.a. delivery of BCNU but concentrate on the main results of i.a. ACNU treatment.

The material consists of 79 cases with malignant brain tumour treated by arterial chemotherapy. In 13 cases BCNU as well as ACNU i.a. was used initially; all others had only ACNU i.a. as the chemotherapeutic agent.

Our study is not a phase III trial and its design underwent some changes with increasing clinical experiences.

Criteria for inclusion into the study were

- histologically proved malignant supratentorial glioma according to the WHO classification;
- age > 16 years;
- Karnofsky score > 60;
- expected survival time without adjuvant chemotherapy > 8 weeks;
- no signs of systemic malignant diseases.

Table 3. *Some of the Main Factors Influencing the Clinical Outcome of Chemotherapy*

Patient	→ age ≷ 50 years → Karnofsky score ≷ 70	
Tumour	→ pathologic features	→ macroscopic: location—volume—vascularization microscopic: classification and grading
	→ capillary permeability	→ within the tumour (BTB) within the Brain Adjacent Tumour tissue (BAT)
	→ resistance to chemotherapy of cell subpopulations	→ primary resistance acquired resistance: effect of sublethal dosage and/or mutagenic effect of cytostatic drugs
	→ effects of previous treatments (surg., RT, steroids, chemoth.)	→ amount of cell kill changes of capillary vascularization or permeability
Drug	→ properties	→ MW (≷ 300)—hydro/lipophilicity (log p)—plasma protein binding —ionization pharmacokinetic (distribution—BBB—BTB—clearance)
	→ toxicity	→ neurologic: early and delayed systemic: early—delayed—cumulative
	→ effects on	→ cell cycle: specific—non specific
	→ use of	→ single drug combined therapy: simultaneous—sequential
	→ orally	→ very lipophilic drugs–high patient acceptance
	→ i.v.	→ bolus injection—sequential administration—bone marrow rescue
	→ i.a.	→ infraophthalmic—supraophthalmic—superselective infusion flow rate: high—low—intermittent—continous dialysis of jugular vein blood bone marrow rescue
Delivery	→ intracavitary → intrathecal → monoclonal antibodies	

Table 4. *Review of Single Agent Intraarterial Chemotherapy Trials Since 1980*

Author	Study design	Tumor type and percent	Number (eval.) (enter.)	Pretreatment conditions	Treatment groups dose schedule every ( ) weeks	Results MTP weeks	Results MST	Complications/comments
Greenberg[16] 1980	BCNU phase I	A III/IV	6	OP (4) OP + RT (2)	200–300 mg/sqm (6–8)	—	12–28	retinal toxicity 1 CR + 3 PR + 1 SD + 1 PD
Bremer[3] 1982	BCNU phase II	metast.	20	RT	300 mg/sqm (4–6)	—	—	periorbital erythralgia, disorientation, focal seiz. only Complications are reported
Kapp[27] 1982	BCNU phase 1	GBM	2	—	700 mg/sqm cumulative		18 LEP	ipsilateral blindness
Greenberg[18] 1984	BCNU phase II	A III/IV 30% A I–IV 70% (recurr.)	36	OP (12) OP + RT (24)	200 mg/sqm (6–8)	25 20	54 —	ipsilateral blindness
Safdari[54] 1985	BCNU phase II	MG	10	OP + RT	280 mg/sqm (8–10)	—	—	preliminary report
Hochberg[25] 1985	BCNU phase II		79	OP + RT RT	400 mg (4)	— —	54 49–64	20% LEP
Johnson[26] 1987	BCNU phase II	GBM 90% A II 10%	20	RT	150 mg/sqm (6)	—	—	preliminary report blindness 2, LEP 1
Shapiro[55] 1987	BCNU phase III	MG	128 i.v. v.s. 155 i.a.	OP + RT	200 mg/sqm (8)	interim analysis		survival i.a. vs i.v. worse $p = 0.05$ blindness 25, LEP 13
Yamashita[68] 1983	ACNU phase II	MG	16	OP + RT	80 mg/sqm (8)	—	—	not statistically significant different surv. rate i.a. vs i.v.

Yumitori[70] 1984	ACNU phase II	MG 40% metast. 20% mal. Lymph. 40%	13	OP + RT	100 mg. FD (6)	—	25	decreased systemic toxicity with phenobarbital therapy
Papavero[49] 1987	ACNU phase II	A III 27% GBM 73%	79 85	OP + RT (70) OP (5) biopsy (4)	150 mg. FD (6)	32	40	only mild toxicity results not better than i.v. BCNU
Stewart[60] 1982	CDDP phase I	GBM 45% melanoma 35% others 20%	11	RT	60–100 mg/sqm (2–8)	—	20	6 PR + 2 SD + 2 PD CNS toxity
Stewart[61] 1983	CDDP phase II	MG (Prim) 45% (Rec.) 20% metast. 25% others 10%	49	OP + RT	100 mg/sqm (4)	—	91 16 19	8 PR 3 CR, 8 PR bilat. deafness 2 following vertebral artery infusion
Feun[11] 1984	CDDP phase II	MG 67% metast. 33%	30 35	RT	60–120 mg/sqm (4)	12 13		6 PR, 5 SD CNS toxicity
Oldfield[45] 1987	CDDP phase II	MG	4	—	100 mg/sqm (4)	—	—	hemodialysis of regional venous blood
Hidalgo[22] 1987	CDDP phase II	metast. 100%	8	RT (simultaneous)	40–60 mg/sqm (1)	—	—	5 CR, 2 PR, 2 SD further studies recommended
Greenberg[17] 1984	AZQ Phase I–II	A II 20% A III 40% A IV 40%	14	OP + BCNU i.a.	10–15 mg/sqm (23 days)	—	16	AZQ i.a. of marginal effecti veness and no advantage over AZQ iv
Feun[14] 1987	VP 16 Phase I	GBM 60% Metast. 40%	15 28	RT	varying (4)	16		response rates are not better than results re-ported for VP 16 iv

A = astrocytoma; MG = malignant glioma; GBM = glioblastoma multiforme; OP = operation; RT = radiotherapy; FD = fixed dose; MTP = median time to progression; MST = median survival time; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; LEP = leukoencephalopathy

Table 5. *Review of Combined Intraarterial Chemotherapy Trials Since 1980*

Author	Study design	Tumor type and percent	Number evaluable / entered	Pretreatment conditions	Treatment groups dose schedule every ( ) weeks	Results MTP weeks	Results MST	Complications/comments
Kapp[29] 1984	BCNU i.a. CDDP i.a. Phase II	A III/IV GBM	12 14	OP + RT	CDDP 150 mg + BCNU 300 mg FD (6)	—	44	— supra-ophthalmic infusion
Vance[65] 1986	BCNU i.a. CDDP i.a. phase II	A III/IV GBM	9	OP + RT	CDDP 110 mg + BCNU 300 mg FD (6)	—	44	modest reduction in CDDP dose dramatically reduced response rate
Feun[13] 1986	BCNU i.a. CDDP i.a. phase II	MG 66% metast. 34%	23 36	RT	CDDP 60 mg/sqm + BCNU 100 mg/sqm (4–6)	14	34	supraophthalmic infusion; severe neurologic deficits
Calvo[6] 1985	CDDP i.a. BCNU i.v. Phase II	MG	21	OP 10 RT 6 chemoth. 1	CDDP 100 mg + BCNU 300 mg (4)	CR 32 PR 16 SD 12		

West[68] 1980	BCNU i.a. VCR i.v. PCZ p.o. phase II	MG GBM 60%	26	OP + RT 8 OP 18	BCNU 100 mg/sqm + VCR 1 mg/sqm + PCZ 100 mg/sqm (6)	—	30	high systemic toxicity rate
Lehane[33] 1984	CDDP i.a. CCNU p.o. phase II	A III 40% A IV 50% A II 10%	45	OP + RT	CDDP 100 mg/sqm (4) + CCNU 100 mg/sqm (6)	—	90	ipsilat. blindness (2) twofold increase of MST
Bremer[4] 1984	BCNU i.a. VCR i.v. PCZ p.o.	A III/IV 20% GBM 80%	21	OP + RT	BCNU 100 mg/sqm VCR 2 mg/sqm + PCZ 100 mg/sqm (6)	survival rate: 62% 1 year 24% 2 years		mild toxicity 4 pts were reoperated upon
Feun[12] 1986	CDDP i.a. Bleomycin phase I	A III/IV 30% GBM 40% metast. 30%	10 11	OP + RT	CDDP 60 mg/sqm + Bleomycin 25 U i.v. (2–4)	follow up 12 weeks only PR 4, SD 2 PD 4		CDDP plasma level in jugular vein were twice the peripheral plasma level

A = astrocytoma; MG = malignant glioma; GBM = glioblastoma multiforme; OP = operation; RT = radiotherapy; FD = fixed dose; MTP = median time to progression; MST = median survival time; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; LEP = leukoencephalopathy

Primary tumours were treated by

– maximum feasible tumour resection;

– intraarterial infusions of ACNU at the 3rd, 5th, and 7th postoperative day in the first 20 cases but later only on the 7th postoperative day

– radiotherapy with 5,000 rads to the whole brain, increased to 6,000 rads midline tumour dose through bilateral opposing fields over five weeks. Only more recently has radiotherapy been postponed until tumour recurrence was evident in spite of i.a. chemotherapy;

– intracarotid infusion of ACNU every six weeks for 5 to 9 times, depending on the clinical picture.

Recurrent tumours, after operation and/or radiation therapy alone, were treated by intracarotid infusion of ACNU after admission into the study and then every six weeks.

300–400 mg phenobarbitone was given orally from two days before to two days after i.a. ACNU infusion. At all other times 200 mg phenobarbitone was given as constant prophylactic antiepileptic medication.

ACNU was delivered each time in a dosage of 150 mg diluted in 30 ml DW over 5 minutes.

Steroids were given only in patients with marked peritumoural oedema – the daily dose ranged from 8 to 16 mg.

Follow-up ranged from 1 to 54 months, median follow-up being 10 months.

Complications will be reviewed on page 69.

The main results can be summarized as follows:

The median number of chemotherapy cycles was 4 (range 3–9). As might be expected anaplastic astrocytomas and oligodendrogliomas (WHO III, n = 19) responded better to the therapy than glioblastoma multiforme (WHO IV, n = 60). This fact was revealed both by the longer median time to tumour progression (MTP) of 60 vs 24 weeks, and by the median survival time (MST) of 72 vs 28 weeks. The MTP was assessed by CT scan as well as by the Karnofsky score.

The overall MST was 40 weeks and comparable to the results reported by administration of BCNU intravenously, but there were less systemic and neurotoxic side-effects then after i.v. BCNU.

Three survivors are still living more than 42 months after the beginning of therapy. On the whole, the chemotherapy seemed more suitable to prolong an acceptable quality of life, than to improve a poor one, in other words, patients with a good Karnofsky score maintained their high level whereas patients with low rating did not improve significantly.

VI. Techniques of Arterial Delivery of Cytostatic Agents

1. The Different Possibilities of Intraarterial Drug Delivery

a) Percutaneous Puncture of the ICA

This technique is quick and simple in experienced hands and can be repeated as often as necessary under local anaesthesia on outpatients. We avoid the need for radiological control of the correct placement of the needle tip by blue dye injection. Erroneous placement in the external or common carotid artery can be seen by transitory blue color of the homolateral face. In the few cases in which it is difficult to find the ICA, it may be helpful to use an ultrasound device[41].

Percutaneous puncture has a very low risk of embolic complications. The disadvantage of this technique consists in a smaller Rd compared to the superselective catheterization of the main tumour feeding artery, because of the inverse correlation between Rd and the fraction of the cardiac output flowing through the cannulated artery.

b) *Catheterization of the internal carotid artery* with infra- or supraophthalmic tip placement[28, 29] *or of the vertebral artery* – depending on the tumour location –

Severe ocular complications were observed after infraophthalmic delivery of BCNU[7, 15, 18, 19, 58] and of cisplatin[11]. The supraophthalmic administration of BCNU and the replacement of its ethanol diluent by 5% dextrose in water (D5W)[32, 52] did not reduce the incidence of brain toxicity. Therefore the i.a. delivery of BCNU has been abandoned since the beginning of 1987.

Catheterization of the carotid artery is more time consuming and expensive due to the need for television amplifier X-ray control. It is also more burdensome for the patient than percutaneous puncture and therefore less suitable for outpatients, but if attempted direct puncture for one or another reason fails catheterization is the best way to overcome this difficulty.

c) Superselective Catheterization of the Main Tumour Feeding Artery[64]

Unfortunately this is even more sophisticated and needs special knowledge and requirements. As demonstrated by Tyler *et al.*[64] however it provides the highest tumour drug concentrations. Until now the possible clinical advantages have not been substantiated by controlled clinical trials, probable due to the difficulty of this method of drug delivery.

d) Arterial Catheterization Combined with Haemodialysis of the Jugular Vein Blood[45, 46]

This difficult technique may reduce the systemic but not the neurotoxicity of arterial high-dose cytostatic therapy. It has not yet been evaluated as to a sound clinical balance of related problems and advantages.

e) Subcutaneous Implantation of a Pump for Continuous or Bolus–Dose Drug Delivery[51]

This variant has been developed for combined delivery of cell cycle specific and nonspecific drugs (e.g. 5FU and BCNU). Because of disappointing clinical results, it was quickly given up in the treatment of brain tumours.

Considering the short survival time of patients with malignant brain tumours and the enormous number of factors influencing the clinical outcome (Table 3), we recommend the percutaneous puncture of the carotid artery, because of its very low complication rate, satisfying acceptance and the possibility to use this treatment on outpatients.

f) Bolus Injection vs. Infusion; the Non-Uniform Drug Streaming Phenomenon

The experimental work of Lutz, Saris and coworkers[38, 53] showed that at low infusion rates (2–4 ml/min) irregular laminar flow occurs, causing non-uniform distribution of the drug to the infused region. This fact could explain the episodic occurrence of focal brain toxicity in vivo. To improve intravascular drug mixing, reduce laminar flow along the vessel wall and the probably related occurrence of focal cerebral toxicity, they suggest placement of the catheter tip in an infraophthalmic position and increase of infusion rate to at least 6–8 ml/min or even to 17–24 ml/min.

Experimental data show that drug mixing is better when the catheter tip is placed in the infraophthalmic part of the ICA and, independently from the position, by the use of a higher infusion rate. In many intracarotid treatment protocols in the literature however infusion rates of 2 ml/min have been used. We inject the drug at a rate of 6 ml/min. Saris *et al.*[53] have emphasized the importance of a phased, pulsatile infusion (diastole-phased pulsatile infusion pump) during the slow blood flow phase of local diastole in order to obtain the best mixing of injectate with blood.

Certainly, it is by no means necessary to have a low infusion rate, because the agents suitable for i.a. delivery rapidly cross the BTB.

2. Dosage of i.a. Chemotherapy of Malignant Brain Tumours

Only ACNU and, as second choice, Cisplatin seem to be suitable for intraarterial chemotherapy of brain tumours. Therefore dosage recommendations are given only for these two agents.

a) *Dosage of ACNU.* According to literature reports and our own experience we recommend infusion at each session of 150 mg ACNU, diluted in 30 ml DW at an infusion rate of 6 ml/min into the proximal ICA. There is insufficient data with regard to an optimal infusion rate, when the agent is delivered by supraselective catheterization.

b) *Dosage of Cisplatin.* We have no own experiences with this agent. According to the literature[9, 11, 22, 46, 61, 62] a dosage of not more than 60 mg/sqm is recommended and can be repeated every four weeks according to the clinical course.

VII. Complications

These can be related to artery puncture or catheterization or to systemic and neurotoxicity.

1. Puncture or Catheter Related Complications

In the literature a 1% major morbidity associated with carotid artery catheterization is reported[40]. The complications of the combined series of the Neurosurgical Departments of Düsseldorf and Homburg/Saar with a total of more than 300 intraarterial infusions of ACNU are summarized in Table 6. In the Düsseldorf Department catheterization was preferred whilst direct puncture of the ICA was used in the Homburg Department.

2. Complications Related to Neurotoxicity

As can be seen from Tables 4 and 5 marked neurotoxic side-effects occurred in all series with i.a. BCNU delivery. The same holds true for the reports on arterial treatment with a combination of several cytostatic agents[4, 6, 12, 13, 29, 32, 65, 68]. Both of these treatment forms therefore should not be used.

As regards arterial ACNU treatment neurotoxic side-effects have been seen in 4% in the combined material of the Homburg and Düsseldorf Departments, half of them = 2% being mild and half of them severe (Table 6).

To obtain more insight into the TIA producing mechanism we monitored 24 patients during i.a. drug infusions by EEG and transcranial doppler ultrasound (TCD) simultaneously and in 10 cases also recorded somatosensory evoked potentials (SSEP). Neither control infusions of 0.9% physiological saline solution nor uncomplicated ACNU infusions had any influence on the recordings. If a TIA occurred, which happened twice during the recordings, only the EEG was altered, but major vasospasm as cause of the TIA could be excluded by TCD. It is more likely therefore that TIAs during ACNU infusions are caused by irregular laminar flow and consequent non-uniform distribution of the infused agent to the infused area, as discussed on page 68.

Experimentally it has been demonstrated that BBB disruption, for instance caused by i.a. hyperosmolar mannitol infusion prior to the delivery of a cytostatic agent, results in a marked increase of neurotoxicity[23, 55, 66, 67]. Some few personal observations of severe neurotoxic deficits occurring during simultaneous radiation and intraarterial chemotherapy might indicate that radiation induced impairment of the BBB is similarly deleterious with regard to increased neurotoxicity. We will subsequently discuss the advisability to start with chemotherapy after operation of malignant brain tumours and to add radiation therapy only later when the effectiveness of cytostatic therapy comes to an end.

To our best knowledge no data are available as to a possible increase of neurotoxicity related to peritumoural oedema and its disturbances of the BBB.

Published reports on i.a. Cisplatin delivery do not allow a statistical evaluation of its neurotoxicity, but it seems to be within a tolerable range if a dosage of 60 mg/sqm is not exceeded[11, 22, 46, 61, 62].

3. Systemic Toxicity

An inherent advantage of i.a. chemotherapy is that „trapping" of the drug during the initial pass through the tumour reduces the amount of recirculating drug and can thereby reduce systemic toxicity. Nevertheless the systemic side-effects (e.g. haematologic toxicity of nitrosourea compounds or renal toxicity of Cisplatin) in clinical practice are mostly the dose limiting factors.

As shown in Table 6 systemic toxicity related side-effects have occurred in 7% of the combined Homburg and Düsseldorf material, being mild in 4% and severe in 3%.

In order to decrease the myelosuppression related to nitrosourea compounds the concommitant systemic administration of phenobarbitone has been suggested[67]. In our experience[48] it is mainly the acute haematologic toxicity which could be controlled in this manner, whereas the cumulative delayed bone marrow depression has been uninfluenced.

Other authors proposed autologous bone marrow rescue[24, 44, 57, 59] or dialysis of the jugular vein blood[45,46] to minimize the haematologic toxicity. In our opnion these invasive methods burden the patients more than justified by significantly better results. In consequence the neurologic toxicity becomes the dose limiting factor.

In clinical protocols evaluating Cisplatin, the use of hyperhydration and osmotic diuresis combined with filtering (0.22 μ filter) of the infusion immediately prior the the i.a. delivery is now an accepted procedure to reduce its toxic side effects.

Table 6. *Complications Related to 307 Intraarterial Infusions of ACNU 2mg/kg* (combined series of the Neurosurgical Department of Düsseldorf and Homburg)

	*D'drf (101)	**HOM (206)
Major complications		
Hemiplegia contralateral	1	1
homolateral		1
Blindness	1	
Visual impairment		
Severe leukopenia (< 2,000/cu mm)	3	2
thrombocytopenia (< 50,000/cu mm)	3	1
Minor side effects		
Transient contralateral hemiparesis	1	5
Seizures		1
Reversible leukopenia (< 3,000/cu mm)	1	5
thrombocytopenia (< 100,000/cu mm)	1	4
Hepatic disease	1	1
Severe nausea	2	4
vomiting	3	9

Other complications

— Brief unconsciousness following intravertebral artery delivery in one case
— Occlusion of ICA during catheterization without neurological symptoms in one case
— Transient hemiparesis during catheterization prior to the infusion of ACNU

* Düsseldorf: 92 ICA + 9 vertebral artery
** Homburg/Saar: ICA only

VIII. How to Individualize and Improve Arterial Chemotherapy of Malignant Brain Tumours

In order to get a more individual choice of cytostatic agent and to avoid ineffective medication two more pieces of information seem to be of possible importance:

1. Selection of Cases

a) According to Tumour Classification

How can be expected, anaplastic gliomas who III more than glioblastomas seem suitable to the chemotherapy. The incidence in younger patients and the relative homogeneity of the cell pattern may explain this fact.

b) Karnofsky Score

In patients with KS > 70, the chemotherapy prolongs the acceptable quality of life, whereas a low rating seldom has been improved.

c) The Transcapillary Transport of the Cytostatic Agent into the Tumour

After experimental data[31] have been obtained by quantitative autoradiography (QAR), it is now possible to quantify the blood to tissue transfer constant (k 1) and inversely the tissue to blood transfer constant (k 2) of a tumour by dynamic CT[20]. These data enable analysis of the extent to which the **BTB** is broken in a particular tumour, which influences directly the magnitude of the "first pass" advantage of i.a. drug delivery.

If the permeability of the tumour to the contrast medium (e.g. Conray) is the same as normal brain tissue, no real advantage could be expected by arterial drug infusion. On the contrary, the bigger the selective permeability of the tumour to the contrast medium compared to the normal brain (for ACNU the ratio should be > 40), the higher the concentration of a cytostatic agent expected within the tumour.

d) The Chemoresistance of Tumour Cells in vitro

The chemosensitivity of cytostatic drugs can vary between individual tumours as well as between different regions in the same tumour. This could explain the wide variation in response to chemotherapy among patients with identical tumour classification. The results of in vitro assays for determination of chemosensitivity of tumour cells up to now seem to correspond to the in vivo response only up to 55%; but if the in vitro assays show a resistance of tumour cell lines against a given agent than the in vitro result and in vivo response seem to agree in about 90%[63]. More experience is needed to assess if this way to select out patients, who are not likely to benefit and to save them from useless but burdensome medication, really gives reliable results.

2. Sequence of Conservative Therapeutic Methods: Radiotherapy or Cytostatic Therapy First?

In most series arterial chemotherapy has been given as a kind of last resort after operation or biopsy and radiation therapy. There may be advantages to change this sequence and treat cytostatically before radiation therapy.

The possible advantages are:

– better quality of survival time for the period until acquired chemoresistance occurs;

– possibility to differentiate between chemotherapy induced toxicity and radiation side-effects. On the other hand there may even be a risk of

increased neurotoxicity if radiation has been given before cytostatic therapy, related to a radiation-induced impairment of the BBB of otherwise healthy brain tissue which allows an easier transfer of even less lipoid soluble agents into the brain.

Radiation therapy with 60 Gy tumour target should be started at the time of even slight tumour progression. Recently we have changed our treatment policy as indicated above, but no conclusions are possible as yet. Only a controlled trial would allow an assessment of the validity of these considerations.

IX. Conclusions

There is experimental evidence, supported by uncontrolled clinical experience (phase I and II trials), that intraarterial delivery of cytostatic agents can be superior to i.v. chemotherapy if certain preconditions are fulfilled.

1. Advantages of i.a. Delivery

– Higher drug concentration in the tumour tissue which allows treatment by lower dosage;

– less neurotoxicity as a consequence of the possible dose reduction;

– less systemic side-effects as a consequence of the lower dose and of the first pass drug "trapping".

2. Preconditions

a) Which Should be Fulfilled

– Tumour located within and irrigated by one single vascular territory, or as an exception also by both ICAs, the ICA system being more easily accessible than the vertebro-basilar artery system;

– use of drugs with a favourable relation of cytostatic effect versus neurotoxicity when given interaarterially. Different from i.v. or oral delivery high lipoid solubility seems not necessarily an advantage for i.a. treatment.

b) Additional Favourable Preconditions Independent of the Route of Drug Delivery

– Small tumour volume;

– tumour sensitivity for the specific drug; exclusion of chemoresistance by in vitro assay;

– histological picture of anaplastic astrocytoma or oligodendroglioma, glioblastoma being less likely to respond positively to chemotherapy;

– sufficient capillary permeability within the tumour as measured by dynamic CT;

– age < 50 years;
– Karnofsky score > 70.

3. If the Mentioned Preconditions Are Fulfilled and Arterial Treatment Has Been Decided upon, we Suggest the Following Schedules

– 3-(4-amino-2-methyl-5-pyrimidinyl) methyl – 1-1(2-chloroethyl)-1-nitrosourea (ACNU, Nimustine), dose: 85 mg/sqm q 6 wk;

– or in cases with tumour resistence against ACNU cis-diamminedichloroplatinum (CDDP, Cisplatin), dose: 60 mg/sqm q 4 wk;

– ACNU should be preferably administrated on an outpatient basis by direct puncture of the ICA, if the tumour is within its field of circulation. If it lies in the vertebro-basilar system catheterization of a vertebral artery is necessary for drug delivery. Cisplatin should be administrated by catheterization of the ICA and supraophthalmic tip placement, in order to avoid its ocular toxicity.

Delivery of a cytostatic agent by superselective catheterization of the tumour feeding arteries is justified and promising if the tumour is vascularized by only one or two main feeding arteries.

The administration of phenobarbitone has in our experience lowered the acute myelosuppression due the nitrosourea compound ACNU, but did not reduce cumulative bone marrow toxicity.

Intracarotid infusions of hyperosmolar agents prior to i.a. delivery of cytostatic agents raises neurotoxicity without any therapeutic advantage and is therefore contraindicated.

Up to now controlled phase III trials comparing the effectiveness of i.v. and i.a. delivery of cytostatic agents have only been done with BCNU without evidence of any advantage of arterial administration; on the contrary, it has been proven more neurotoxic. Certainly BCNU is not suitable for i.a. cytostatic therapy.

ACNU and Cisplatin have not yet been tested in a controlled phase III trials, but it seems worthwhile to do so. This should be done in comparison to i.v. BCNU treatment which is at present the benchmark of cytostatic therapy. It is one of the aims of this paper to encourage such controlled trials which require the cooperation of several departments in order to get sufficient data within a reasonable time period.

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B. Technical Standards

Benign Extramedullary Tumors of the Foramen Magnum

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With 13 Figures

Contents

Introduction

Masses located at the craniovertebral junction comprise a variety of neoplastic and non-neoplastic processes, which have in common an insidious, often bizarre, clinical course resembling that of degenerative diseases of the nervous system, due to the frequent coexistence of signs of both posterior fossa and long tract involvement.

A substantial body of literature has dealt with tumors of the foramen magnum. Under this label, cases have been reported of either intra-axial or extra-axial tumors located at the level of the craniocervical junction and/or high cervical region, whether or not they extend into the posterior fossa (Cohen 1975).

In a 1980 paper (Guidetti and Spallone 1980) we stressed that the term "foramen magnum tumors" should be confined to tumors extending, symmetrically or asymmetrically, into both posterior fossa and spinal canal, as previously proposed by Arseni and Ionesco (1960). Following the guidelines of Cushing and Eisenhard (1938), we defined our cases as craniospinal or spinocranial according to the predominant location and site of origin, intracranial or high cervical. This chapter considers benign extra-axial tumors of the foramen magnum whose histology makes them potentially curable and thus of extreme interest to clinicians. On the other hand, the difficulty of the clinical, and sometimes of the radiological, diagnosis and treacherous location of these lesions, make them a formidable challenge for those involved in their clinical management.

Anatomy of the Region of the Foramen Magnum

The occipital bone surrounding the foramen magnum, the atlas and the axis with their complex osteo-ligamentous relationship together constitute the craniocervical junction, a detailed anatomical description of which is beyond the scope of the present study because we consider only intradural masses located at the foramen magnum.

Relevant neurovascular structures located intradurally at the level of the foramen magnum are the laterally situated first and second cervical roots, the anterolateral spinal accessory nerves and the vertebral arteries as they course intradurally from the lateral to the anterior surface of the medulla and give rise to the unpaired anterior spinal artery. The PICA originates from the vertebral artery, in most cases close to the foramen magnum, and the hypoglossal nerve arises from the anterior medulla, just above the level of the foramen and courses anterolaterally to emerge from the hypoglossal canal. All these structures may easily be affected by intradural foramen magnum masses which, in their upward extension, may even dislodge the IX–X complex, the basilar artery and, more rarely, other cerebellopontine angle nerves, and inferiorly may reach occasionally C_3 as

well as lower cervical roots. Involvement of the cord (at the cervico-medullary junction) is obviously a constant feature and that of the cerebellum not uncommon, according to the site of the mass.

Since the upper limit of the cord is arbitrarily fixed at the level of the origin of the first cervical root, the foramen magnum is occupied by the medulla. At this level, there is the decussation of the pyramidal tracts, which interrupts the anterior median sulcus, whilst posteriorly the fasciculi gracilis and cuneatus continue without distinction from medulla to cord, without any change in the appearance of the posterior surface.

We refer the reader to specific publications for the topographical anatomy of the cervico-medullary junction (Delmas 1975; Netter 1983).

Tumors of the Foramen Magnum. Frequency and Site

Intradural extramedullary tumors of the foramen magnum account for 2.5 to 10% of all intraspinal masses and for approximately 1% of all brain tumors (Table 1). Meningiomas and neurofibromas are the most common benign extramedullary tumors located in this region. Cases of teratoma and epidermoid have also been reported (Abrahamson and Grossman 1923; Aring 1974; Elsberg and Strauss 1929; Weinstein and Wechsler 1940; Yasuoka *et al.* 1978).

Reports of lipoma (Bucy and Gustafson 1938; Misch 1935), cavernous hemangioma (MacCarty *et al.* 1959), and meningeal melanocytoma (Limas and Tio 1972) are exceptional.

Table 2 summarizes oncotype and site together with the age and sex of the patients with foramen magnum tumors observed in our institution. Meningioma was the most common histological subtype. As in other large series (Yasuoka *et al.* 1978), the meningioma: neurinoma ratio was 2 : 1. Neurinomas originate most commonly from the C_2 root. Most of the lesions were located anterolaterally, although 6 out of 26 were located anteriorly to the cord and these represented a considerable surgical challenge.

Clinical Signs and Symptoms

Several authors (Cohen 1975) have drawn attention to the protean clinical presentation of tumors of the foramen magnum. A long, often remitting, clinical course is commonly observed in patients with these lesions. The time between onset of symptoms and diagnosis in our first 18 patients averaged three and a half years, ranging from three months to 13 years. The interval in the more recent 8 cases was similar. The interval between was also remarkable in these patients: 14 months on average (range: 20 days–5 years). However, the rather long time usually required for a correct diagnosis and appropriate treatment is explained by the fact that misdiagnosis is not uncommon and patients are treated for some other disease,

Table 1. *Incidence of Extraaxial Tumors of the Foramen Magnum*

Authors	N. of cases		
Elsberg and Strauss 1929	5	3 meningiomas 1 neurinoma 1 dermoid	3.7% of 185 spinal tumors
Salazkin 1953	9	5 meningiomas 4 neurinomas	0.75% of 3.984 CNS tumors
Arseni and Ionesco 1960	10	8 meningiomas 2 neurinomas	2.5% of 234 spinal tumors
Yasuoka *et al.* 1978 (Mayo Clinic series, years 1957–1976)	57	37 meningiomas 19 neurinomas 1 teratoma	3.2% of 1 139 neuraxis meningiomas
Present series	26	17 meningiomas 9 neurinomas	1.3% of 1 305 brain meningiomas 11.1% of 154 spinal meningiomas

Table 2. *Localization and Oncotypes*

Case	Sex	Age	Localization	Histology
1	f	35	L. antero-lateral spinocranial	meningioma
2	f	57	anterior craniospinal	meningioma
3	f	26	R. antero-lateral hourglass	C_1 neurinoma
4	f	51	R. anterior hourglass	C_2 neurinoma
5	m	60	L. antero-lateral craniospinal	meningioma
6	m	30	R. postero-lateral hourglass	C_2 neurinoma
7	m	26	R. antero-lateral craniospinal	meningioma
8	f	53	R. antero-lateral spinocranial	meningioma
9	m	40	R. antero-lateral	C_1 neurinoma
10	f	44	L. antero-lateral craniospinal	meningioma
11	m	20	R. antero-lateral craniospinal	meningioma
12	f	40	L. postero-lateral craniospinal	meningioma
13	f	31	L. anterior	C_2 neurinoma
14	f	43	anterior craniospinal	meningioma
15	f	65	anterior spinocranial	meningioma
16	f	13	L. anterior	C_2 neurinoma
17	f	43	L. postero-lateral spinocranial	meningioma
18	m	25	L. anterior hourglass	C_2 neurinoma
19	f	51	anterior craniospinal	meningioma
20	f	54	L. antero-lateral hourglass	C_2 neurinoma
21	f	50	L. antero-lateral	C_1 neurinoma
22	f	39	R. antero-lateral spinocranial	meningioma
23	m	20	R. antero-lateral spinocranial	meningioma
24	m	50	L. antero-lateral spinocranial	meningioma
25	m	72	L. antero-lateral craniospinal	meningioma
26	f	48	R. postero-lateral craniospinal	meningioma

Table 3. *Erroneous Diagnoses Made in Our Patients*

Diagnosis	N. of cases	%
Multiple sclerosis	6	23.1
Spondylotic myelopathy	6	23.1
Syringomyelia	1	3.9
Intraaxial tumor	2	7.7
Vascular disease	2	7.7

In two patients diagnosis of multiple sclerosis preceded another erroneous diagnosis.

sometimes with spectacular symptomatic relief, before a foramen magnum mass is suspected. Table 3 summarizes the diseases for which 14 of our patients were long treated. It is noteworthy that three of them underwent surgery elsewhere for the presumed lesion, intra-axial tumor in two cases, cervical spondylosis in the third, with significant-temporary relief of symptoms, before the correct diagnosis could be established. Five more cases, for a total of 8 out 26 (30%), had significant remissions, whether or not related to medical and/or physical treatment is not known, which obviously contributed to the long delay between onset of symptoms and tumor surgery. Yasuoka *et al.* (1978) dealt exhaustively with the problem of differential diagnosis from diseases that a tumor of the foramen magnum may simulate. They include cervical spondylosis, multiple sclerosis, syringomyelia, intramedullary tumor, Arnold-Chiari malformation, carpal tunnel syndrome, normal pressure hydrocephalus, amyotrophic lateral sclerosis and basilar impression. A more recent report from another Mayo Clinic group (Meyer *et al.* 1984) claimed that in three out of their 102 cases of benign tumors of the foramen magnum lumbar spine disease was suspected since the patients presented with dysesthesia of one lower limb. "Vascular disease" was the misdiagnosis attached to two of our patients before they were seen here.

Attempts to define a typical clinical syndrome of tumors of the foramen magnum have generally been unrewarding. Blom and Ekbom (1962) described "early clinical signs" of these lesions, pseudoastereognosis (Arseni and Ionesco 1960) or "piano-playing fingers" phenomenon being the most peculiar. However this symptom, also called tabetic pseudoathetosis (Blom and Ekbom 1962) or stereoanesthesia (Rubinstein 1938; Weinstein and Wechsler 1940), consisting of clumsiness of the hands with loss of position sense and of ability to recognize the size and the shape of objects in spite of normal primary sensation, was reported by no more than one third of our patients as in others' (Yasuoka *et al.* 1978). Suboccipital and/or neck pain is a common early symptom of these lesions. It was the first symptom in three quarters of our patients (Table 4).

It is usually worse on the tumor side, insidious in onset, often mild and easily relieved by common analgesics. It may be exacerbated by movements of the neck and so may easily be attributed to cervical spondylosis. In the early stage of the disease anything which increases intraspinal pressure such as sneezing, coughing etc, may exacerbate this pain but not as a rule in the later stage of tumor development. Sensory disturbances in the form of paresthesias, and cold or burning dysesthesias are another early symptom of these lesions. Yasuoka *et al.* (1978) describe two stages of clinical progression of tumors of the foramen magnum. In the first stage suboccipital and/or neck pain dysesthesias, usually of the upper limbs, are the only complaints, which are commonly attributed to cervical spondylosis. At this

Table 4. *Early Clinical Symptoms in Our Cases*

Symptoms	First symptom		Second symptom	
	N. of cases	%	N. of cases	%
Suboccipital and/or neck pain	20	76.9	2	7.7
Cold dysesthesias	3	11.5	3	11.5
Headache, vomiting, diplopia	2	7.7	3	11.5
Paresthesias (tingling, numbness, etc)	0	–	8	30.8
Weakness of upper limbs	1	3.9	8	30.8
Weakness of lower limbs	0	–	4	15.4
Burning dysesthesias	0	–	1	3.9
Sphincter disturbances	0	–	1	3.9

stage the neurological examination is usually non-contributory. Later, weakness of the extremities, sensory disturbances, not uncommonly with "cape distribution", and urinary problems occur, symptoms that may suggest an intramedullary lesion as the underlying problem. However, although this staging is broadly acceptable, it may not apply to all cases. Weakness of an upper limb was an early symptom (either the first or the second) in one third of our patients and weakness of a lower limb in 15%. Bogorodinskij (1936) and Cohen and McRae (1962) considered that progressive weakness, which had been previously described by other authors (Elsberg 1925; Elsberg and Strauss 1929), was typical of foramen magnum tumors. Initially it involves one upper limb, then the ipsilateral lower limb, followed by the contralateral lower limb and finally by the contralateral upper limb. This pattern of progression of motor weakness was reported by approximately half of our patients (Table 5), but was not observed by Yasuoka *et al.* (1978) in their large series. These authors noted paraparesis of the upper extremities with lower limb monoparesis, but did not record cases of paraparesis of the lower extremities with upper limb monoparesis. Bogorodinskij (1936) described other forms of progression, such as paraparetic and mixed types of motor weakness. As stated above, paresthesias in the form of tingling and/or numbness are a frequent complaint of patients with foramen magnum tumors. They usually involve one or both upper limbs, and as a rule are considered to be due to cervical spondylosis. Occasionally

Table 5. *Clinical Symptomatology at the Admission*

Symptoms	N. of cases	%
Suboccipital and/or neck pain	26	100
Headache, vomiting, diplopia	6	23.1
Motor weakness	22	84.7
"typical" progression *	14	53.9
atypical progression	8	30.8
Sensory disturbances	20	76.9
paresthesias	12	46.1
cold dysesthesias	8	30.8
burning dysesthesias	5	19.2
hypesthesias	6	23.1
Sphincter disturbances	10	38.5
Respiratory troubles	6	23.1
Hoarseness	5	19.2
Dysphagia	4	15.4
Hormonal disturbances	1	3.9

* Weakness of one upper limb, followed by the ipsilateral lower limb, then by the controlateral lower limb, finally by the controlateral upper limb.

they may affect the lower extremities, thus simulating a lumbar spinal disease (Meyer *et al.* 1984).

Cold dysesthesias were described long ago in cases of tumors of the foramen magnum (Elsberg and Strauss 1929) and have been considered typical of these lesions (Beatty 1970). However their frequency ranges from less than 10% (Meyer *et al.* 1984) to approximately 30%, as in our series. Furthermore it must be remembered that intramedullary lesions may also give rise to abnormal cold sensations in the extremities. Burning dysesthesias have also been described. They were reported by 5 of our patients (19%) and typically preceded the onset of hypesthesia.

Bladder disturbances and respiratory trouble are encountered in the later stages of the clinical history of patients with tumors of the foramen magnum. Their frequency approximates 30% in our experience, but Meyer *et al.* reported recently (1984) that respiratory dysfunctions were present in only 6% of patients in the large Mayo Clinic series. Dysphagia and/or dysphonia are other not infrequent late symptoms of these lesions, their frequency averaging 10% in our and in other series (Meyer *et al.* 1984). Occasional instances of hallucinations (Guidetti and Spallone 1980; Nittner

1975), hormonal disturbances (Guidetti and Spallone 1980; Smolik and Sachs 1954), chronic hemifacial pain (Koempf and Botzler 1980) have also been described. Patients presenting with symptoms and signs of slowly progressing intracranial hypertension with few or no other relevant symptoms have also been described (Yasuoka *et al.* 1978). Symptoms indicating increased intracranial pressure, such as headache, vomiting and/or diplopia, were a major complaint in approximately a quarter of our patients.

The complex anatomy of the foramen magnum region may well explain the extreme variability of the clinical symptoms of these lesions. The subarachnoid space is relatively wide at this level, and may accommodate tumors up to a certain size with little or no harm to the neighbouring neurovascular structures. The latter may be involved later in different ways, depending on the actual location and growth pattern of the tumor. For example, tumors located anterolaterally are more likely to present clinically with the above "typical" progression of motor weakness, but are less likely to involve the posterior columns in such a way as to cause pseudoastereognosis. The latter is more likely to be related to anterior or posterior masses, which may exert pressure on the posterior columns either directly or by pushing them against the bone (Blom and Ekbom 1962). The involvement of the cranial nerves and of the upper cervical roots and its consequent clinical presentation obviously depends on the actual location of the mass.

In summary, the clinical manifestations of a tumor of the foramen magnum vary considerably. The occurrence of neck and/or suboccipital pain before symptoms and signs of long tract and cranial nerve involvement should lead to the suspicion of a mass located at the level of the cervicomedullary junction. Weakness starting and/or predominating in one upper limb may be another diagnostic clue, as well as astereognosis in the absence of other signs of parietal lobe involvement, such as sensory inattention and agraphesthesia. However the clinical diagnosis is virtually impossible at an early stage, and may remain very difficult even at an advanced stage.

Neurological Examination

The neurological findings in our patients at the time of admission are briefly summarized in Table 6. Table 7 shows for comparison the percentages of the main neurological signs reported by the recently published large Mayo Clinic' series (Meyer *et al.* 1984). The neurological findings on admission are roughly similar in these two series of patients. Differences, such as those in the percentages of motor weakness, might perhaps be explained by the fact that a fair number of the Mayo Clinic patients (20%) had a normal neurological examination on admission, while none of our patients was neurologically normal.

Table 6. *Neurological Findings in our Patients*

Signs	N. of cases		% of cases
Stiffness of the neck	22		84.7
Lhermitte's sign	2		7.7
Motor weakness	24		93.3
ipsilat. hemiparesis	9		34.7
tetraparesis	10		38.5
triparesis	3		11.5
paraparesis	2		7.7
Increased tendon reflexes	25		96.1
Atrophy of the hands	9		34.7
Atrophy of the arms	2		7.7
Sensory loss	23		88.4
Hypesthesia (pain, temp., and/or touch)	20	controlat. 15 bizarre location 5	76.9
C_2 hypesthesia	8		30.8
Loss of joint sensation	14	ipsilat. 8 over the entire body 5 bizarre location 1	53.9
Pseudoastereognosia and/or tabetic pseudoathetosis	8		30.8
Nystagmus	11		42.3
Dysmetria, ataxia, etc.	6		23.1
Cranial nerve palsy	15	9 XI 5 IX–X 4 V 2 VII–VIII 2 XII	57.6
Papilledema	2		7.7
Bernard-Horner syndrome	2		7.7

Involvement of the pyramidal tracts in the form of increased deep tendon reflexes and/or motor weakness was the most frequent neurological sign in patients with tumors of the foramen magnum on admission to the hospital. It was observed almost invariably in our cases. Hemiparesis ipsilateral to the lesion was a very frequent finding and was usually associated with sensory deficits of the Brown-Séquard type. The Babinsky sign is also present in the majority of patients with these lesions.

Table 7. *Incidence of Neurological Findings at Admission. Comparison Between Mayo Clinic' Series and Ours*

Sign	Mayo Clinic %	Present series %
Increased tender reflexes	70.6	96.1
Weakness	67.6	93.3
Sensory loss		
pain and temperature	37.3	46.1
joint sensation	26.5	53.9
touch	21.6	30.8
dissociated loss	24.6	26.9
cape distribution	6.8	7.7
C_2 hypesthesia	17.6	30.8
Brown-Séquard syndrom	29.4	30.8
Atrophy		
hands	12.8	30.8
arms	6.8	7.7
Ataxia incoordination	37.3	23.1
Nystagmus	24.5	42.3
Cranial nerve palsy		
V	5.9	15.4
VII–VIII	2	7.7
IX–X	13.6	19.2
XI	27.8	34.7
XII	7.8	7.7
Papilledema	6.8	7.7
Bernard-Horner syndrom	3.9	7.7

Sensory loss, that is hypesthesia for pain, temperature and/or touch is a very frequent finding, often "dissociated" (25% in our experience). A "cape distribution" suspended sensory loss may also be present, although in a minority of cases (around 7% in ours as well as in Mayo Clinic's experience). This, combined with dissociated sensory loss may easily suggest an intramedullary lesion. Loss of joint sensation may also occur in most cases. When located ipsilaterally to the tumor, as in 30% of our patients, it may contribute to a Brown-Séquard pattern. Hypesthesia in the C_2 territory is a very important sign, which may prompt a clinical suspicion of a tumor of the foramen magnum. However, it was observed in no more than one third of the cases in some large series (Guidetti and Spallone

1980; Meyer *et al.* 1984). In fact, foramen magnum tumors may not extend far enough into the spinal canal to encroach on the C_2 root in such a way as to cause hypesthesia. Krayenbühl (1973) has stated that the C_1 root also contains sensory fibers projecting into C_2 territory, a fact which may explain the occurrence of occipital pain in the absence of objective signs of C_2 root involvement.

A rather peculiar clinical sign indicating disturbances of deep sensation in the hands, frequently detected in patients with these tumors, is the pseudoastereognosis (Arseni and Ionesco 1960), otherwhere called tabetic pseudoathetosis (Blom and Ekbom 1962), stereoanesthesia (Rubinstein 1938; Weinstein and Wechsler 1940), "piano-playing fingers" phenomenon (Blom and Ekbom 1962) mentioned earlier. All these terms denote an inability to recognize objects placed in the hands without looking at them, and loss of position sense of the hands, which causes athetoid-like movements of the fingers if the patient is asked to hold up his arms with the eyes closed. In an attempt to account for this phenomenon, Blom and Ekbom (1962) suggested that chronic lesions of the dorsal columns might affect the cerebellar components of deep sensation of the arms while sparing those of the legs, which supposedly (Ferraro and Barrera 1934) pass through the lateral columns. If so, either anterior or posterior masses would be more likely to cause pseudoastereognosis. This sign was observed in approximately one third of the patients in our series and in others' (Meyer *et al.* 1984; Yasuoka *et al.* 1978). Obviously, it cannot be demonstrated unless the strength of the upper extremities is relatively intact (Blom and Ekbom 1962).

Atrophy of the intrinsic muscles of the hands is a relatively frequent finding – from 17% to 52% in several series (Stein *et al.* 1963; Yasuoka *et al.* 1978), 30% in our experience – whose pathogenesis has still to be clarified. Most authors (Cohen and McRae 1962; Krayenbühl 1973; Liveson *et al.* 1973; Symonds and Meadows 1937; Yasuoka *et al.* 1978) agree that a mechanism of vascular compromise in the territory of the anterior spinal artery appears to be most likely. However, Stein *et al.* (1963) found no evidence of anterior horn cell damage in the lower cervical segments in a case of spinocranial meningioma with atrophy of the hands who came to autopsy without having undergone surgery. These authors stressed, however, that cellular changes might be too subtle to be detected by conventional microscopic examination.

The blood supply to the lower spinal segments is provided by the anterior spinal artery which anastomoses with the radiculo-medullary artery of the sixth cervical root (Lazorthes 1961). Therefore a possible role of the radicular medullary arteries in the pathogenesis of the supposed vascular damage underlying these lesions might also be considered.

A mechanism of venous engorgement and resulting cord edema has

also been conjectured (Brain *et al.* 1952), but considered unlikely (Cohen and McRae 1962; Krayenbühl 1973), in view of the numerous anastomoses and weath of collaterals that the cervical veins possess. However, Taylor and Byrnes (1974) have recently observed venous stasis with capillary hemorrhages in the lower cervical cord of monkeys in which masses have been induced experimentally at the foramen magnum level.

A stretching mechanism related to anchoring of the compromised spinal cord to dentate ligaments was considered some time ago (Cohen and McRae 1962) and later suggested again by Bartal *et al.* (1972), in order to explain the phenomenon of atrophy of upper and lower extremities, that is occasionally observed in patients with foramen magnum tumors. However this hypothesis has not received wide attention.

Yasuoka *et al.* (1978) have recently suggested that enlargement of the central canal, possibly related to disturbances of the CSF flow due to the presence of a mass at the craniocervical junction, might explain most of the puzzling clinical signs observed in patients with these lesions, such as suspended sensory loss and intrinsic muscle atrophy. A case of syringomyelia associated with a foramen magnum meningioma has been described more recently (Hirata *et al.* 1985). Following removal of the lesion, this patient showed prompt recovery from his preoperative symptoms, namely upper arm atrophy and suspended sensory loss, a fact which would suggest "an interference with circulation rather than syringomyelia" as the likely pathogenetic mechanism. In this case, only delayed CT following intrathecal injection of contrast allowed demonstration of the syringomyelic cavity. In this respect, NMR might offer more consistently evidence of any central canal enlargement. In the only case of our series in which NMR was performed no syringomyelic cavity was detected although no atrophy of the hands was present.

Perhaps this problem might be solved by careful arteriographic studies of cases of foramen magnum tumors focused on the flow pattern of the anterior spinal artery and lower cervical radicular arteries, by means of digital subtraction angiography, combined with NMR and/or CT evaluation of possible enlargement of the central canal of the spinal cord. EMG results, although controversial (Yasuoka *et al.* 1978), might be also valuable for this purpose. Nystagmus, usually of the horizontal type, is another frequent finding (25–40% of the patients), whilst ataxia and/or incoordination is detected in a far from negligible number of patients: 20–38% in several large series (Guidetti and Spallone 1980; Meyer *et al.* 1984). Deficits of the lower cranial nerves are infrequent except for cranial nerve IX involvement, which occurred in approximately 30% of our and in the Mayo Clinic' patients, and trigeminal sensory loss. Actually, due to their anatomical location, these structures are likely to be dislodged by masses passing through the foramen magnum. Single cases have been described

of paresis of the motor branch of cranial nerve V (Shishikina and Kuvshinova 1961), and of onion-like trigeminal hypesthesia mimicking a demyelinating disease in a foramen magnum meningioma (Craig *et al.* 1956). Infrequent findings are the lhermitte sign, which may lead to an erroneous suspicion of multiple sclerosis, and features of the Bernard-Horner syndrome. The latter, usually incomplete, are slight ptosis and pupillary inequality (Stein *et al.* 1963). Papilledema was observed in less than 10% in ours as well as in the Mayo Clinic' patients. Arseni and Maretsis (1974) have tentatively explained the occurrence of papilledema in spinal neoplasm as a possible result of disturbances of the CSF circulation related to the increase in the total protein content of the spinal fluid. However, Meyer *et al.* (1984) have stated that the intracranial extension of tumors of the foramen magnum was a major factor in the pathogenesis of papilledema in their patients.

In conclusion, neurological signs in patients with these lesions are protean and often misleading. Clinical signs of long tracts involvement may closely resemble other surgical and nonsurgical diseases of the spinal cord. The presence of diagnostic neurological signs such as hypesthesia in the C_2 territory, deficit of cranial nerve IX, pseudoastereognosis is not at all constant. Other signs such as atrophy of the intrinsic muscles of the hands and cape sensory loss may be misleading. So, diagnosis of tumor of the foramen magnum can be placed only occasionally on the clinical evidence.

Ancillary Investigations

Neurophysiological Investigations

Electroencephalography was performed in a few patients with foramen magnum tumors, and was usually noncontributory. Electromyography was performed in three of our patients, all of whom had atrophic changes in the intrinsic muscles of the hands. In two patients the EMG showed signs of denervation of these muscles, such as fibrillary action potentials in the C_7–T_1 radicular distribution. In the remaining case there were signs of upper motor neuron involvement.

Conflicting EMG results have been reported by Yasuoka *et al.* (1978) in their large series of patients with tumors of the foramen magnum. Previously there had been only a few reports on EMG findings in patients with atrophy of the hands and foramen magnum tumors (Cohen and McRae 1962; Liveson *et al.* 1973). EMG in these cases showed, as a rule, signs of anterior horn cell involvement at low cervical level. However, Yasuoka *et al.* (1978) concluded that there is not sufficient EMG evidence in the literature or in their own experience to substantiate the hypothesis

that anterior horn cell involvement, possibly by a mechanism of vascular insufficiency, is the only explanation for the pathogenesis of atrophic changes of the hand muscles in patients with tumors of the foramen magnum.

We did not perform evoked potential studies in our patients, and we know of no one who has reported using them in patients with these lesions.

Lumbar Puncture

A lumbar puncture was performed in 21 of our 26 patients, as a rule during myelographic examination. Approximately half of the patients had either complete or partial block in the Queckenstedt test together with marked elevation of the total protein content (range 130–1100 mg%), whilst 7 cases showed a normal manometric response with a usually moderate total protein elevation in the spinal fluid ranging from 40 to 130 mg% (average 83 mg%). In 5 patients (19%) the results of CSF examination were unremarkable. A recent report from the Mayo Clinic (Meyer *et al.* 1984) claimed an even higher rate – approximately 50% – of negative CSF findings, but different results have been reported by others (Stein *et al.* 1963). It must be remembered, however, that other spinal lesions such as cervical spondylosis may occasionally (Brain *et al.* 1952; Guidetti 1958) increase the total protein content in the CSF, as pointed out by Stein *et al.* (1963). Because of this and the relative frequency of negative findings lumbar puncture is of secondary value in the diagnosis of benign tumors of the foramen magnum.

Radiology

Plain Roentgenograms

Plain X-ray evaluation of tumors of the foramen magnum included standard A-P and lateral views, the Towne basal projection and the oblique 35° views for demonstrating the intervertebral foramina. Plain X-rays are usually the first radiological investigation performed in patients with these lesions, although they do not often suggest a mass at the foramen magnum. In our experience, the findings were positive in 12 cases (46%), in half of which they consisted only in radiological signs of cervical spondylosis such as intervertebral space narrowing with osteophytosis. In 6 cases (23%) the findings indicated a possible mass lesion, that is:

– Signs of pedicle and/or long erosion with enlargement of an intervertebral foramen – or increased C_1–C_2 interlaminar distance – which were present in four cases of hourglass neurinoma.

– A hyperostotic lesion located anterolaterally at the foramen magnum was shown in a case of meningioma. This finding was highly relevant to

a correct diagnosis in this patient, who had been treated for multiple sclerosis for three years (Guidetti and Spallone 1980).

– Radiological signs of long-standing increased ICP were detected in a 26 year old woman with a spinocranial neurinoma, who presented clinically with almost nothing but signs of slowly progressing intracranial hypertension.

In conclusion, the diagnostic relevance of plain roentgenography in cases of foramen magnum tumors is secondary but by no means negligible. Actually, in our series as well as in the material of others (Hirano *et al.* 1983; Krenkel and Friedmann 1967; Lové and Adson 1941; Yasuoka *et al.* 1978) pedicle erosion and enlargement of an intervertebral foramen – or widening of the C_1–C_2 interlaminar distance – were relatively common findings in cases of spinocranial neurinoma. Positive plain X-ray findings in the presence of foramen magnum meningioma appear to be exceptional.

Air Studies

Metzger *et al.* (1971) have reported excellent results with air studies in the radiological diagnosis of tumors of the foramen magnum. Other authors (Tristan and Hodes 1958) had warned against their use in the presence of these lesions, due to the tendency for the air to pass posteriorly at the level of the foramen, so that an anterior mass might be missed. An air study was conducted in 4 of our cases, the last of which in 1976. This test demonstrated the lesion in three cases. An anterior meningioma was missed in the remaining patient. In all cases opaque myelography subsequently ensured better anatomical definition of the mass.

Contrast Ventriculography

Contrast ventriculography was performed early in our experience in three cases, whose main symptoms and signs were related to increased ICP (Fig. 1). This invasive test has subsequently been abandoned.

Opaque Myelography

It is generally agreed that myelography with contrast medium is the main diagnostic test when a foramen magnum mass is suspected.

The introduction of water-soluble contrast media (Scholten and Hekster 1977) has reduced the risk of short – and long – term complications related to this test. However tumors of the foramen magnum may escape myelographic demonstration (Howe and Taren 1973), partly because of the relative width of the subarachnoid spaces at the level of the cranio-cervical junction (Bull 1974; Du Boulay and McDonald 1964).

To avoid these potential diagnostic pitfalls, a high degree of technical accuracy is required when performing opaque myelography for a suspected

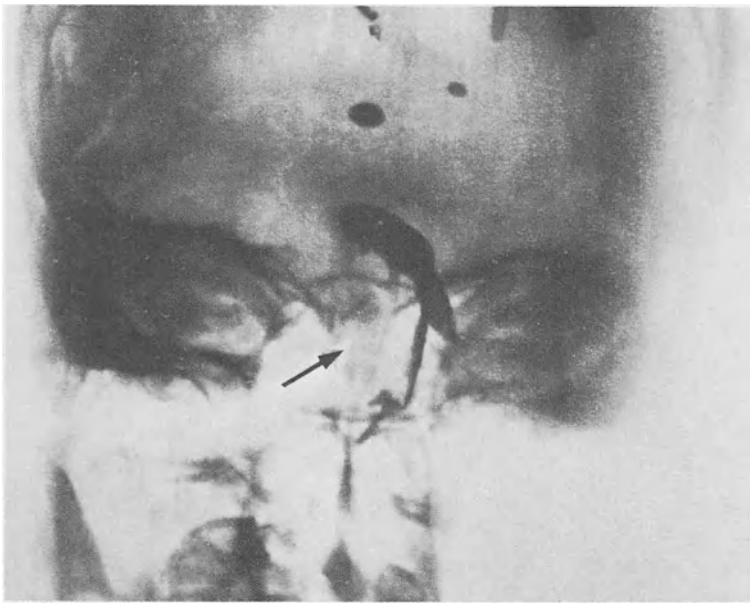


Fig. 1. Contrast ventriculography reveals a large mass (arrow) at the foramen magnum with posterolateral displacement of the cervicomedullary nervous structures

Fig. 2. Contrast myelography shows a total block at C.2

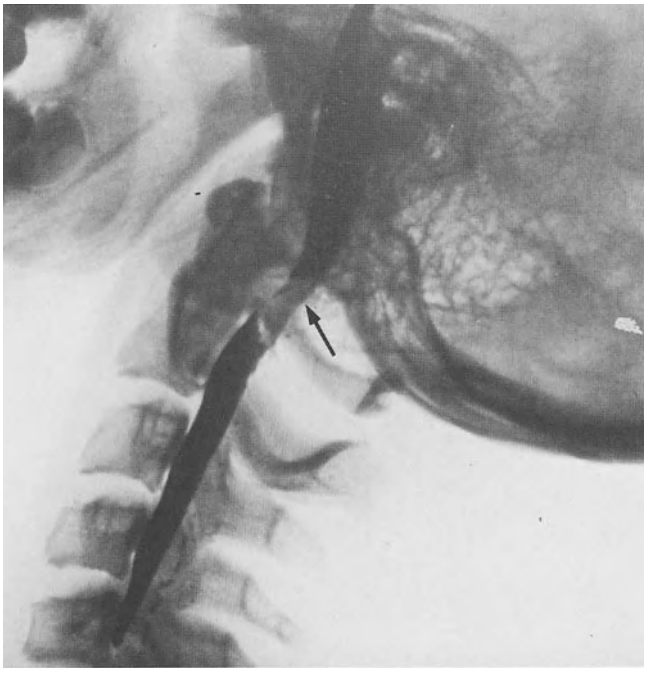


Fig. 3. Contrast myelography shows the anterior subarachnoid spaces interrupted by a mass (arrow)

foramen magnum tumor (Aring 1974; Du Boulay and McDonald 1964; Howe and Taren 1973). The contrast medium should be injected by lumbar puncture, in order to avoid the risk of injury to the displaced cord inherent in either a cisternal or a lateral high cervical puncture. In our experience around 9 cc of contrast, or slightly more with the newly introduced metrizamide and Iopamidol, was sufficient for adequate imaging of the foramen magnum region. The anterior subarachnoid space must be visualized as far as the pontine cistern in doubtful cases (Malis 1958). In three of our patients who had undergone opaque myelography elsewhere the tumor was missed through inadequate demonstration of the foramen magnum region. The lateral inclination maneuver described by Margolis (1976) is also useful for decreasing the possibility of missing an anteriorly located mass. Myelography with the patient in the supine position has been advocated by some authors (Aring 1974; Bull 1974; Du Boulay and McDonald 1964) in doubtful cases, but it has never been necessary in our experience.

Opaque myelography was performed in 21 of our patient. This test has invariably offered convincing radiological demonstration of the tumor as well as an adequate indication of its site and size in most cases (Figs. 2 and 3). Meyer *et al.* (1984) state that myelography was diagnostic in 95% of the cases in their large series from the Mayo Clinic.

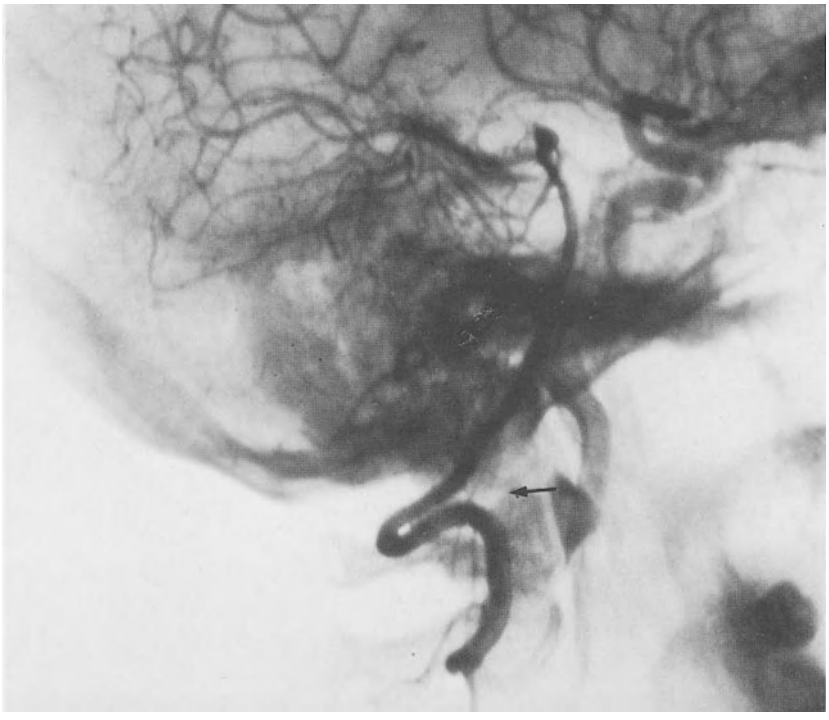
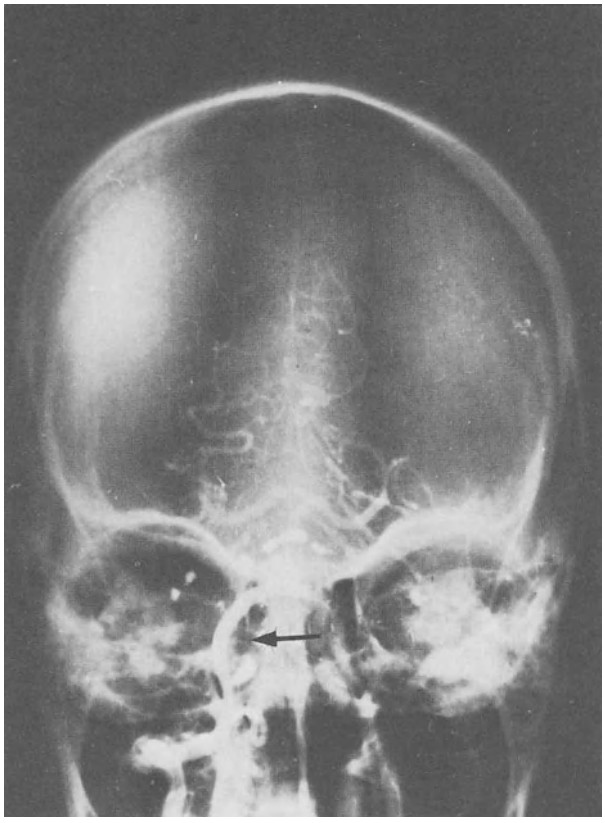


Fig. 4. Selective vertebral angiogram shows that the anterior spinal artery is displaced posteriorly (arrow)

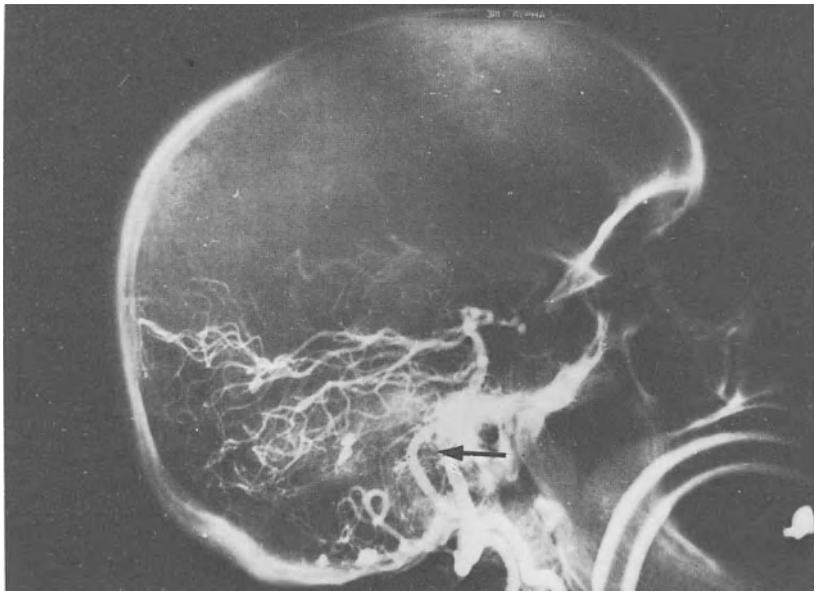
Angiography

Angiography has become part of the radiological work-up on tumors of the foramen magnum only in recent years (Gabrielsen and Seeger 1973; Marc and Schechter 1975). We performed angiography in 10 of our cases. In all these patients the vertebral artery of the supposed side of the tumor was injected, and frequently the distal segment of the contralateral vertebral artery was also visualized.

In 8 cases one carotid artery was also studied. Carotid angiograms were not positive except in one case in which signs of hydrocephalus were present. Vertebral angiography was interpreted as normal in 2 of these 10 patients (20%) early in our experience. In the remaining cases this examination invariably demonstrated abnormalities, namely PICA displacement (3 cases), anterior spinal artery displacement (4 cases) (Fig. 4) vertebral artery displacement (2 cases) (Fig. 5 A, B), posterior meningeal artery hypertrophy (1 case) (Fig. 6), and vascular blush (3 case). Hypertrophy of the posterior meningeal artery and blush occurred only in cases of meningioma. Table 8 summarizes the angiographic findings in our patients. As stated by Ga-



A



B

Figs. 5 A and B. Selective vertebral angiogram shows that the vertebrobasilar arteries are displaced laterally and posteriorly (arrow)

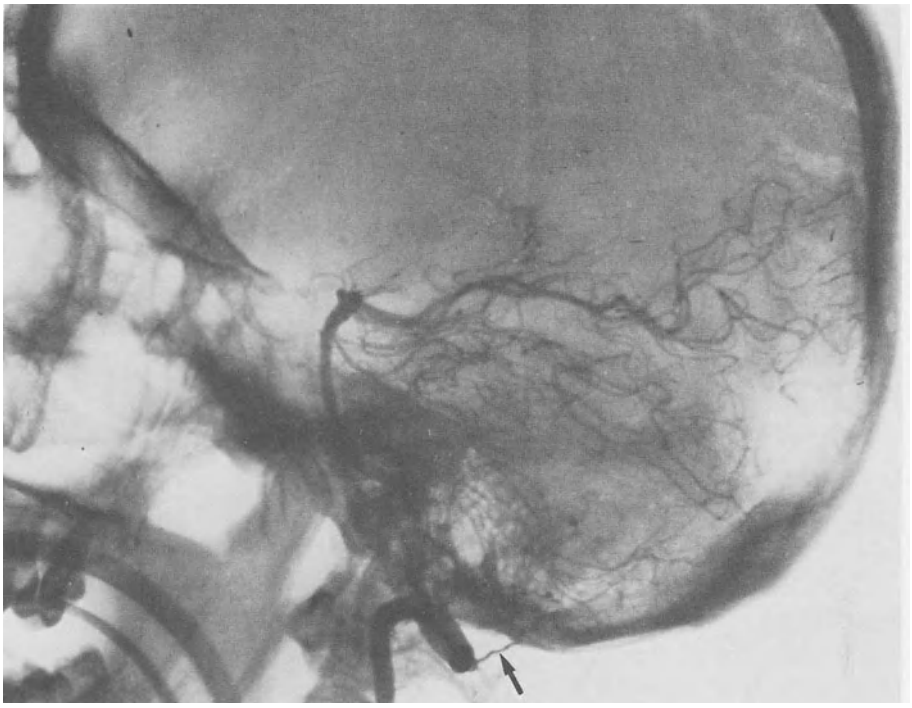


Fig. 6. Selective vertebral angiogram reveals hypertrophy of the posterior meningeal artery supplying the meningiomas (arrow)

Table 8. *Angiographic Findings in Our Patients*

Type of angiography	N. of patients	Findings
Carotid angiography	8	No abnormality *
	10	2 no abnormality 3 PICA displacement 4 ASA displacement 2 VA displacement 1 post. mening. art. hypertrophy ** 3 vascular blush **

* One case showed angiographic features of hydrocephalus.
** Meningioma.
PICA: posterior inferior cerebellar artery. ASA: anterior spinal artery. VA: vertebral artery.

brielsen and Seeger (1973), prerequisites for vertebral angiography to be diagnostic in tumors of the foramen magnum are optimal technique, and good quality radiological pictures, including subtraction views when required. Recent reports from Mayo Clinic groups (Meyer *et al.* 1984; Yasuoka *et al.* 1978) suggest the role of angiography in the management of tumors of the foramen magnum should be limited. We feel that angiography may delineate the degree of vascular involvement by the tumor, when this is to be expected, such as in the presence of large lesions, and this might be helpful in surgical planning. In one of our cases, reported previously in detail, angiography showed displacement and segmental narrowing of one vertebral artery, suggesting vessel encasement by the tumor (Spallone *et al.* 1980).

Computed Tomography

The first paper on the CT diagnosis of benign extramedullary tumors of the foramen magnum was published by us in 1980 (Spallone *et al.*). It dealth with the first two of our patients who underwent CT scanning. In both cases – a neurinoma and craniospinal meningioma, both located anteriorly – this test was diagnostic, and offered clues for possible preoperative diagnosis of nature, such as mode of contrast enhancement, presence of signs of bony erosion, shape and homogeneity of the mass. Subsequent experience with a completely thrombosed giant basilar aneurysm mimicking a foramen magnum tumor, which was diagnosed by CT scan (Spallone 1982) seemed to point to computed tomography as the main diagnostic test for tumors of the foramen magnum. However more recent cases have not altogether borne out our previous expectations. In fact, CT demonstrated the lesion in three subsequent cases (Fig. 7) but not in a case of intradural spinocranial neurinoma despite contrast enhancement with a third generation scanner. This gives a diagnostic accuracy of approximately 75%, which matches the recent experience of the Mayo Clinic (Meyer *et al.* 1984). Intraspinal injection of contrast may obviously offer excellent delineation of the mass at CT (Vancoillie and Veiga-Pires 1979; Hirata *et al.* 1985) but this makes this test as invasive as myelography.

Nuclear Magnetic Resonance

On recent evidence NMR is becoming the procedure of choice in the diagnosis of diseases of the spine. Although demonstrations of foramen magnum tumors shown by NMR are still few (Crockard 1985), some authors (Meyer *et al.* 1984) have stated that this test is becoming the procedure of choice for lesions of the foramen magnum. NMR was performed in one of our cases (Fig. 8), in which it demonstrated the lesion so beautifully

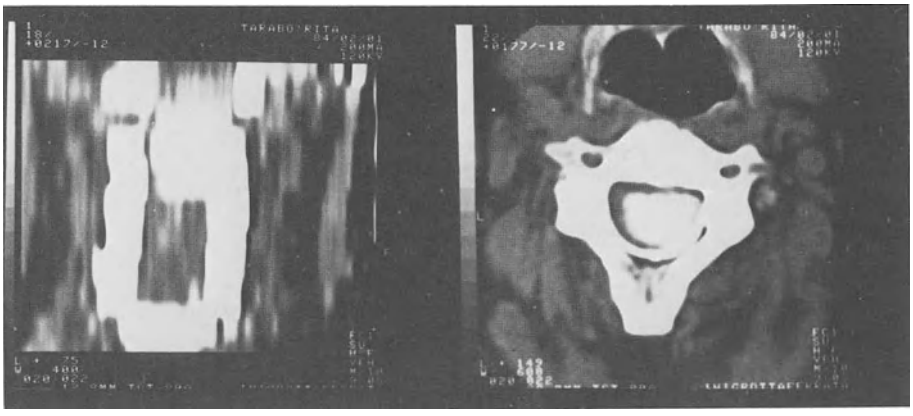


Fig. 7. CT scan reveals a large enhancing meningioma of the foramen magnum

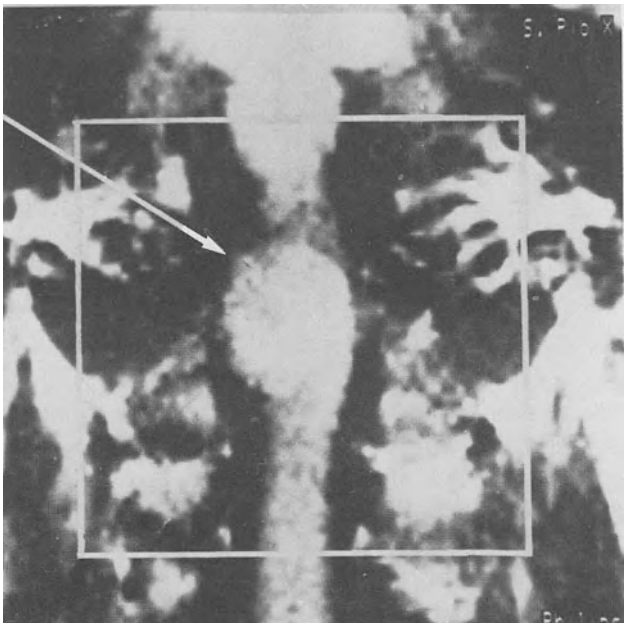


Fig. 8. MNR shows a hyperdense tumor of the foramen magnum (arrow)

that other tests were unnecessary. Accordingly, we too are inclined to think that NMR will replace other, more invasive, diagnostic tools for tumors of the foramen magnum, and it appears to be superior to CT scan in the diagnosis of these lesions. CT scanning might remain important for the preoperative diagnosis of nature.

Operative Management

In benign tumors of the foramen magnum the aim of surgery is radical removal of the tumor and of any infiltrated dura mater and bone. However, total removal of a bulky meningioma, especially if it arises from the anterior margin of the foramen magnum, carries risks that have to be closely assessed by the surgeon and discussed with the patient. The first condition for a satisfactory outcome is careful preparation of the patient for the operation, care being taken to detect and correct any malfunction of other organs or system. In patients with tumors of the posterior cranial fossa the degree of tolerance to bending of the head should be evaluated beforehand in order to position it correctly on the operating table and avoid marked flexion of the neck which may occasion impairment of nervous structures. Dexamethasone in a dose of 12 mg should be given for three days before the operation and for three days after it, but no antibiotics are routinely used.

Operative Approach

The posterior midline approach proved appropriate in all our patients except one, who had already undergone surgery by posterior approach elsewhere; in this case the meningioma was removed by transcervical-transclival approach. We prefer this more complex route to the transoral approach, which has the disadvantage of crossing a contaminated field and which in the case of removal of dura mater, necessary in meningiomas, increases the risk of a cerebrospinal fistula and meningitis. This preference is supported by the fact that we have been able to find only two published cases in which the transoral route was used for intradural tumors. The first, a sarcoma removed partially, was described by Mullan *et al.* in 1966 and the second, a neurinoma, was described by Crockard and Bradford in 1985. From what has been reported we agree with Pásztor and others who consider the transoral approach suitable only for extradural diseases of the structures constituting the craniovertebral junction. For information on this approach we refer the reader to the description by Pasztor in Vol. 12 of this series (recently Miller and Crockard reported two cases transoral subtotal removal of foramen magnum meningioma. Cerebrospinal fluid fistula was avoided by dural repair using a thrombin glue and long term CSF diversion).

Anesthesia

The classic principles of neurosurgical anesthesia apply also to tumors of the foramen magnum. General anesthesia with positive pressure ventilation and orotracheal intubation is the rule. Orotracheal intubation is preferred in these patients because it is tolerated better in cases in which the endo-

tracheal tube has to be kept in situ postoperatively until the patient is fully conscious and breathing normally.

The practice of relying on spontaneous respiration, common at one time, for the detection of any signs of nervous system impairment, was abandoned years ago when it was realized that the onset of cardiocirculatory problems (arrhythmias, bradycardia or tachycardia, a fall or sudden rise in blood pressure) precedes breathing problems, requiring a halt in the operation and prompting increased gentleness in surgical maneuvers. Further valuable information is supplied by an analysis of the somatosensory evoked potentials recorded during the operation.

In patients operated on in the half-sitting position it is advisable to place the blood pressure transducer at the level of the head so that actual intracranial arterial pressure values are known. Venous pressure is monitored by means of a catheter inserted via the brachial vein into the right atrium. This catheter can also be used, if necessary, for aspirating any air emboli evidenced by clinical and EKG signs and by the signals transmitted by ultrasound doppler placed on the chest at heart level. In our experience of over 1.000 patients operated on in the halfseated position we have never encountered air emboli that called for therapeutic measures. We attribute this fortunate record to an obsessive concern with spreading hemostatic wax on the bony margins as soon as they are exposed, constantly spraying the operative field with warm physiologic saline, never opening the venous sinuses unless they have been sealed off, and lastly never using high frequency ventilation in these patients.

Positioning (Figs. 9 A and B)

It is the surgeon's responsibility to see for himself that the patient is properly positioned on the operating table. Correct positioning facilitates and speeds the operation. An incorrect position complicates the surgical maneuvers and lengthens the operation. There is no ideal position for patients with tumors of the posterior cranial fossa. The half-seated position reduces bleeding, facilitates respiration and venous return and affords an almost dry operative field. But it has disadvantages: the possibility of a sudden fall in blood pressure, a very serious occurrence in debilitated elderly patients; appearance of an air embolus; and the fact that the use of the operating microscope in this position is more fatiguing for the surgeon, who in addition cannot make full use of the help of a coworker. Most of our patients were operated on in the half-sitting position but in the past few years we have found the lateral dorsal position satisfactory. Whatever the chosen position, which we decide according to the patient's age and state of health and to the tumor site, the head is fixed, in slight flexion, in a Mayfield headrest, anchored to the operating table. The lower limbs,

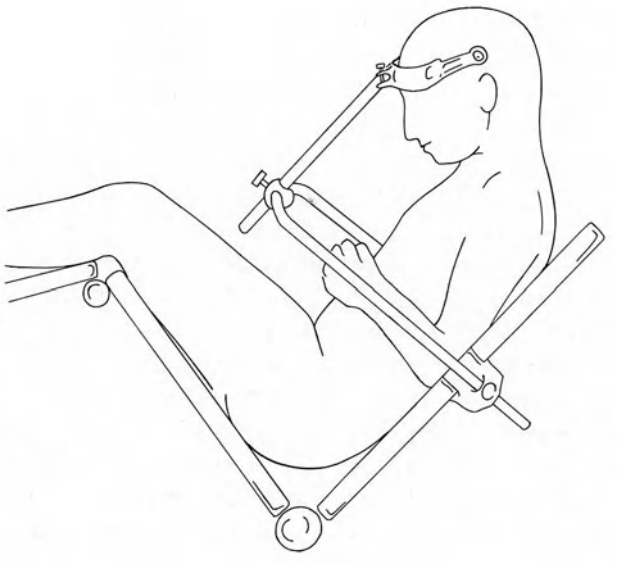


Fig. 9 A. Drawing showing half-sitting position

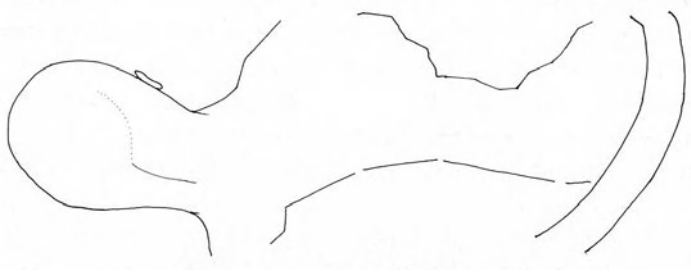


Fig. 9 B. Drawing showing the lateral dorsal position. Medial incision is extended obliquely upward in tumors extending to the cerebellopontine angle (dotted line)

bound with elastic bandage, are placed together semiflexed, in order to avoid lumbar and sciatic pain in the postoperative period, while the upper limbs are semiflexed and supported.

If the dorsal position is chosen, the patient is placed on the table in the lateral position with the head slightly bent and rotated 25° and raised slightly above heart level. In this position the cerebellum falls by force of gravity to the opposite side, thereby giving the surgeon more room in which to maneuver. This position has proved especially helpful in the case of large tumors arising from the anterior margin of the foramen magnum.

Technique

The surgical approach must be decided upon beforehand, on the basis of tumor site, type and size. As all but one of our patients were operated on

either by midline or midlateral suboccipital approach, we shall focus mainly on this route.

Having ascertained that the patient is correctly positioned on the operating table, the surgeon uses a knife tip to mark out the access route, which is then generously infiltrated with novocaine-epinephrine. The operating field is covered with sterile towels and a burrhole drilled 7 cm above the external occipital protuberance and 3 cm from the midline. An incision is made in the dura mater and a silicon catheter is inserted through the burrhole as far as the foramen of Monro. If the cerebrospinal fluid pressure is high, CSF is drawn off, drop by drop, in order to prevent ventricular collapse and formation of a subdural hematoma. The other end of the catheter is placed in a sterile bag and the CSF pressure is monitored continuously. The catheter is kept in situ for 24–48 hours and then removed. In only one patient, who developed hydrocephalus some months after the operation, did we have to set up a ventriculoperitoneal shunt.

The next step in the operation is a skin incision from 4 cm above the inion to cervical vertebra 5. In patients in whom the tumor extends toward the cerebellopontine angle or arises from the anterior margin of the foramen magnum the skin incision is extended from 2 cm below the inion into the mastoid region. The skin is retracted and a Y-shaped incision made in the fascia, likewise retracted. The incision continues, practically bloodless, remaining strictly on the median raphe. The muscles and aponeuroses on the occipital squama and the spinous processes and are freed with electric knife and periosteal elevator. After retraction of the muscles, two drillholes are made aside the median sinus, care being taken not to damage it. The occipital squama, spinous processes and transverse processes are removed with a Leksell rongeur and the atlas with a Kerrison rongeur by subperiosteal route. If a venous sinus is accidentally damaged, it is sutured with fine needles or covered with Surgicel or muscle (Figs. 10 A and B).

If the meningioma is inserted on the anterior dura mater of the foramen magnum, it is advisable to remove the posterior portion of the joint facets of the atlas and occipital bone with an electric drill and diamond burr. In carrying out this maneuver, under the operating microscope, the surgeon must take extreme care not to damage the vertebral artery, which runs in a deep bony groove in contact with the atlantooccipital joint capsule immediately behind the lateral mass of the atlas. Bleeding from the venous plexus, which accompanies the vertebral artery before perforating the dura mater, is arrested by bipolar coagulation or Surgicel. The removal of a portion of the joint facets affords lateral access to the tumor, which avoids damaging compression of the nervous tissue. If the tumor develops into the cerebellopontine angle, the craniectomy must be extended as far as the retromastoid region (Fig. 11).

Having covered the musculocutaneous margins with pledgets soaked in

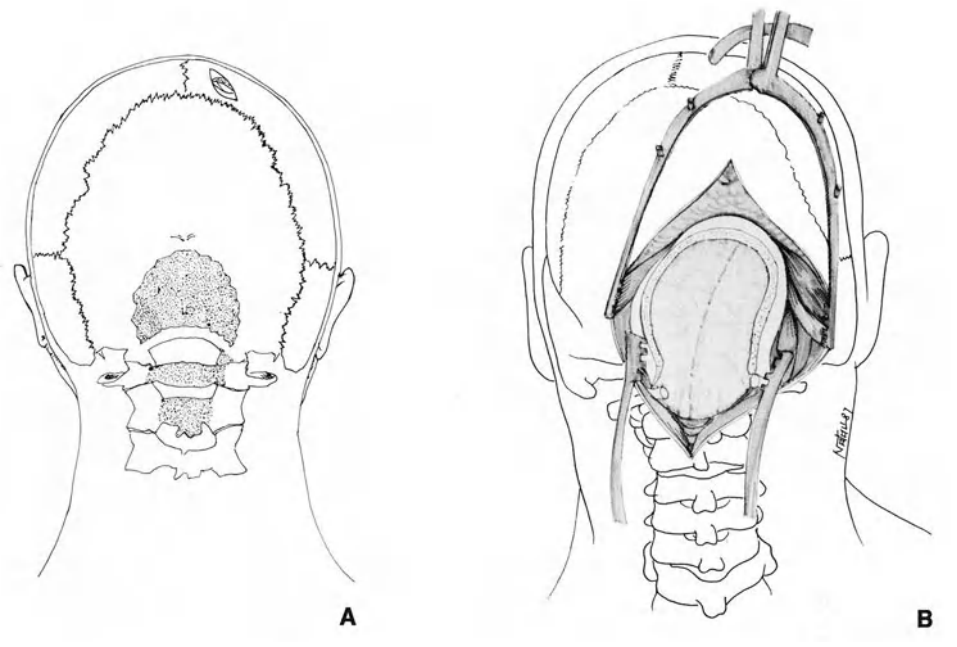


Fig. 10 A. A shaded area indicates size of craniotomy and laminectomy

Fig. 10 B. Drawing showing craniectomy, laminectomy and dural incision

physiologic saline, the surgeon makes a Y incision in the dura mater and retracts its margins with stay sutures. In patients in whom the tumor extends into the cerebellopontine angle he opens the dura obliquely upward as far as the junction between the transverse sinus and the sigmoid sinus. In incising the dura it is wise to section the venous sinuses between two silver clips or ligatures. If the dura has been opened correctly, the underlying arachnoid will be found to be intact. The arachnoid is opened and separated as far as necessary. On introducing the microscope or loupe into the operating field, one can discern the site, size and nature of the tumor and its relationships with the surrounding structures. When the tumor has been located, the surrounding subarachnoid spaces are occluded with sponges soaked in physiologic saline to prevent the spread of blood and tumor fragments.

The great majority of subdural tumors of the foramen magnum lie laterally or anterolaterally, displacing the nervous structures dorsolaterally. In cases in which the meningioma is situated anteriorly the medulla oblongata and high cervical cord are pushed backward and cover the tumor, giving the impression to an inexperienced eye that the tumor is intra-axial. This mistake must be more frequent than is thought, considering that we had to reoperate on as many as two patients in whom the diagnosis at first operation had been intra-axial tumor.

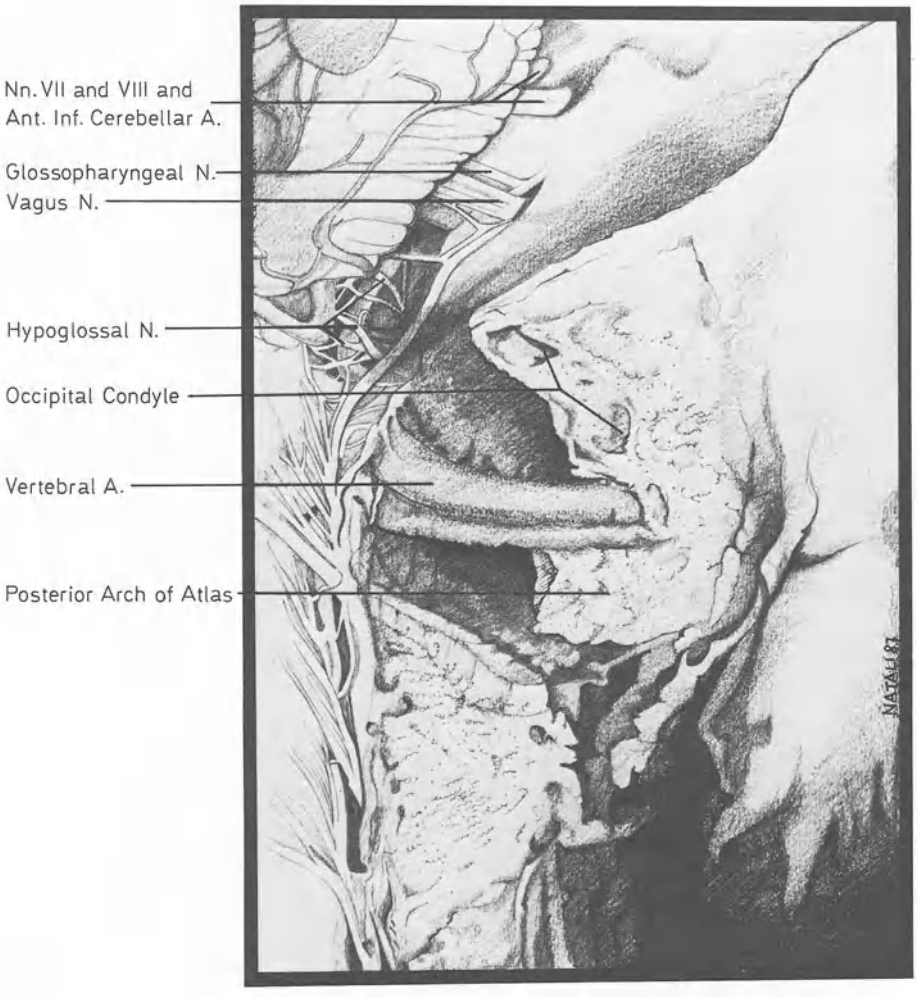


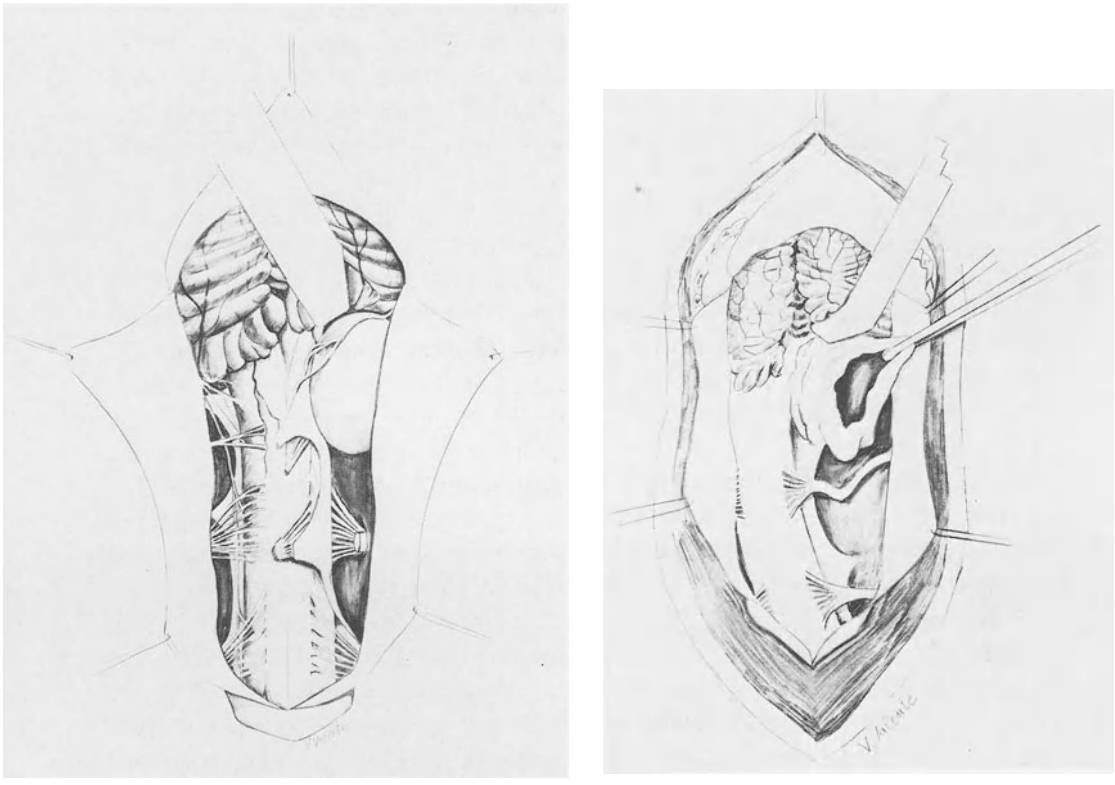
Fig. 11. Craniocervical junction. Subarachnoid space of right posterior fossa and vertebral canal. Removal of the foramen magnum is carried out laterally to include part of the occipital condyle and part of condyle of atlas. Cerebellum is displaced to the left

In the case of anterolateral tumors the dentate ligament, the roots of C_1–C_2 and part of those of the spinal accessory nerve appear to the surgeon to be stretched and pushed backward. Having sectioned the dentate ligament as laterally as possible together with the roots of C_1–C_2, he separates those of the spinal accessory nerve gently from the tumor capsule, displaces them upward and protects them with a sponge. Raising the ipsilateral tonsil and the lower portion of the cerebellum with a spatula, he then gently rotates the spinal cord toward the opposite side, exerting gentle traction

on the dentate ligament. As a rule, the whole of the tumor then appears and sponges are placed between the tumor capsule and nervous tissue. If the tumor is large or situated anteriorly it is helpful to section two or more dentate ligaments and the ipsilateral and contralateral roots in order to mobilize the cord more freely. Care must be taken to spare any radicular arteries when sectioning the nerve roots.

In the case of a small neurinoma block removal is possible without injury to the nervous tissue. If the neuroma is large the best course is to evacuate the contents after cautery and incision of its capsule. An ultrasonic aspirator is very useful for this purpose as it ensure rapid evacuation of the tumor contents without damage to neighboring tissues. In neurinomas that extend into an intervertebral foramen the foramen should be generously opened and, with the intracanalicular stump under traction, the root cut in healthy tissue. Sometimes it is best to remove the intrathecal portion first, sectioning it at the level of the foramen, and then the intracanalicular portion. If the extrathecal mass is large, it should be removed by anterior cervical approach at a later stage. The rare meningiomas with posterior attachment are removed with ease by sectioning the dura mater, after cauterizing it with a bipolar coagulator, around the base of the tumor attachment. In the case of an anterolateral insertion the tumor capsule, released from the anchorage of the dentate ligament, roots of C_1–C_2 and spinal accessory nerve, is coagulated and incised. In none of our patients did we succeed, without damaging the nervous tissue, in reducing the supply of blood to the tumor by sectioning first the dural insertion of the tumor in order to interrupt the blood flow from the posterior meningeal, occipital and sometimes the ascending pharyngeal arteries. After the tumor capsule has been incised, the tumor is emptied piecemeal of its contents using a sharp spoon, bipolar coagulation and Olivecrona scissors. Once the tumor has been emptied, the capsule is gently separated from the neighboring tissues and removed piecemeal. In these maneuvers the surgeon must always bear in mind the course of the underlying vertebral artery in order not to injure it (Figs. 12 A and B).

In the case of large meningiomas, especially those with insertion on the anterior margin of the foramen magnum, it is useful to remove part of the atlantooccipital joint facets, and in those developing toward the cerebellopontine angle the portion of the occipital squama that extends as far as the mastoid process. After evacuation of the tumor content, gentle traction is exerted on the capsule to separate it from neighboring vascular and nervous structures. In this maneuver the surgeon must distinguish the vessels and nerves that run around the tumor and are only displaced and stretched from those that are embedded in the tumor. In the first situation the vessels and nerves must be gently separated and protected with sponges. The small arteries that supply the tumor must be identified, not stretched,



A B

Fig. 12 A. Drawing showing foramen magnum meningiomas ventrolateral to the spinomedullary junction. The ipsilateral tonsil is raised and the dorsal roots and dentate ligaments sectioned. The spinal accessory nerve is gently separated from the tumor capsule and displaced upward

Fig. 12 B. As the capsule is collapsed, adhesion are dissected using microdissectors and bipolar coagulation. The capsula is gently separated from neighboring tissue and removed

in order not to tear them from their base of insertion, and then coagulated and sectioned flush with the tumor. In this first situation the tumor can be radically removed. In cases in which the nerves and vessels are embedded in the tumor, the tumor can be slit, under the microscope at high magnification, and removed around the arteries and nerves, but often in these cases it is wise to leave a thin layer of tumor attached to the arteries and nerves and rely on gentle coagulation of the residue. In these maneuvers the surgeon must establish a close working relationship with the anesthetist and the neurophysiologist who monitors the evoked potentials, and halt the operation momentarily if the nervous structures signal distress. After

removal of the tumor the infiltrated dura mater must be removed as far as possible and the remainder throughly cauterized with a bipolar coagulator. Rigorous hemostasis is followed by the Valsalva maneuver to show up any bleeding points, which must be further coagulated. If the operation is straightfoward, the dura mater can be closed with interrupted sutures; otherwise it is left open with the marginstacked back. The dural defect is protected with a suitable dural substitute, or fascia lata. The patient is then wheeled to his bed and placed with his head at an angle of 30°. The orotracheal tube is not removed until the patient is perfectly lucid and his breathing strong. The pulse, blood pressure, temperature, breathing and CSF pressure must be monitored. The ventricular catheter is usually removed after 24–48 hours.

Transcervical Transclival Approach

We used this route of access in only one patient with a meningioma inserted on the anterior dura of the foramen magnum, which had been partially removed at another hospital by suboccipital approach. The approach used was the one described by Stevenson *et al.* in 1966 with slight variation.

The patient is placed on the operating table in the supine position with the head rotated about 25° to the left and hyperextended in order to increase the submandibular and peripharyngeal spaces. General anesthesia is induced by nasotracheal intubation, which allows the mouth to be tightly closed. To widen the retropharyngeal space we use the maneuver described by Fry and Fry in 1980 and used in traumatic lesions of the extracranial ICA, which allows forward dislocation of the mandibular condyle. (In practical terms, the ipsilateral condyle is dislocated by inserting the index and middle finger into the buccal cavity and gripping the mandible between them and the thumb outside. With repeated traction on the mandible, while the thumb of the other hand exerts compression on the condyle in the same direction, the articulation eventually works loose. A more vigorous pull dislocates the condyle anteriorly. The maneuver is facilitated by the administration of curare.) This done, an incision is made in the skin from the mastoid process to the mandibular angle, thereafter curving along the anterior margin of the sternocleidomastoid muscle. After incision of the platysma and section of the external jugular vein, the superficial cervical and temporomandibular fasciae are incised. The carotid sheath is opened, the neurovascular bundle is moved gently to one side and the parotid gland is displaced medially and upward until the facial nerve, digastric muscle and hypoglossal nerve are exposed. After section of the posterior belly of the digastric muscle at the level of the intermediate tendon and superior thyroid and lingual arteries, the hypoglossal nerve is isolated and displaced downward. Then follows section of the stylohyoid muscle, which runs parallel to the digastric muscle, and of the stylomandibular ligament. If

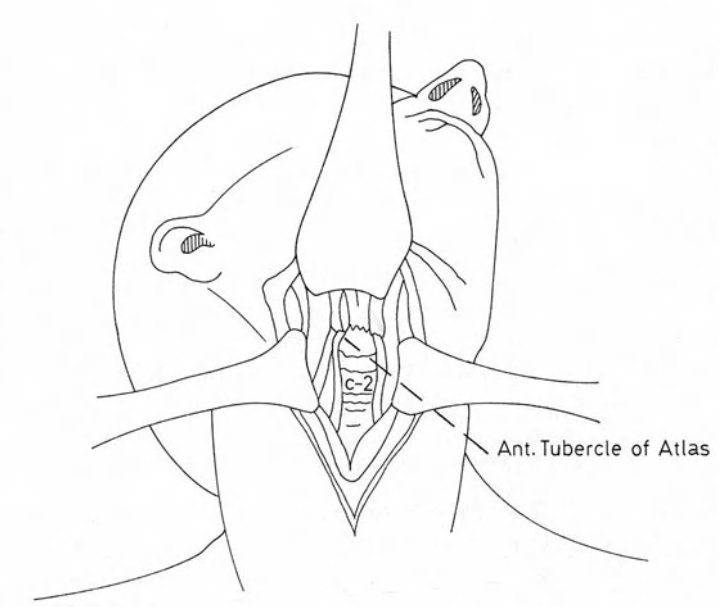


Fig. 13. Drawing showing retraction necessary to achieve exposure of the arch of atlas

the styloid process is too long and obstructs vision, it is partially fractured. Section of the stylopharyngeal bundle and of the one that extends from the epipharyngeal fascia to the prevertebral fascia reveals loose connective tissue, which allows easy blunt separation of the prevertebral from the pharyngeal fascia as far up as the pharyngeal tubercle, lying about 2 cm from the foramen magnum. After upward and medial displacement of the nasopharynx with a deep bladed retractor, the prevertebral fascia is incised longitudinally from the foramen magnum to C_3 and the neck muscles are separated subperiosteally and retracted laterally. With the microscope shifted into the operating field, an electric microdrill fitted with diamond burr is used to displace the atlas 8–10 mm to the right and left of the midline. Drilled at its base with a microdrill, the odontoid peg is removed, after section of the alar and apical ligaments. The lower portion of the clivus is then removed by microdrill and undercutting forceps, care being taken not to damage the inferior petrosal sinus and hypoglossal nerve. The tectorial membrane and posterior longitudinal ligament are incised to disclose the tumor infiltrated dura mater, which is cauterized with a bipolar coagulator and incised. The tumor is removed piecemeal with bipolar forceps and scissors on the same principle as for the suboccipital approach. After meticulous hemostasis, the residual cavity is filled with abdominal fat graft and Tissucol*. The muscles and prevertebral fascia are sutured

* Tissucol Oesterreichisches Institut fuer Haemoderivate Ges. M.B.H. Vienna.

and likewise the other musculocutaneous layers. To prevent the formation of a CSF fistula, CSF drainage is set up for 48 hours by means of a lumbar subarachnoid catheter (Fig. 13).

Postoperative Care

Patients operated on in the sitting position are kept in the half-sitting position postoperatively, with no less than 30° elevation of the head. The surgical drains are removed as a rule 24–48 hours after the operation. Vital signs must be carefully monitored during the first three postoperative days. This applies particularly to the respiratory parameters. We lost one patient – whose clinical details will be given in the following section – due to sudden onset of apnoea on the third postoperative day. For mild respiratory irregularities analeptics and/or oxygen may be sufficient but intubation and mechanical assistance may be warranted in some cases. Blood pressure should also carefully controlled, since there is a confirming risk of hypotension in patients maintained in the half-sitting position. Obviously any change in the postoperative neurological status should prompt appropriate measures to exclude the possibility of a postoperative epidural clot. Steroids, which are started 48 hours before surgery, are continued for three days following the operation and then gradually tapered off. We routinely give gastroprotective medication during steroid treatment, in order to minimize the known risk of gastrointestinal complications. Finally early physiotherapy will shorten the time required for neurological recovery and hasten neurological recovery even in patients with advanced symptoms.

Clinical Results

Total mortality related to the surgical procedure was 11% (3 out 26 cases). A 57 year old woman, the second patient in our series of tumors of the foramen magnum, was operated on for 4 × 4 cm anterior craniospinal meningioma. Eight months before she had undergone elsewhere a high cervical laminectomy with intradural exploration, at which a bulging cord had been observed and an intramedullary tumor diagnosed. This only halted the progression of symptoms, which prompted revaluation of the case and reoperation by ourselves. Surgery was difficult due to the size and the location of the tumor as well as from the adhesions resulting from the previous operation. However, it was completed apparently with success. The patient awoke from anesthesia with no new neurological deficit, and had an initially normal postoperative course, except for a couple of episodes of slowing of respiration, which lasted no more than three hours and appeared to subside on the second postoperative day. However she had a fatal apnea during sleep three days following operation. Sleep-induced

apnea, possibly related to surgical injury of the medullary respiratory centers, was presumed in this case (Guidetti and Spallone 1980).

The second fatality occurred in a 25 year old man described in detail in a previous paper (Guidetti and Spallone 1980). He had undergone intradural exploration elsewhere with a misdiagnosis of intramedullary tumor. He came to our observation in extremely bad general and neurological condition, but showed remarkable recovery after removal of an anterior neurinoma originating from the C_2 root, which had been missed at the previous operation. However be developed wound dehiscence with CSF leak 12 days following operation. Wound revision did not prevent recurrence of the leak, and septic complications eventually supervened. The patient died from meningitis 25 days after surgery.

The third fatality related to surgery occurred in a 51 year old woman with a large anterior craniospinal meningioma. The tumor was approached from the right cerebello-pontine angle. The right vertebral artery, which was deeply embedded in the tumor, was inadvertently injured during piecemeal removal of the lesion. Bleeding from the artery was controlled, and removal of the mass eventually proceeded uneventfully. However the patient awoke with a syndrome of lateromedullary infarction and remained severely disabled. She died in a nursing home a few months later. In the remaining 23 cases the early postoperative course was as a rule free of significant complications. Reoperations were not required except in one patient (case 21), who developed communicating hydrocephalus following uneventful removal of a C_1 antero-lateral neurinoma. She recovered completely following ventricular shunting. Of these 23 patients, one requires some form of assistance at home, but he is able to perform most of his daily activities without help. Two patients died from unrelated causes 14 and 28 years after surgery. The remaining 20 patients are presently leading normal lives. A mild weakness, already present preoperatively, was still observed in three of these patients when last seen. Neurological examination was grossly normal in the remaining patients. Follow-up in these cases ranges from 2 to 34 years. Equally good long-term results have been recently reported in a large number of patients from the Mayo Clinic (Meyer *et al.* 1984). These authors reported a better surgical mortality (5%) than ours, but a further 5% deaths from recurrence, while we had no cases of incomplete tumor removal and know of no recurrences.

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The Management of Spinal Epidural Metastases

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With 12 Figures

Contents

In 1959, in our first study on 24 cases of epidural metastases[19], we noted that a feeling of deep pessimism was apparent in all previous publications with regard to the outcome of these patients. The same feeling is still perceptible in most recent studies. Since 1959, several papers from our departments[21, 22, 57, 60, 76, 79, 85, 98, 104, 114, 128, 179] were dedicated to the problem of cancerous paraplegia, expressing in short our determination to find out the best management for these patients. We cannot adopt a defeatist attitude even if the final results still remain quite disappointing in many cases. In fact the main action for improving the results has always been and still is the promptness in making the diagnosis followed by the right therapeutic measure.

Introductory Relevant Data

For the first time in 1865, Charcot and his pupil Tixier, describing paraplegia in cancer patients, called it painful paraplegia because the pain often remained predominant during the course of the disease. Thus for little more than one century have vertebral metastases been clearly identified although the vertebral localization of malignant tumours commonly occurs. One might roughly estimate that 5% of cancer patients will show epidural infiltration, although all epidural infiltrations are not clinically evident. Considering all sites of metastasis, the vertebral localisation however appears less frequent than for example pulmonary or hepatic deposits. In this respect, like cerebral secondary lesions, the frequency of epidural infiltrations increases in parallel with longer survival of patients.

The high percentage of metastases among series of vertebro-spinal tumours is well represented in Tables 1 and 2, being above 50%. The frequency of epidural carcinomas is in parallel with the high occurrence of carcinomatous tumours in patients with malignant disease. According to Chade (1976) and Baldini (1979) carcinomas represent 90% of epidural metastases (Table 3).

The metastatic invasion of the vertebral axis is mainly osseous and secondarily epidural. Subdural and intramedullary localisations are rare: 5 cases out of 134 for Constans *et al.* (1973), 4 cases out of 105 for Kretschmer (1979). Edelson *et al.* (1972) found six cases of intramedullary lesions of 175 metastatic spinal cord lesions, a percentage of 3.4 which seems unusually high[9, 14, 40, 80, 86, 157, 166, 174, 190].

All authors have noted that metastatic infiltration first affects the vertebral body before the epidural space and that the tumour remains confined

Table 1. *Distribution of Vertebro-spinal Tumours* (Klein *et al.* 1984)

	No.	Sex	Average age (years)
Meningioma	47 (15.30%)	M 6 F 41	59
Neurinoma	26 (8.46%)	M 11 F 15	52
Ependymoma	9 (2.93%)	M 6 F 3	39.9
Astrocytoma	6 (1.95%)	M 3 F 3	35.7
Lipoma	5 (1.62%)	M 3 F 2	51.6
Epidural metastasis	197 (64.2%)	M 113 F 84	59.9
Miscellaneous	17 (5.53%)	M 11 F 6	
Total	307		

Table 2. *Frequency of Epidural Metastases in a Large Group of Vertebro-spinal Tumours* (Arseni *et al.* 1959)

Number of vertebral tumors	Primary tumours	Metastatic tumours	Myosarcomas secondarily invading the spine
350	103	231 (66%)	16

Table 3. *Distribution of Spinal Epidural Metastases in Carcinomas and Sarcomas*

	Carcinoma	Sarcoma	Melanoma
Chade	158 (91.9%)	9 (5.2%)	5 (2.9%)
Baldini	125 (90.3%)	15 (10.8%)	

Table 4. *Spinal Metastasis: Location of the Primary Tumour in 1,038 Clinical Cases**

Location of primary tumour	% of cases of spinal metastasis	
Lung	15	Approximately half of all cases
Breast	14	
Lymphoma	11	
Unknown	9	
Sarcoma	8	
Myeloma	7	
Prostate	7	
Kidney	6	
Gastrointestinal	4	
Miscellaneous	18	

* Data are pooled from the literature for 1957 through 1978.
Perry Black, 1979.

within the epidural space, the dura mater being indeed a resistant barrier to any kind of infiltration.

The site, and therefore the nature, of the primary lesion, responsible for the vertebral seeding has been of interest to many authors. In 1,038 cases pooled from the literature, Perry Black (1979) found 15% of vertebral metastases originating from the lung and 14% from the breast (Table 4); it is worthwhile noting that in 9% of the clinical cases, the original site of the tumour could not be detected. We have personally collected 1,477 cases from the literature and our own cases; we found 15.6% of epidural metastases coming from the lung, 16.5% from the breast and 9.2% from the prostate (Table 5). In this large number, the primary tumour remained undiscovered in 12.5% of clinical observations.

In a post-mortem series of 127 vertebral metastases, Barron *et al.* (1959) found 25% originating from the lung and 15% from the breast. The patient being still living, the primary tumour remained undiagnosed in 26 cases

Table 5. *Location of the Primary Tumour*

	Arseni 1959	Barron 1959	White 1971	Constans 1973	Paillas 1973	Chade 1976	Baldini 1979	Kretsch-mer 1979	Dunn 1980	Personal series 1987	Total	%
Lung	39	31	31	4	12	27	20	11	19	37	231	15,6
Breast	27	20	37	30	8	23	24	10	7	58	244	16.5
Kidney	9	12	13	2	8	25	9	10	8		96	6.5
Prostate	16	6	23	5	4	19	16	5	21	22	137	9.2
Thyroid	2	3	8	11	2	20	5	3			54	3.6
Gastro-Intest.	15	6	11	3	6	10	11	1	6		69	4.6
Hemato-sarcoma		29	35	35	3			20	16	21	159	10.8
Miscella-neous	81	18	59	29	5	7	7	13	17	66	302	20.5
Unknown	42	2	9	15	12	16	33	32	10	14	185	12.5
	18.18%	1.57%	3.98%	11.19%	20%	10.88%	26.40%	30.47%	9.61%	6.4%		
Total	231	127	226	134	60	147	125	105	104	218	1,477	

Table 6. *Metastasizing Neoplasms Whose First Manifestation Was That of Spinal Cord Disease*

	Number of cases seen at P.M.: 127		Diagnosis of primary tumour established during life: 101	Diagnosis of primary tumour unknown prior to operation or autopsy: 26
Lung	31–25%		23	8
Breast	20–15%	55.9%	20	0
Lymphoma	20–15%		15	5
Kidney		12	7	5
Myeloma		9	6	3
Sarcoma		8	6	2
Prostate		6	5	1
Rectum		6	6	0
Uterus		3	3	0
Thyroid		3	3	0
Miscellaneous		9	7	2

Barron K. *et al.* 1959.

Table 7. *Malignant Tumours Verified at Autopsy* (1950–1956)

Primary tumour	Number of patients	Spinal infiltration	%
Lung	225	11	4.9
Breast	93	6	6.5
Lymphoma*	86	4	4.6
Stomach	85	1	1.2
Rectum	45	3	7.0
Prostate	40	4	10.0
Kidney	40	3	8.0
Ovary	36	0	0
Myelomas	21	3	14.0
Thyroïd	17	1	6.0
Uterus	16	1	6.0

* Hodgkin disease, lymphosarcomas, leucemias, ... etc are included in lymphomas.
Barron K. *et al.* 1959.

(20.47%). At autopsy, the primary lesion was not found in 2 cases (1.57%) (Table 6). Considering the primary tumour verified at autopsy, Barron *et al.* (1959) noted that among 225 pulmonary tumours, there were 11 cases (4.9%) of epidural metastases and among 93 mammary carcinomas, there were 6 vertebral localisations (6.5%) (Table 7).

The analysis of Barron is interesting because he emphasized the fact that the percentages of epidural metastases are not appreciably different from one type of tumour to another, when the number of primary lesions is taken into account. *The frequency of vertebral metastases of pulmonary or mammary origin directly depends on the great number of lung and breast cancers.*

Clinical Presentation

It is worthy of note that the first clinical manifestation of the disease is often in relation to the vertebral localisation. In a global series of 884 cases,

Table 8. *The Spinal Metastasis Was the Initial Symptom of the Disease*

	Total number of cases	Initial symtom	Percentage
Constans *et al.*	134	41	30
Arseni *et al.*	231	79	34.3
Kretschmer	105	38	36.2
Auld and Buerman	50	29	58
Paillas *et al.*	60	30	50
Knollmann *et al.*	109	42	38.53
Personal series*	195	38	19.50
Total	884	297	33.5

* The information on our personal cases is not always available for every clinical aspect, so that the number of cases is variable according to the tables.

Table 9. *Sex Distribution and Mean Age*

		Chade	Klinger	White	Personal series
Spinal metastases	m	61.8%	59%	58%	49%
	f	38.2%	41%	42%	51%
Mean age (years)			55	52	56

Table 10. *Distribution of Metastases in the Spine*

Vertebral level	Barron 1959	White 1971	Constans 1973	Paillas 1973	Chade 1976	Kretschmer 1979	Baldini 1979	Dunn 1980	Klein 1984	Knollmann 1984	Personal series 1985	Total	%
Cervical and cerv. thor.	14	20	12	5	17	3	14	8	12	9	13	127	8.1
Thor. and thor. lum.	83	186	87	50	108	90	83	75	116	74	163	1,115	70.3
Lumbar and sacral	30	20	30	5	46	12	42	21	69	26	42	343	21.6
Total	127	226	129	60	171	105	139	104	197	109	218	1,585	

the vertebral metastasis made the diagnosis of cancer in 297 cases (33.5%) (Table 8).

There is no significant difference with regard to the sex of the patients and the greatest number of cases is seen between 50 and 60 years of age (Table 9).

An another significant observation concerns the distribution of epidural metastases along the vertebral column. Analysing 1585 clinical observations, 127 cases (8.1%) were at the cervical level, 1115 (70.3%) at the thoracic level and 343 (21.6%) in the lumbo-sacral region (Table 10). This topographical distribution is of significance in regard to the clinical evolution and some characteristics of treatment, as we shall discuss later.

The clinical presentation of epidural metastases depends indeed on several factors, among which are the level of the vertebral lesion, the histologic type of the tumour, the possibility of several vertebral localisations, the relative importance of vascular or compressive components in the pathophysiology. In addition, we must keep in mind that patients submitted to chemotherapy at the time of their vertebral lesion, can present neuropathy and paresthesiae suggesting a vertebro-spinal lesion.

As we have stressed at the beginning of this chapter, pain is of first importance in epidural metastases, often being the only symptom for weeks or months. Pain may be local, resulting from irritation, distension of ligaments and articular facets and/or spine instability, or radicular, irradiating along a specific dermatome. According to all series, pain is present in 75 to 90% of the cases, particularly when the cervical or lumbar level are involved. The vertebral pain, remaining localized at the level of the lesion, is constant, dull, pricking and penetrating, aggravated by movements, mainly flexion and during the night. The radicular pain is acute and intermittent, exacerbated by strain and irradiated within the field of the involved root.

The neurological signs, of whatseever character, have an unforeseeable evolution. They may appear quite suddenly; they may result within a few hours or days in a sensorimotor paraplegia; in other cases, they need several days or weeks to develop to paraplegia. Various factors account for this variable evolution; the well-known vulnerability of the high thoracic spinal cord; tumoural infiltration of arterial walls in the epidural space, sometimes resulting in vascular obstruction and sudden medullary infarction[19, 57]; obstruction by extradural deposits of the rich venous network in the epidural space, provoking extravasation and oedema within the spinal cord[83, 88]; the collapse of a vertebral body producing mechanical compression of the dural envelop. The solid consistency of some tumoural deposits may also result in a rather slow and progressive compression of the spinal cord, although, as it will be stated later, myelography may visualize a complete obstruction to the dye column when there is as yet no neurological deficit[104, 153].

All these factors make the evolution of the clinical signs unpredictable. However, as a general rule, as soon as a motor deficit appears, the evolution to paraplegia is rapid.

Nevertheless, it remains hard to understand why the diagnosis is made so late in many patients. At the admission in our department, we found, in agreement with many authors, 20% of the patients already paraplegic and 50% to 70% suffering for several days, or even several weeks, from motor disorders, or sensory or sphincter disturbances. So great a misappreciation of clinical signs partially accounts for the frequent poor outcome of the patients.

Barron *et al.* (1959) reported 7 cases out of 127, with herpes zoster eruption in the dermatome corresponding to the metastatic level. In one of these cases, at autopsy, tumour cells were infiltrating the root. In two other patients, the herpetic eruption was observed nearly one year before the onset of clinical signs. Without doubt, such an eruption results from the activation of a latent virus by tumour cells invading the posterior root ganglion. In 1964, we also reported 3 cases of herpes zoster eruption among 11 clinical observations of Hodgkin's paraplegia[21]. The appearance of a zoster eruption within a vertebral dermatome in a cancer patient could be considered as the first clinical sign, forerunner of the epidural deposit.

Cytology of the CSF is not affected by the epidural infiltration for all that dura mater is not infiltrated. The level of cerebrospinal proteins is in general moderately elevated, depending on the degree of obstruction to the theca.

Clinical Grading

Attempts to grade the clinical condition of the patient before and after treatment have been made in order to facilitate a valid comparison of results. Two major complaints, most important for the patient, have been considered: the first one is related to the possibility to retain or to recover ambulation; the second consists in reducing or suppressing the pain.

The evaluation of ambulation performance is made according to various scales close to each other.

White *et al.* (1971) proposed the following simple scale:
grade 1: ambulatory
grade 2: nonambulatory: some motor function
grade 3: paraplegic: no motor function

Shaw *et al.* (1980) produced five gradations:
grade 1: able to walk normally
grade 2: weak legs but able to walk unaided
grade 3: walking but with aid
grade 4: unable to walk but able to move the legs
grade 5: paraplegic

Constans *et al.* (1973, 1983) propose a somewhat more complicated grading:

grade 1: pain or minor neurological symptoms: normal social and professional activities

grade 2: mild neurological symptoms: normal social life but interruption of professional activities

grade 3: moderate neurological syndrome (paraparesis, sphincter disturbances, columnar pain); active life impossible

grade 4: serious neurological syndrome (paraplegia, comple sphincter deficit)

grade 5: medullary syndrome of spinal cord transection

What we need is a simplified scale, convenient for everybody on the medical nursing staff. We commonly use the scale proposed by Shaw.

The measure of pain is easily made, applying together the pain score and the narcotic score developed by Tong *et al.* (1982).

I. Severity of pain at treatment site
0: none
1: mild
2: moderate
3: severe

II. Frequency of pain at treatment site
0: no pain
1: occasional (less than daily)
2: intermittent (at least once a day)
3: constant (most of the time)

Pain score = (pain severity) × (pain frequency)

I. Type of pain medication administered
0: none
1: analgesic (aspirin, bufferin, anacin, darvon)
2: mild narcotic (one-half grain codeine, percodan, etc)
3: strong narcotic (one grain or more of codeine, morphine, demerol, etc)

II. Frequency of pain medication administration
0: none
1: less than daily
2: once per day
3: more frequently than once per day

Narcotic score = (medication type) × (medication frequency)

Thanks to these two modalities of grading, ambulation and pain, an objective appreciation of various therapeutic approaches can be achieved.

Radiologic Work-up

Modern imaging techniques determine the diagnosis and evaluation of the extension of spine lesions. Production of new watersoluble contrast media for myelography, the development in computed tomography (CT) and magnetic resonance imaging (MRI) bear witness to the rapid evolution of

technology within a few years. Although the MRI still remains not very accessible in case of emergency, its value in the exploration of spine lesions is already without doubt: in the near future, MRI may replace myelography in demonstrating vertebro-spinal tumours.

The new watersoluble contrast media (Iopamidol and Iohexol) with their reduced osmolarity, are better tolerated; they are compatible with CT scan exploration because of their moderate radio-opacity. CT myelography still remains a basic exploration in the appreciation of vertebro-spinal tumour involvement.

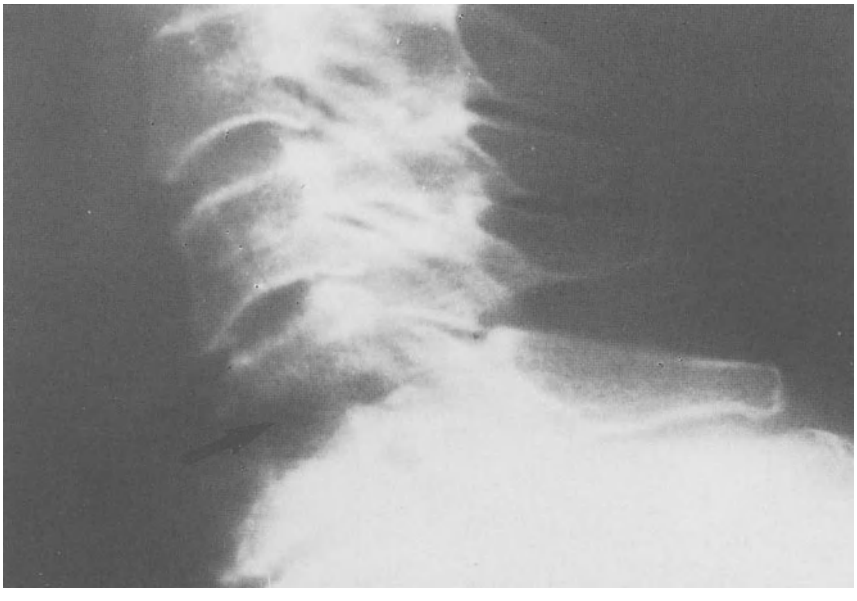
In addition to their diagnostic value, the radiologic studies have contributed to the understanding of the frequency of vertebral metastases in absence of lung involvement. The angiographic studies of Batson (1941), Anderson (1951) and Abrams (1957) have emphasized the possible role played by the vertebral veins in the metastatic dissemination; this system of rich and valveless connections works as a reservoir in which emboli can freely travel both upward and downward, by-passing the lungs. The experimental researches of Coman (1951) have clearly demonstrated the direct entrance of tumour emboli into the vertebral venous system.

Bone scintigraphy, as well as *plain radiography* are valuable screening tests for vertebral metastases (Baldini *et al.* 1979, Fruhling 1986); bone scintigraphy can even detect involvement of the spine before the appearance of bone changes on plain films (Rubin *et al.* 1969, Constans *et al.* 1983). *Conventional tomography* is still useful in the differential diagnosis between metastatic involvement of the vertebral body and spondylodiscitis (Fig. 1). *Myeloscintigraphy* was carried out by Constans *et al.* (1983) for patients in poor condition. *Vertebral phlebography* is no longer indicated for diagnosis in epidural metastases.

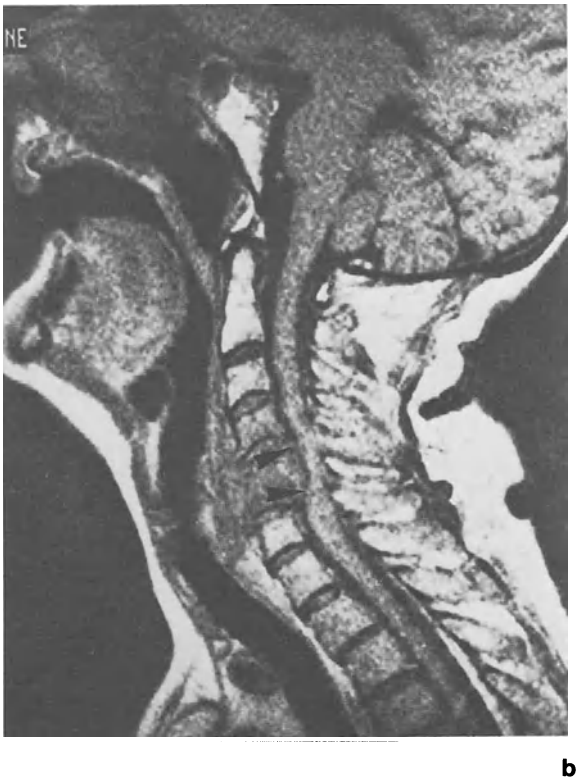
The CT scan with high resolution can detect vertebral infiltration not yet seen on plain X-rays. In fact, the size of the vertebral infiltration is not always correlated with the size of the associated epidural infiltration[53]. It is estimated that at least 85% of epidural metastatic tumours are associated with vertebral body infiltration (Takakura *et al.* 1982).

Myelography has made great advances over the last 25 years, following the various discoveries in contrast solutions (Almen 1969, Eldevik 1982). It is our practice to proceed to myelography as soon as the diagnosis of epidural infiltration is suspected on standard radiographic films and/or computed tomographic images. The injection of the contrast solution is made after lumbar or cervical puncture; the amount of solution injected is determined under fluoroscopic control; in general we use 10 ml of solution of 240 mg I/ml. The CT scan is systematically performed 30 to 90 minutes after the completion of myelography.

The most characteristic finding of epidural infiltration is a partial or complete block of the opaque solution. Generally, the margin of the column



a



b

Fig. 1 a and b. Conventional tomography (a) and MRI SE 600/30 (b) of a spondylodiscitis (due to staphylococcus aureus). Note the wide destruction of vertebral bodies of C 5 and C 6, the disappearance (arrow) of the normal discal space, and the paravertebral extension with anterior epiduritis and compression of the spinal cord (arrowheads)

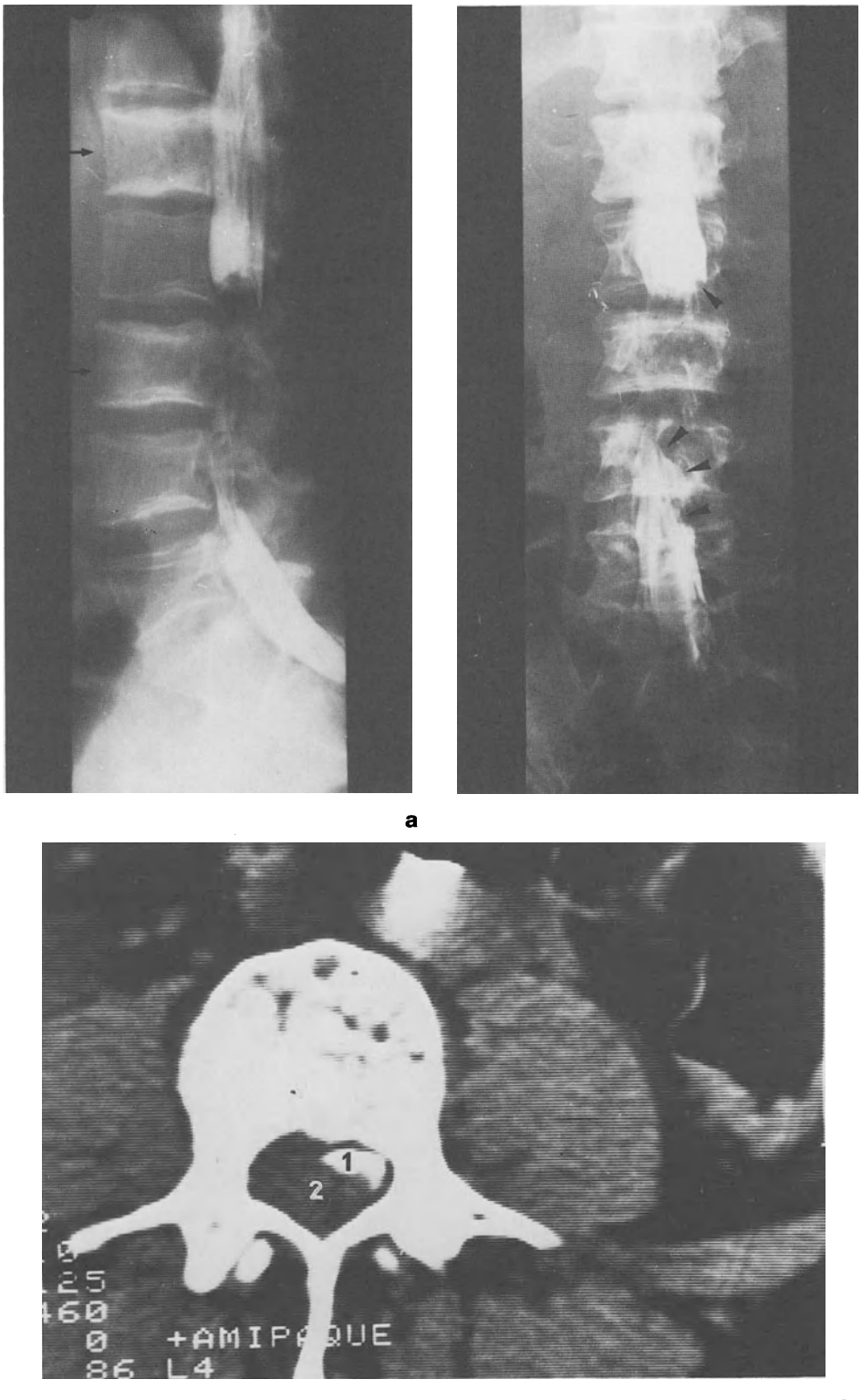


Fig. 2 a, b and c. Epidural involvement by Hodgkin's disease. Myelography (a and b) with water-soluble contrast medium. Note the typical irregular margins of the opacified dural sack (arrowheads). There is sclerosis of some vertebral bodies, that are infiltrated (arrows). CT at L 4 level (c) shows some contrast (*1*) visible on the right side of the canal, and tumoural tissue occupying the greatest part (*2*)

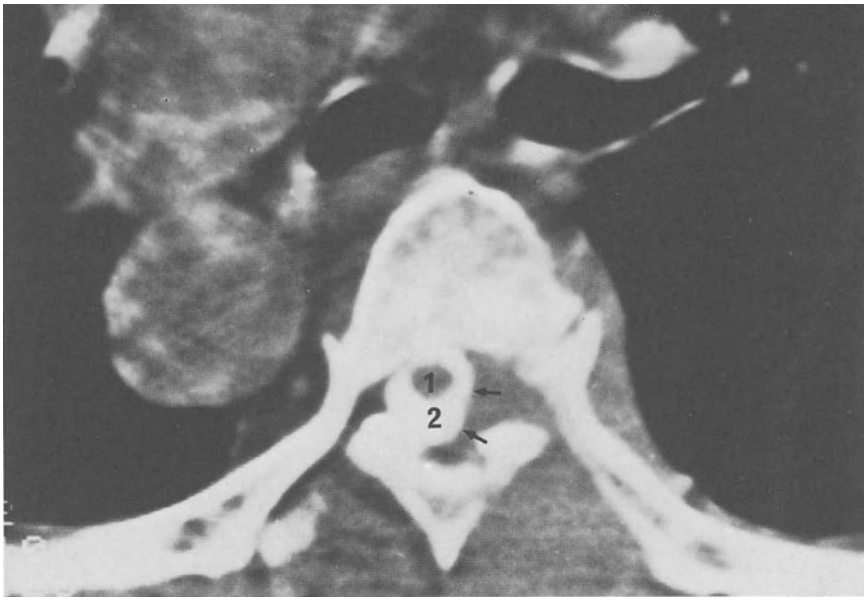


Fig. 3. CT myelography. Note the right epidural infiltration with compression of the dural sac by tumour (arrows). Spinal cord (*1*) is well visualized in opacified (*2*) subarachnoidal space. The anterior and posterior extension of the tumour with involvement of the posterior arch is well demonstrated

of dye at the level of the block is irregular and indented (Fig. 2). The site of the compression is either anterior, posterior or lateral, or may corresponds to complete envelopment of the duramater (Fig. 2c). Rubin *et al.* (1969) and Longeval *et al.* (1975) have observed that in patients with minimal or no neurological signs, encroachment of the duramater or even a complete epidural block can often be demonstrated on myelography.

While the block appears complete on myelography, the CT scan often demonstrates some continued passage of the contrast solution, thanks to a better densitometric resolution (Fig. 3); this finding frequently permits detection of the upper and lower limits of the epidural tumour on the same image and therefore avoids a second spinal puncture.

When the volume of the epidural infiltration is small, myelography only indicates an encroachment on the duramater; in such cases, several views are sometimes necessary to demonstrate these small defects; it may happen that only the myelo-CT will visualize these early lesions (Fig. 4). The detection of epidural metastases at the sacral level does not usually necessitate myelography, CT clearly demonstrating the neoplastic tissue within the fatty epidural space (Fig. 4).

The exploration of the cervical spine by *Magnetic resonance imaging* may be performed with a cylindrical head coil; in the thoracic or lumbar

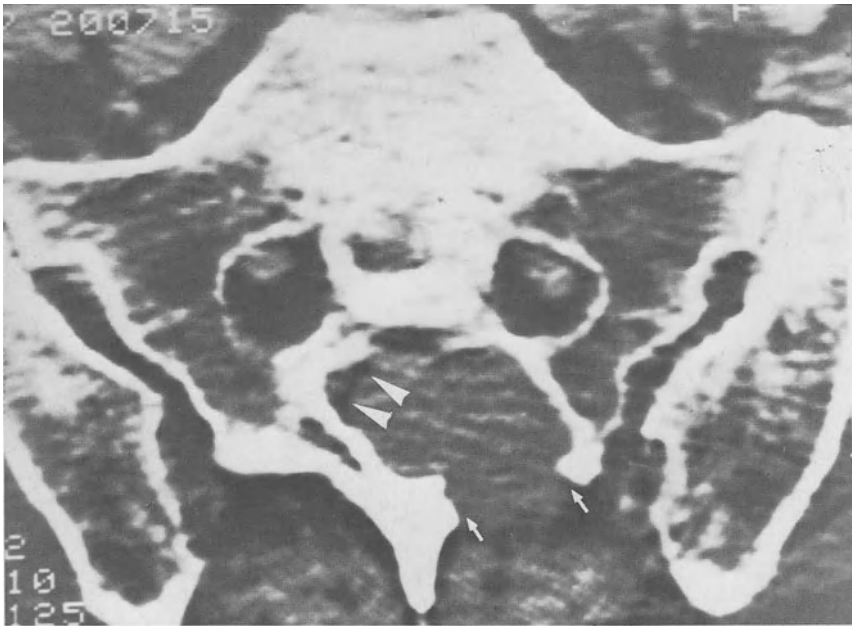
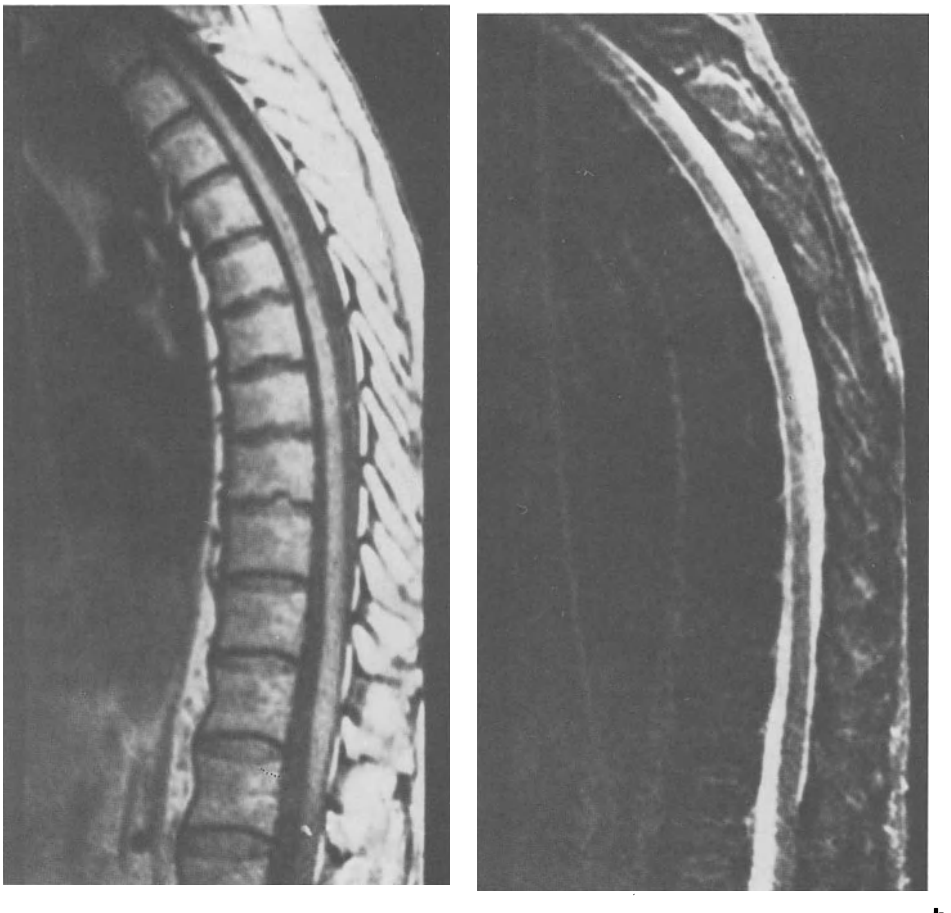


Fig. 4. Plain CT of the sacrum. Infiltration of the sacral epidural fat (arrowheads) and cortical effraction (arrows) by a soft-tissue mass (metastase of a breast carcinoma)

levels, surface coils are used. The technique T 1 weighted, reproducing a so-called anatomic image (Fig. 5 a), is adequate to demonstrate epidural compressive lesions; the tumour mass appears on these sequences as an area of intermediate signal; the adjacent bone infiltration is likewise well demonstrated (Fig. 6 a).

The advantage of sagittal sections lies in the immediate demonstration of the extent of the lesion. In a search for a small-sized lesion, it may be useful to complete the examination by a T2 weighted so-called pseudo-myelographic sequence (Fig. 5 b), on which the contents of the dural sac can be differentiated from the bone and ligamentous structures of the spinal canal. However the capacity of MRI to detect small lesions in the epidural space still has to be evaluated.

The differential diagnosis of epidural metastases from primary tumours of the spine or infectious lesions sometimes has to be considered (Lemort *et al.* 1986). The preservation of the disk in case of metastatic tumour must be underlined. A percutaneous needle biopsy, under radiological control, may be necessary. CT with intravenous injection of contrast solution generally allows differentiation of metastatic infiltrations from neurinoma and meningioma although the metastatic tumour could be also enhanced to some extent by the contrast medium[164].



a b

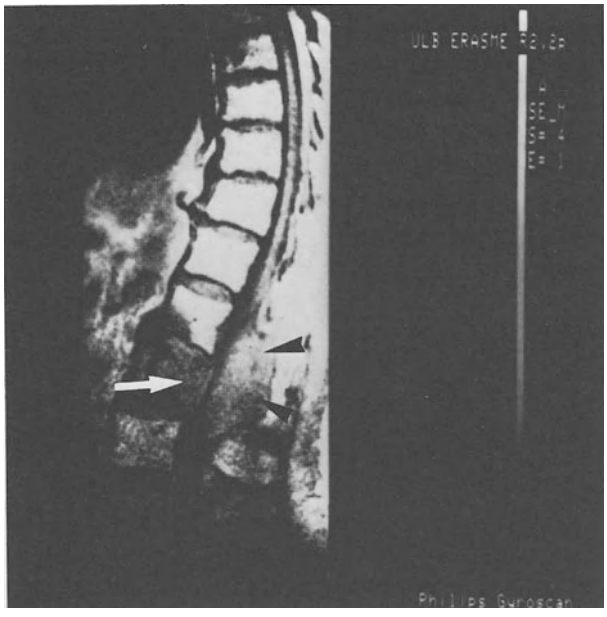
Fig. 5 a and b. MRI of a normal spinal canal with T 1 weighted (a) and T 2 weighted (b) sequences (SE 400/30 and SE 2000/150). Note the "anatomical" view of the spinal cord on the T 1-weighted sequence (a) and the "myelographic" aspect of the image on the T 2-weighted sequence (b)

An actual (1987) decisional algorithm for radiological work-up of epidural metastases is provided on Fig. 7.

Treatment

The therapeutic modalities currently in use for the management of epidural metastases include surgery alone or in combination with radiotherapy and/or chemotherapy, radiotherapy alone or followed by surgery and/or associated to chemotherapy, chemotherapy alone in particular diseases.

Although 30%[62] to 50%[138] of the patients with spinal and/or epidural malignancies may survive more than one year, their life expectancy nev-



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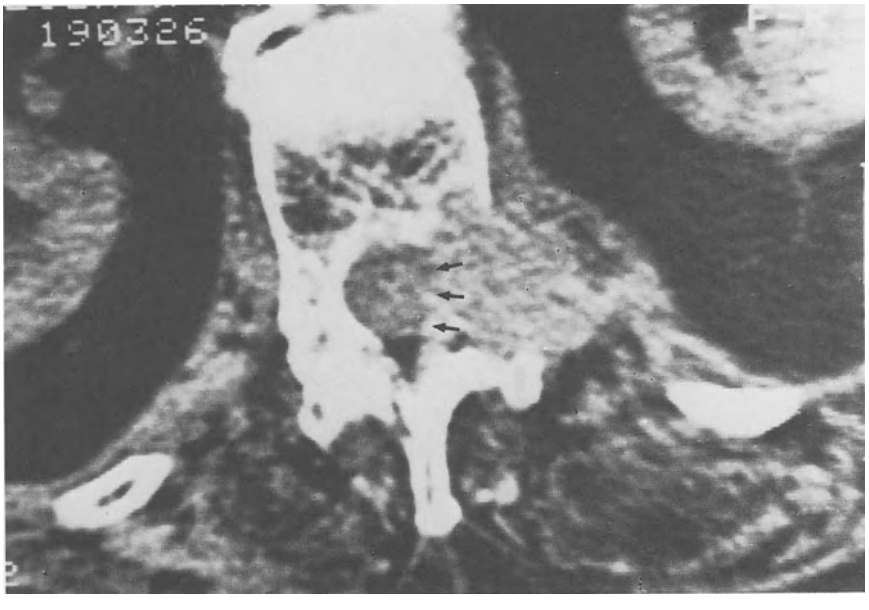


b

Fig. 6 a and b. Metastase of a thyroïd carcinoma. MRI (SE 600/30) (a) demonstrates large tumoural extension in the lumbar canal (arrowheads) as well as infiltration of the vertebral body of L 3 (white arrow). (b) CT (without myelography) at the level of L 2; lysis of right pedicle and epidural extension (arrows)

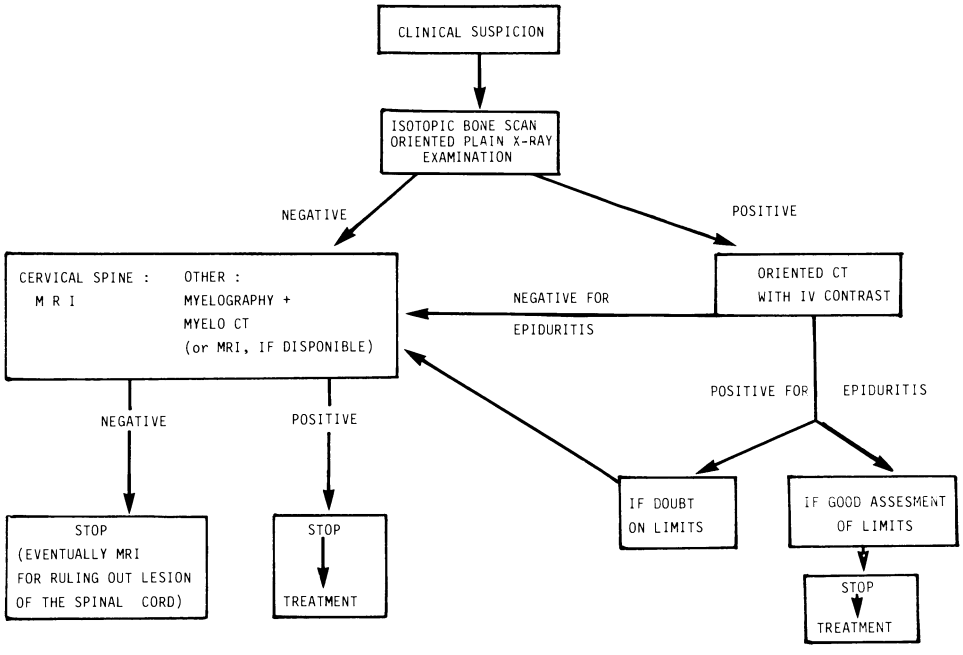


Fig. 7. Algorithm (1987) for the radiological work-up of epidural metastases

ertheless is limited and their medical condition poor. The final therapeutic strategy is to protect or to improve their quality of survival; the goal is to decrease vertebral and radicular pain, to preserve or improve neurologic function and to maintain or restore ambulation without rigid external support.

A. Surgery

Surgery can quickly obtain all these goals in selected patients by two combined means. Spinal decompression decreases congestive local pain and improves motor and sensory function, spinal stabilization minimizes vertebral pain, protects neural structures and improves ambulation.

Decompression and stabilization can be carried out simultaneously, at least partially, by either a posterior or an anterior approach to the spine. The technical possibilities and aspects of those approaches, and their precise possible indication considering the patient's general medical condition and the site and extent of the local malignancy must be considered.

I. The Posterior Approach

The common surgical technique[6, 8, 24, 64, 70, 188] consists of a laminectomy decompressing the spinal cord with removal of the epidural tumour as far

as necessary to obtain a pulsating dura mater. The bone removal has to be carried out at least one level above and one level below the vertebral lesion. The lateral extension of the bone removal has to be considered with regard to the stability of the spine, remembering that the vertebral body may be heavily eroded. The portion of the tumour ventrally located has to be approached very carefully and the surgeon must refrain from extensive too removal in order to avoid damage to the compromised spinal cord (Gilbert *et al.* 1978).

The extent of removal partly depends on the pathology of the tumour. For plasmocytoma for instance, resection of the tumour need not to be carried out beyond simple decompression of the spinal cord, seeing that this type of tumour is highly radiosensitive[22]. Consequently an intraoperative biopsy is mandatory as soon as the tumour is approached. In selected cases, a preoperative percutaneous needle biopsy may be performed.

It is not usual practice to open the dura and to divide one or two posterior roots to alleviate the radicular pain but such has to be considered in cases with severe very pain. The fear of subarachnoid seeding of tumour cells following opening of the dura mater is not supported by surgical experience. In all cases, decompression of nerve roots is mandatory, Livingston and Perrin (1978) crush the involved roots in patients with thoracic girdle pain.

Intraoperative difficulties mainly come from diffuse and sometimes severe bleeding which persists until sufficient tumour is removed, with the relief of venous stasis. In case of intraoperative bleeding difficult to control, Livingston and Perrin (1978) advise opening the dura and stitching the edges back over the wound margins in order to compress the residual tumour situated ventrolaterally.

Most often, the consequences of laminectomy on the undetermined stability of a spine infiltrated by tumour tissue is neglected. So, posterior decompression is rarely completed by a stabilization technique in the same operative stage while the anterior approach implies in itself decompression and stabilization.

a) Posterior Decompression

All along the spine, the same posterior approach can be used.

With the patient, in prone position, through a median skin incision, after subperiosteal dissection, the laminae are removed as required, following the longitudinal tumour extension, with a thin bite rongeur to decompress the spinal canal. Sometimes, facet removal allows decompression of the involved nerve roots. This maneuver increases vertebral instability, especially at cervical level.

The visible epidural neoplastic tissue is removed posteriorly and posterolateraly. Any spinal cord manipulation must be avoid; removal of

anterior and lateral tumour from this posterior approach without radicular section must be avoided.

After verification of a full longitudinal decompression of the spinal cord, the muscles are closed in the usual fashion without drainage. The advantage of covering the exposed dura mater by devascularized fat graft has not been demonstrated in man.

b) Posterior Stabilization

Through the same posterior approach, stabilization can be obtained by different means depending on the involved spinal segment[17, 68, 78, 118].

1. Cervical Level

Generally, surgery is easier when skeletal traction is placed before and maintained during the operation not only to achieve realignement in patients with cervical metastatic fracture-dislocation but also in all other cases.

1.1. Suboccipital Level

At suboccipital level, stabilization can be obtained by different methods even if a C 1 laminectomy is performed for relief of pressure on the cord. In those cases, the subperiosteal exposure should be extended from the occiput to the articular processes of the 3th and the 4th cervical vertebrae.

Using wires plus plastic, it is possible to stabilize the occipito-cervical junction[71, 126]. Two burr holes are made on each side of the midline about 3 cm superior to the foramen magnum. The dura is separated from the skull and an additional narrow hole for wire loops is drilled protecting the dura on each side near the burr holes. The heavy wires (10/10) are passed through these holes and are twisted around the spinous processes of C 2, C 3, and C 4. Wires are also passed beneath the intact lateral part of the C 1 neural arch and beneath the laminae of C 2. After covering the exposed dura with a layer of gelfoam for protection from the heat during polymerization of the plastic, all these materials are then encased in acrylic.

After C 1 decompression, it is also possible to perform suboccipito-spinal arthrodesis with an inverted Y plate[66, 67, 184]. After plate modeling, the material is initially screwed into the two articular processes of C 2 under direct vision (12 mm screw); great care must be taken to respect the vertebral arteries, the direction of the drilled holes for reception of the screws must be orientated 20° medially in the C 2 articular processes and pedicles. Then, the same screws are inserted in the articular processes of C 3 and C 4 as in the occiput.

The technique of bone grafting with a large segment of iliac cortex and cancellous bone, where an occipitospinal bone graft can be layed, after C 1

laminectomy, from the occiput to the decorticated surfaces of C 2 and C 3 laminae and fastened in place with wire loops[28] can be applied[20] to other cases than epidural carcinomatosis but, this method should be avoided because, following the short life expectancy of these cancerous patients, spinal stability must be immediate but also because associated corticoids and/or radiotherapy may induce failure bone fusion.

1.2. Lower Cervical Level and Cervicothoracic Junction

At lower cervical level and at the cervicothoracic junction, posterior stabilization after decompression for malignancy can be obtained by wires plus plastic[71, 154, 156] or by screwed plates in the articular processes[149]. Stabilization by rib grafts[138] is probably not so advisable in these conditions.

When wires and plastic are used, wires are passed around, or better, through the spinous processes of the two vertebral levels above and the two vertebral processes below the laminectomy site which is transversed by the wires crossing once or twice from one side to the other. This twisting adds strength to the wire-acrylic matrix[71]. The acrylic is then molded into position encasing the stainless material. Dura is protected by gelfoam and cement is irrigated by copious amounts of saline to cool the polymerizing methyl-methacrylate. During the placement of the cement, it is recom-

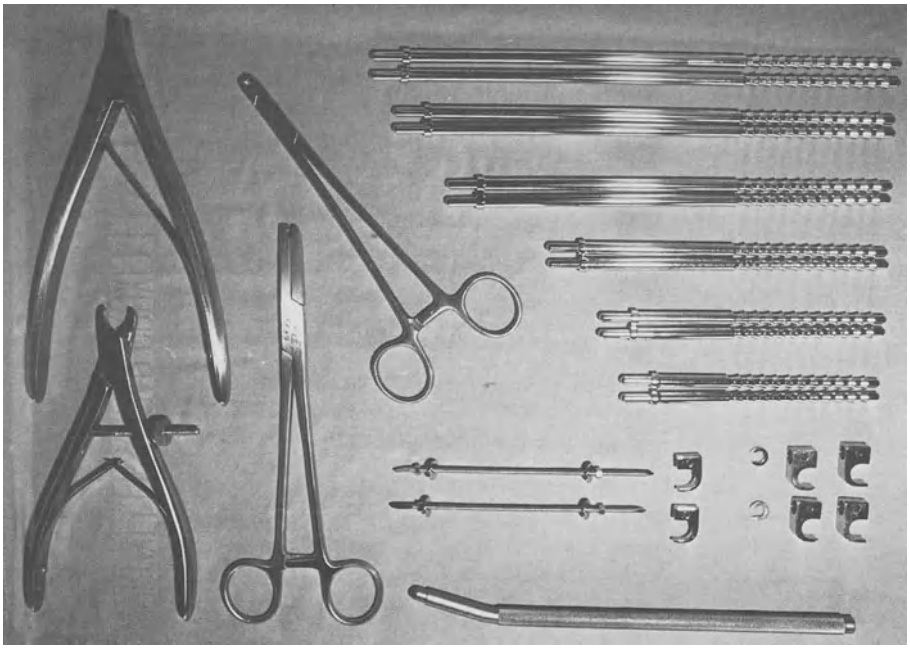


Fig. 8. Harrington's instrumentation for posterior spinal stabilization at thoracic, lumbar and lumbo-sacral segments

mended to leave the spinous processes exposed to a depth of 1 cm so that closure of the soft tissue will not be interfered with at a later stage[30, 156].

With plates screwed bilaterally in the articular processes, at least two levels above and below the laminectomy, the cervical spine can be stabilized. A multiperforated plate is molded on the articular processes on each side. With a slow drill, through the plate holes placed exactly in front of the middle of each articular process, a hole drilled is straight ahead, or slightly obliquely laterally (10°), through the articular process into the pedicle. If the drill is directed 30° caudally from this penetration point, the screw will be inserted across the joint space. It is mandatory that the holes for screw reception are drilled exactly in the center of each articular process, on the tip of their arch moulding. To prevent the drill from wandering, an impression is made before in the centre of each articular process by an awl.

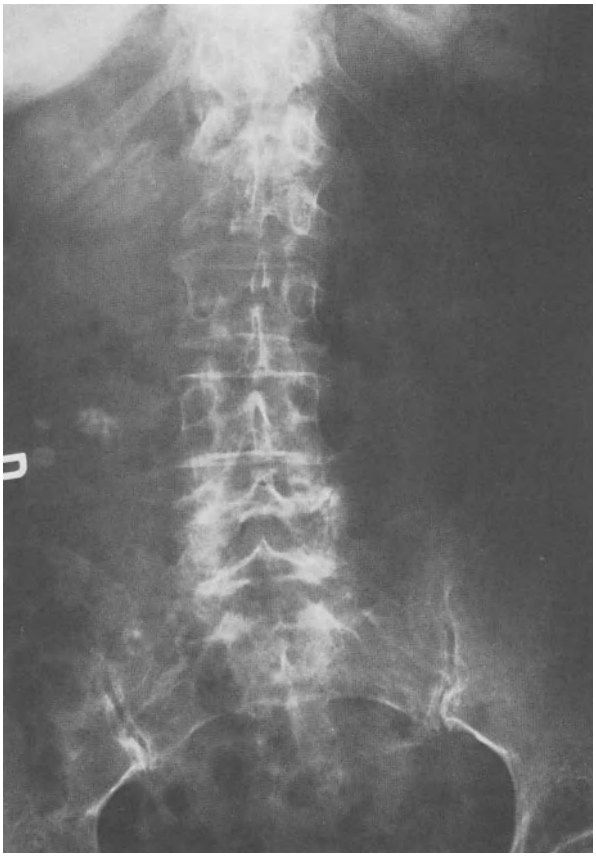


Fig. 9a

Fig. 9. Large vertebral infiltration (L 1, L 2, L 3) by a thyroid carcinoma. (a) plain X-rays, (b) stabilization with Harrington's rods

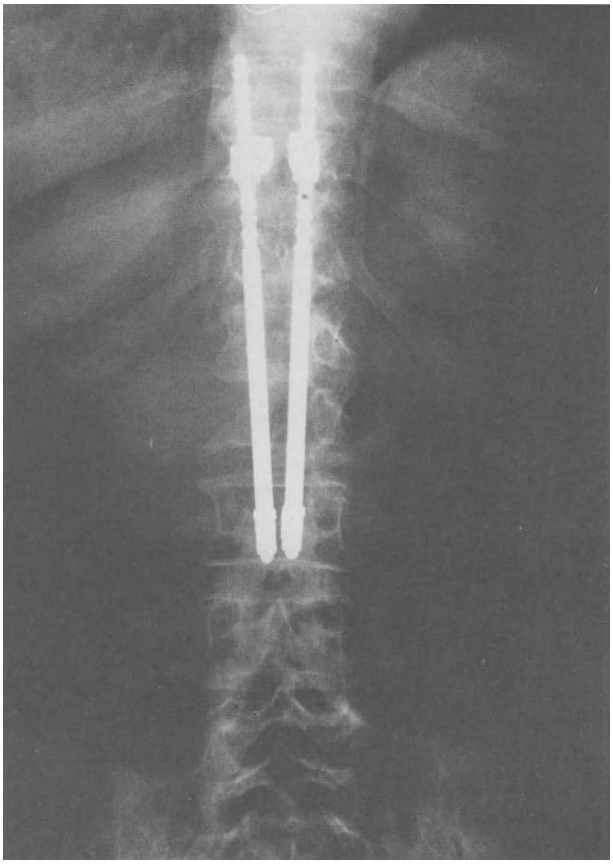


Fig. 9b

The direction of the hole can be controlled by direct vision through the laminectomy. It is useful to remember that the nerve roots lays in an other transversal plane corresponding to the inferior segment of the posterior joint space and that the vertebral artery is situated anteriorly and more medially.

Then, 14 mm length screws are placed in the articular processes to fasten the plates. If the articular process is infiltrated by tumour tissues, after curetting, the screw is placed and coated with acrylic.

2. Thoracic and Lumbar Levels

At thoracic and lumbar levels, spinal stabilization with Harrington's instrumentation[43, 72] is easy to perform. Symmetrically, on each side, a rod is placed between two hooks seated two levels above and two levels below the impaired spinal segment to exert a force of distraction inducing spinal extension and stabilization (Figs. 8 und 9a, b).

To place the superior hooks, it is useful to remove the spinous process of the selected vertebra and to cut a notch in the inferior lip of the most lateral part of the inferior articulation. The definitive hook is then pushed deep under the inferior facet of the vertebra. This down oblique seating of the hook is important to prevent secondary displacement. The bottom hook is seated on the superior laminar ridge of the vertebra. In order to make this area accessible, it is necessary to remove the superior border of the spinous process, to resect the ligamentum flavum and to make a notch in the lateral part of the superior border of the lamina by resection of the medial part of the articular process. An appropriate rod is first passed through the eye of the inferior hook. The rod is tightened to the desired length in a staggered fashion. The hooks and the end of the bars can be embedded in Methyl methacrylate.

At thoracic level, hooks with sharp edges can also be placed more laterally at the base of the transverse process through the internal costo-transverse ligament. In the lower lumbar region, it is recommended to place the inferior hooks not on the L 5 or S 1 laminae but more posteriorly and as far lateral as possible on a sacral bar perforating the two posterior and superior iliac crests.

Other rod patterns exist to stabilize thoracic and lumbar spine with

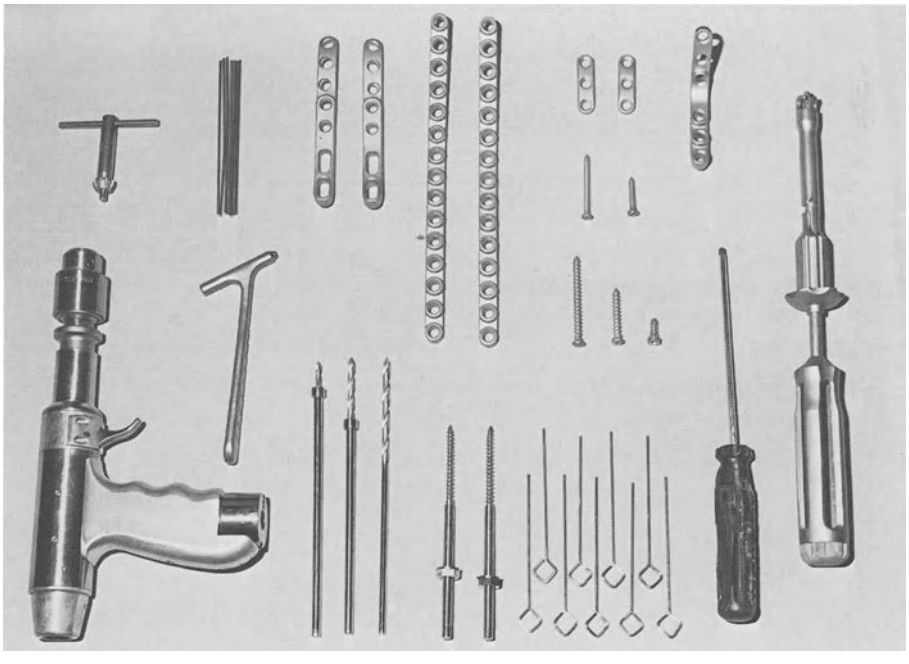


Fig. 10. Roy-Camille's plates for posterior spinal stabilization at sub-occipital cervical, thoracic and lumbo-sacral levels

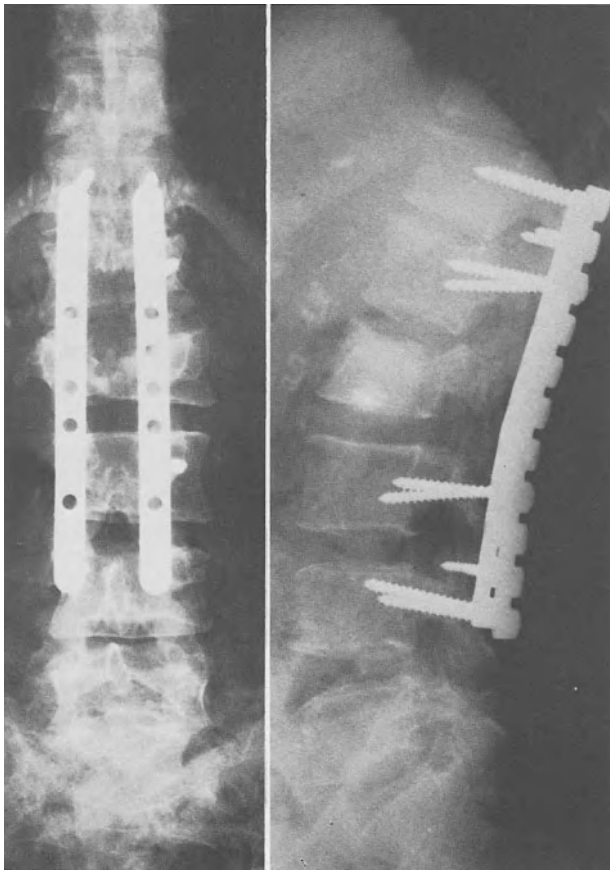


Fig. 11. Decompressive laminectomies and posterior stabilization with Roy-Camille's plates for prostatic spinal infiltration complicated by compressed fracture

malignant tumours as in the instrumentation of Luque[109]. On the other hand, the Knodt's bars[95] are frequently too short on tumorous spines.

Plates can be also used to immobilize the thoracic and/or lumbar spine through a posterior approach; Roy-Camille and co-authors[150, 151] have well described this technique (Fig. 10). It is preferable to use multiperforated plates with oval holes to be able to change the screw orientation rather than the original plates with regular rounded openings. The setting must be symmetrical and each plate must be screwed into at least two pedicles above and below the impaired segment(s) (Fig. 11).

The spinal periosteum is dissected away laterally until the base of the transverse process is exposed at the different levels. A lateral X-ray is made to demonstrate the sagittal orientation of the pedicles. The plate is moulded on the articular processes on each side. Screwing into the pedicle is per-

formed as follows. An impression is made with a pointed instrument 1 mm below the inferior joint plane exactly in the prolongation of the vertical part of this plane; generally there is a little ridge on that point that is the precise projection of the pedicle. Moreover, this point is on the transverse plane of the transverse process controlled by direct vision. Then, through the plate holes, with a slow drill, a hole (3 mm diameter) is drilled through the pedicle. The twist bit is directed straight ahead or 10° laterally and, in the sagittal plane, following the X-ray, anteriorly, vertically or caudally. Pins are pushed in the hole and, with a new lateral X-ray, their positions in the pedicles are checked. The plates are fixed with pedicular screws 50 or 52 mm length (3.2 mm diameter). At sacral level, to respect the S 1 nerve root, the holes are drilled 45° caudally and 45° laterally from a dimple located on the sacrum just underneath and outside the L 5-S 1 articular process.

3. Comments

The posterior approach with decompression by laminectomy involves a standard technique applicable throughout the length of the spine and permits without important dissection, rapid extension of the decompression over several segments as is often required[132]. The tumorous tissue posterior and posterolateral to dura can be easily removed. Moreover, laminectomy can be made safely patient's in poor general condition.

On the other hand, as spinal cord manipulation must be avoided, from this posterior approach, it is difficult, dangerous and contraindicated to remove tumour located anterior to the spinal cord, a frequent localisation for metastatic proliferation[5, 10, 62, 178]. Decompression by posterior approach may be partial and limited in many cases. According to different authors[101, 133, 192] this approach can increase the risks of postoperative neurological deterioration when the metastasis is placed anteriorly. Moreover, in such cases, surgical resection is impossible through a posterior approach and the patients keep the tumorous tissue, while an anterior approach permits tumour resection. One can assume that the remaining tissue can play an immediate role on pain relief and delayed consequences on the local long term evolution of the malignancy.

The rate of postoperative neurological worsening after isolated laminectomy is about 22% in recent series (Table 11). This could be related to poor neurological condition of those patients, to the frequent anterior location of the metastasis and to spinal instability induced or aggravated by a laminectomy performed in such conditions. This latter factor, which is frequently invoked[5, 90, 115, 116], could, at least partially, explain the low rate of neurologic worsening reported after laminectomy plus posterior stabilization (Table 12).

Table 11. *Results After Spinal Cord Decompression by Posterior Approach (Laminectomy)*

Authors	Number of cases ()*	30 day mortality number* (%)	Morbidity number (%)	Neurologic worsening number (%)	Motor improvement† number (%)
Levy *et al.* 1982	39 (5)[x]	3/39 (8%)	unknown	8/32 (25%)	—††
Nather *et al.* 1982	39 (1)*	0	unknown	unknown	12/39 (30%)
Siegal and Siegal 1985	25 (2)*	2/25 (8%)	5/25 (20%)	5/25 (20%)	9/25 (36%)

()* Number of cervical approach in the series.
† Very difficult estimation because the adopted criteriae for evaluating the results are different following the authors.
†† All patients are walking preoperatively in this series.

Table 12. *Results After Spinal Decompression and Stabilization by Posterior Approach*

Authors	Number of cases ()*	30 day mortality number (%)	Morbidity number (%)	Internal fixation failure number (%)	Neurologic worsening number (%)	Motor improvement number (%)
Perrin *et al.* 1980	20† (10)*	1/20 (5%)	2/20 (10%)	1/20 (5%)	0	18/20 (90%)
Lesoin *et al.* 1982	11	1/11 (9%)	1/11 (9%)	1/11 (9%)	0	9/11 (82%)
Sundaresan *et al.* 1984	19††	1/19 (5%)	4/19 (36%)	1/19 (5%)	0	12/17 (71%)

()* Number of cervical approach in the series.
† No laminectomy in two cases.
†† Three primary osseous tumors of the spine are included.

Hansebout and Blomquist[71], reported that the stability obtained with acrylic plus wire is very effective; they did not observe any case of late instability. However, after posterior methylmetacrylate stabilization for cervical metastatic lesions, Dunn (1977)[48] observed two failures of fixation; he concluded that posterior acrylic stabilization should be used only in patients with minimum vertebral body collapse. Different biomechanical studies have demonstrated that bilateral Roy-Camille's plate or Harrington's rods ensure the same spinal stability in experimental conditions[89]. With these two instrumentations, it is possible to maintain a distraction between the vertebral segments and a force that increases the stability and reduces any localized body collapse. Probably, non distraction instrumentation such as the Luque's system cannot offer similar resistance to bending and to rotational forces[43]. The clinical method of Harrington's rods is easier, faster and not so haemorrhagic as the one of Roy-Camille; however, sometimes, its utilization may be contraindicated by a pathological weakness of the neural arches. As for fractures[16, 46], the failure rate of such internal posterior stabilization in metastatic spine is about 10% (Table 12). While the series of isolated laminectomy and those of laminectomy plus posterior stabilization are not comparable, one must point out that the results obtained after laminectomy associated with posterior stabilization are very encouraging and extremely similar to those reported after anterior decompression and stabilization.

On the other hand, the posterior approach involves dissection through previous or subsequent radiotherapeutic fields; this can induce wound dehiscence and instrumentation infection with loss of stability.

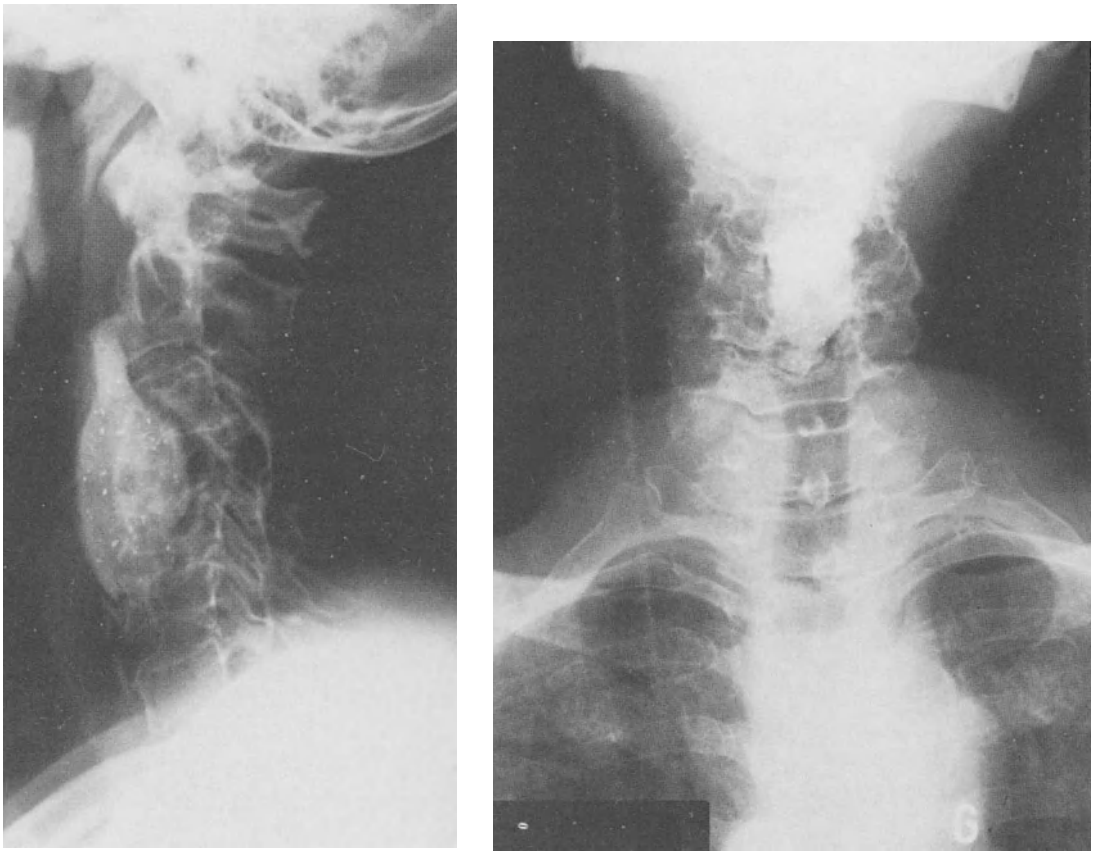
II. The Anterior Approach

Through an anterior or an anterolateral approach, decompression of the neural structures is achieved after a partial or total resection of the vertebral body. Without peroperative stretching of the spinal cord and of the roots, it is possible to remove metastases placed anteriorly in the vertebra and/or in the epidural space.

Replacement of the resected bone is necessary and, as it is very difficult to determine the real spinal stability, instrumental reinforcement by internal fixation is used in all cases. Moreover, this instrumentation keeps the replacement material in place. Practically, through an anterior approach, decompression and stabilization are always associated.

a) General Technical Considerations

The initial dissection of the tumorous vertebral segment(s) is begun from noninvolved vertebrae above and below the lesion. Decompression of the



a b

Fig. 12. Plasmocytoma of C 3, C 4, and C 5. No neurological deficit but instability of the cervical spine. In-lay of methylmetacrylate graft before radiotherapy, seen on lateral (a) and A.P. (b) views

spinal cord is undertaken by gently removing all visible tumour down to the posterior longitudinal ligament and to the epidural space. Curettes, rongeurs and high speed drills are used. The importance of a complete tumour resection has been pointed out by different authors[29, 74, 160, 172]; unresected tumorous infiltration may induce failure secondary stabilization. The residual disc material is also resected and the endplates of the adjacent vertebrae are grooved to enhance fixation of the cement. Bleeding from the spongy bone, from the epidural venous plexus and from the tumour is decreased by absorbable hemostat, free graft of fat or of muscle, light compression and, if necessary, hypotension. To minimize intraoperative haemorrhage, Sundaresan *et al.*[172] propose preoperative angiography and embolization if profuse hypervascularity is demonstrated.

Following tumour resection which frequently implies removal of more than one vertebral body[26, 74, 160, 172], replacement and stabilization are considered[41, 73]. Methymetacrylate is probably the best material replacement for the resected spinal segments (Fig. 12). It affords an immediate stability uninfluenced by radiation and/or chemotherapy. If an autologous bone graft is used[36, 55, 63, 121, 138], these adjuvent treatments may induce not only delayed fusion but also an osteo-porosis of the graft[73]. Before cement insertion, to keep it in place, pins or more sophisticated materials must be inserted through the resected segment into the two adjacent vertebrae while the normal vertebral space is restored using a laminar speader and/or skeletal traction (which may be initiated before surgery in cases of associated fracture-dislocation) to achieve realignement. At cervical level, this material may be pins placed in holes drilled in adjacent vertebrae[29, 31, 172] or AO plates[124] screwed in healthy vertebrae above and below. In thoracic and lumbar segments, for limited univertebral resection, pins are sufficient; for large resection of more than 50% of the vertebral width or of two or more adjacent vertebrae, spinal instability is assumed[160] and use of Knodt rods[74] or of Moe hooks fitted on sacral Harrington bars[160] is indicated. Harrington[73] employs his standard rods anteriorly between the 10th thoracic and the 4th lumbar vertebrae after a very large resection.

It is also possible to lie a long Roy-Camille plate[149] between the two intact vertebrae, the screws in the defect being secondarily incorporated in the cement. So there are different instrumentations to reinforce the acrylic; perhaps, rods have the advantage to achieve an anterior distraction to prevent future kyphosis.

After irrigation of the decompressed area to dislodge free fragments and blood clots to improve acrylic anchorage, care is taken to protect the dura with a layer of gelfoam[172] or fat graft[160] or muscle. Then, Barium impregnated radioopaque cement is instilled in the defect taking care to prevent any acrylic protusion into the spinal canal and is layed around the material to incorporate it in the mass. During polymerisation, a constant saline irrigation avoids adverse thermal effects on neural structures.

b) Specific Anterior Approaches

1. Cervical Level

At C 1 and C 2 level, spinal malignancies may induce not only spinal cord compression but also instability; a C 1–C 2 instability may prove difficult to manage by the anterior transoral approach[54, 134]; posterior approach is preferable. At lower levels, the anterior approach is standard and well codified[39, 146], using a relatively large incision along the anterior border of the sternomastoid muscle allowing exposure from C 3 to Th 1 or upper

part of Th 2. It is easier and safer to do this procedure with head traction when resection of a vertebral body is the surgical goal.

2. Upper Thoracic Level (Th 1 to Th 4)

The approach to the vertebral bodies of the upper thoracic vertebrae may be made either by a costotransversectomy[27, 82, 130] or by a transsternal way[170].

With the patient in the prone position, slightly tilted away from the surgeon, the costotransversectomy is done through a paramedian incision outside the paravertebral mass and centered on the first thoracic vertebrae. It may be done from either side depending on the vertebral involvement. The paravertebral muscles are retracted medially. By instrumental dissection the external rib periosteum is opened and the internal surfaces of the ribbs are separated from the subjacent endothoracic fascia and parietal pleura. The ribs are resected and the pleura reflected forward.

After section of the costotransverse capsular ligaments, the heads and necks of the ribs are removed. Then, the vertebral periosteum is divided and the intercostal vessels are clipped and cut to give access to the tumour. To close the wound, the muscle layers are approximated with interrupted sutures. Chest drainage is not necessary if the pleura is intact.

Because the access to the vertebral bodies by costotransversectomy is limited, Sundaresan *et al.* (1984) describe a transsternal approach to the first thoracic vertebrae. A T shaped skin incision is made with the vertical limb extending over the superior third of the sternum and the transverse part one cm above the clavicles. The right lower insertion of the sternomastoid muscle is divided and reflected upward. The internal third of the right clavicle and the manubrium are resected. By digital dissection between the vessels laterally and the trachea with esophagus medially, an avascular plane is developed to enter the prevertebral space. During this manoeuvre, care must be taken to protect the recurrent laryngeal nerve which lies across the field from lateral subclavian artery to medial larynx. The wound is closed in two layers after reattachment of the sternomastoid muscle to the first rib and the pectoralis major.

3. Median Thoracic Level (Th 3 to Th 10)

For anterior approach to vertebral bodies in the middle thoracic area, a posterolateral thoracotomy is necessary[15, 81, 105]. The patient is placed in a lateral position, depending as to side on the site of the vertebral tumour. Endotracheal collapse of the lung gives better exposure. Through a curvilinear posterolateral incision behind and underneath the vertebral border of the scapula, the superficial muscles are divided. To avoid the scapular

wing, the serratus anterior muscle must be severed along its costal insertion far away from its nerve supply. The periosteum of the rib is removed and the pleura is opened. A self retaining rib retractor provides a good exposure which may be improved by a posterior rib transsection without resection. The mediastinal pleura is divided longitudinally over the involved vertebra and the intercostal vessels are ligated and divided. After decompression and stabilization, the pleura is sutured, the rib cage is approximated by three pericostal silk sutures and the muscles are closed. Pleural drainage is performed.

4. Thoracolumbar Level (Th 11 to L 2)

For this area a left thoracoabdominal approach is necessary[15, 105]. The left side of the flank is elevated. Through a thoracoabdominal incision overlying the 10th interspace, continued across the costal arch and the musculature of the anterior wall, the chest cavity is opened and the peritoneum is peeled of the undersurface of the diaphragm by blunt digital dissection and by moist cotton patties. At that level, costal excision is not necessary; adequacy of the exposure may be obtained by a self retaining rib retractor. Blunt dissection is prolonged below in the retroperitoneal fat to displace the intact peritoneum with the abdominal viscera and the kidney toward the midline. The diaphragm is detached from the spine about one inch from its costal insertion to preserve its innervation. The posterior mediastinal pleura overlying the vertebrae and the spinal diaphragmatic insertion are incised lengthwise with a scalpel to expose the vertebral bodies. The segmental vessels are easier clipped than ligated. Their sections are accomplished well proximal on the anterolateral side of the vertebrae to respect more lateral vascular anastomosis and to avoid any impairment of the poor radicular vascularisation supplying the spinal cord at that level. After tumor resection, stabilization and vertebral replacement, the diaphragmatic pillar, the mediastinal pleura, the diaphragm and the abdominal wall are approximated with interrupted sutures. Pleural drainage and a nasogastric tube are maintained.

5. Lumbar Level (L 3 to S 1)

There are two different approaches to the lumbar vertebral bodies: transabdominal or retroperitoneal[15, 81, 105]. The former must be avoided because the abdominal viscera are difficult to retract and the great vessels mask the spine. Moreover, median dissection of the periaortic plexus frequently induces impotence. For the retroperitoneal approach, the selected side, depending on the tumour extension, is elevated. Through an oblique skin incision, the abdominal muscles are incised and retracted in the direction

on their fibers. The opening of the transversus abdominis is begun laterally to lessen the possibility of peritoneal opening. The transversalis fascia is severed by scissor and by blunt digital dissection or by mounted damp swab sticks in the retroperitoneal fat, the peritoneum and its viscera are displaced medially with the ureter to expose the anterolateral border of the spine. Periosteum is incised and the lumbar vessels are clipped or coagulated. With gentle dissection, vena cava aorta and iliac vessels may be retracted to expose the affected vertebral bodies for resection and fixation. The different muscular layers are approximated with interrupted sutures without drainage. Nasogastric tube drainage is necessary.

6. Comments

With an anterior approach, it is possible to obtain an anterior decompression at any spinal level without spinal cord traction. The majority of epidural tumours arise in the vertebral body and invade the epidural space anteriorly[10, 62]. In those cases, the anterior approach can provide adequate decompression of the cord. The anterior approach may be planned after the demonstration by radiological means of an anterior situation of the malignancy.

This anterior decompression implies body replacement and spinal stabilization which is either a preventive or a necessary measure. Siegal and Siegal[160] assume that the immediate stabilization of the spinal column substantially contributes to their exceptional overall good neurological results after anterior decompression: they report that only 2% of their preoperative paraplegic patients remain non ambulatory! It is very difficult to define the potential instability after tumour resection. For instance, Dewald *et al.*[44] think that exclusive acrylic replacement anteriorly with instrumentation is not sufficient when there is marked destruction of the pedicles or there are several adjacent segments collapsed; in those cases combined posterior fixation should be necessary. Indeed, Harrington[74], Siegal and Siegal[160] and Sundaresan *et al.*[172] report after isolated anterior stabilization secondary displacement of fixation material. So, as for fractures, the diagnosis of clinical instability before surgery and more over after anterior surgery may be difficult to make and its optimal therapeutic classification remains to be established.

Vertebral body resection seems to be a formidable procedure involving the use of different specific approaches for each spinal segment. It requires more technical expertise in general and orthopaedic surgery. However, in the reported large series of anterior approach for spinal malignancy with body resection and replacement, mortality and morbidity rate is low as is the rate of neurological deterioration; moreover, there is a remarkably high degree of neurological improvement (Table 13). Sundaresan *et al.*[172] point

Table 13. *Results After Vertebral Body Resection and Stabilization by Anterior Approach*

Authors	Number of anterior approach ()*	30 day mortality %	Morbidity % +	Internal fixation failure %	Neurologic worsening % + +	Motor improvement %
Harrington 1984	52 (26)	8	12	12	2	78% 29/37
Siegal and Siegal 1985	61 † (2)	7	12	7	8	75% 46/61
Sundaresan *et al.* 1985	101 ††	8	10	9	0	69% 59/78

()* Number of cervical approach in the series.
† 5 primary osseous tumours of the spine are included.
†† 9 primary osseous tumours of the spine are included.
+ General and local morbidity.
+ + Immediate and early impairment.
/n Number of preoperative neurologic motor impairment.

out that the best results are obtained with "de novo" treated patients and they assume that early surgical treatment prior to radiation therapy is mandatory. On the other hand, by the anterior approach, one can probably avoid substantial morbidity related to wound healing since the operative incision lies outside the irradiated field[160, 170].

To reinforce the encouraging results with anterior decompression of the spine for epidural malignancies obtained by some authors[74, 172], Siegal and Siegal[160] compare the treatment results between vertebral body resection and laminectomy. They conclude that anterior decompression seems preferable for ventrally located tumours. However, in their series, the percentage of patients with poor preoperative neurologic status is greater in the laminectomy group than in the anterior resection group. It is impossible therefore to compare the results of the different surgical approaches. Nevertheless, one must point out that the results after decompression systematically associated with stabilization are very similar following anterior or posterior approach and are superior to those obtained after simple posterior decompression (Tables 11, 12, and 13). Probably, spinal stabilization is an important goal in the general surgical strategy of such patients.

B. Radiotherapy

In our practice, when treatment consists of surgery followed by radiotherapy, the radiation is usually started two weeks after surgical decompression. Nevertheless, radiation may be started earlier but the beam set-up should avoid, as far as possible, a recent midline incision made for the posterior approach.

When the first step of treatment consists of radiotherapy alone, or associated with chemotherapy, radiation is started as soon as the myelography with or without CT has confirmed the clinical diagnosis and defined the level of spinal cord compression. The radiation field includes classically the level of the block with a safety margin above and below of two vertebral bodies. The treatment is usually carried out with one single posterior field but can be modified according to each individual patient and particular problems: Thus if the spinal cord compression is due to a paraaortic lymph node growing through the intervertebral foramina, parallel anterior and posterior fields are used to deliver a more homogeneous dose to all the tumour extent.

The total dose delivered varies depending on the fractionation schedule from 30 to 45 Gy in 2 to 4 weeks. The dose should be high enough to relieve patients symptoms but without inducing permanent and irreversible damage to the spinal cord[133, 144, 186]. This total dose has also some influence on treatment results[103, 60]: in a series of lymphoma, Friedman *et al.*[59] observed a response rate of 71 percent for doses in excess of 25 Gy compared to 34 percent for lower doses.

Controversies remain between proponents of initial high doses of radiation (4 to 5 Gy), conventional daily doses (2 Gy) or even lower initial doses (less than 2 Gy)[91, 152, 180]. High initial doses of radiation allow more rapid cell kill, a tumor reduction and then a faster relief of the spinal cord compression. On the other hand some radiotherapists advocate small fractions to avoid inducing oedema and aggravating patient symptoms. In a series of animal experiments carried out on rats with a transplantable lymphoma, Rubin[152] has shown a better response after 3 fractions of 5 Gy compared to 10 times 1 Gy without aggravating spinal cord compression. Similar results were reported by Ushio *et al.*[180]. Clinical experience has also shown the possibility of delivering high daily doses without inducing more symptoms and with a more rapid response: the mean time to achieve response was 98 hours of lymphoma treated with initial high daily doses compared to 160 hours after a conventional schedule with a 2 Gy daily dose[155]. Today, there are no randomized trials to demonstrate the superiority of one radiation schedule but the necessity to obtain a response quickly may favour the use of high initial dose.

One problem when treating patients with spinal cord compression is possible relapse either within or outside the treated volume. The limited tolerance of the spinal cord to radiation (45 Gy in 4.5 weeks) prevents the possibility of a second radiation and requires avoidance of a possible overlap with a prior treatment field. In a retrospective review of 80 patients treated with radiation, twenty one (26.3%) presented a relapse outside the original treatment field. Multiple spinal cord compressions are also not uncommon: 38 out of 78 patients in the Tomita series had more than one site of compression. Multiple spine metastases are common with breast and prostatic cancers[75].

Some have advocated treatment of the whole spine to prevent the possibility of multiple lesions and field overlapping[51]. Hemibody irradiation has been used especially in presence of wide spread bone metastases. This possible advantages needs to be balanced with the acute toxicity and induced myelosuppression. Extensive areas of bone marrow are included in the irradiation field limiting the possibility of a further chemotherapy program. If an active combination is still available, we may prefer to restrict the volume to be irradiated.

C. Chemotherapy

1. Corticosteroids

The well-documented therapeutic effect of corticosteroids on cerebral tumours, particularly on brain metastases, induced clinicians to try them for spinal metastases. The effect of dexamethazone is marked on metastases, with a simultaneous decrease in oedema volume, tumour volume and con-

trast enhancement. The decrease in the tumour volume could be due to inhibitory effect of dexamethazone on the tumour growth (Hatam *et al.* 1983).

Cantu (1968) reported two cases of carcinoma, one endometrial, the other ovarian, with epidural metastases. He observed a rapid and striking improvement of neurological disturbances after treatment with methylprednisolone, one intravenous injection of 40 mg and thereafter 40 mg intramuscularly. Clarke and Saunders (1975) also reported two cases of reticulum cell sarcomas treated with prednisolone; rapid improvement in neurological status was observed.

Posner *et al.* (1977) had a similar experience with 4 patients: one case of mixed lymphoid and epithelial thymoma, a second case of seminoma of the testis; a third patient with Ewing's sarcoma; a fourth of mixed lymphoma. They emphasized the oncolytic effect of glucocorticoids as well as the rapid relief of pain after the onset of steroid therapy.

Ushio *et al.* (1977) working on an experimental model of spinal cord compression in rats injected with carcinoma cell suspension to the T 12 or T 13 vertebral body, observed a marked and immediate but transient improvement of weakness in animals treated only with dexamethazone; this therapeutic effect was more especially marked when the animal was still able to stand and not yet suffering from a severe weakness of the four limbs. None of the animals treated when they were paraplegic regained useful motor function.

Although corticosteroids are considered as a specific chemotherapy for lymphomas, Slatkin and Posner (1983) treat all patients having epidural spinal cord compression with 100 mg of dexamethazone intravenously; after this initial bolus, while other therapy is being instituted (Greenberg *et al.* 1980), they give by oral administration 96 mg of dexamethazone a day, halving the dose each 2–3 days if the patient stabilizes or improves.

Complications could be expected if steroid therapy is maintained at a high dosage too long, mainly if patients have previous gastrointestinal disorders[112].

Stark *et al.* (1982) did not find a difference when comparing the outcome in patients treated with and without corticosteroids either in terms of immediate response to treatment or ability to walk at six months.

Nevertheless, even if better controlled studies are requested for evaluating the oncolytic activity of steroid therapy, we have personally observed that, at least, corticosteroids may produce effective pain relief. Therefore we do agree with Posner[140] that, *concurrently* with other therapeutic approaches, epidural metastases have to be promptly treated with corticosteroids.

A randomized prospective clinical assay of corticoids in the treatment of epidural metastases is presently underweight in the department of Med-

icine of the Institut Bordet (Tueni *et al.*); it consists of two series, one of radiotherapy + dexamethazone, the other of radiotherapy + placebo. The results will be published later, after completion of the study.

2. Chemoembolization

Specific chemotherapy has to be added to surgery or radiotherapy if the histological make-up of the tumour suggests the utility of such treatment. It is not our purpose to develop the various aspects of chemotherapy. However we would like to draw the reader's attention to the recent technique of chemoembolization.

As stated by Courtheoux *et al.* (1985) in a recent paper, "the purpose of chemoembolization is to combine the analgesic effect of ischaemia with the cytotoxic effect of antimitotic drugs delivered in situ".

In case of vertebral metastases, the technique of injection in situ is that of selective vertebral angiography. The drug used by Courtheoux *et al.* was microcapsules of mitomycin C, the cytotoxic activity of which is potientiated in hypoxic tumoural cells. In a few patients, Adriamycin was also injected. It is too early to evaluate the long term results of chemoembolization in vertebral metastases. The rapid effect of the drug on pain and motor deficit which was observed by Courtheoux *et al.* in some patients suggests that chemoembolization could be a valuable adjuvant to therapy in the future.

Discussion

The therapeutic results obtained by one or another technique, applied alone or in combination, are difficult to appreciate, so various are the factors which affect the outcome: histological type of the tumour, patient's neurological and clinical grading, level and characteristics of the vertebral lesion, rapidity of the clinical evolution. The comparison often made between series of patients only operated on, only submitted to radiotherapy, or only treated with corticoids, is worthless in most cases. When such comparison has been made, the patient groups were inhomogeneous and incomparable concerning their general condition, the nature and the extension of their primary tumour, their neurologic impairment and their prior local and general treatments. However, since animal experiments have found no advantage from surgery with radiation as compared with radiation alone[160] and since clinical reports have suggested that the results of radiation alone are equal to those of surgery plus radiation[62, 142], it is generally assumed that surgery is only advisable for patients who have epidural tumours of unknown origin, for well known radioresistant tumours, for spinal relapse after previous radiotherapy or when the disorder

progress during therapy[147]. On the other hand, some recent data not only reinforce the advantages of an early surgical "de novo" treatment[172] but also suggest that, as time passes, the patients submitted early to surgical treatment are more likely to preserve their ability to walk than those treated by radiation[101]. At the present time, with advances in anesthesia and in surgery, mainly in spinal stabilization methods, the indications for surgical treatment of metastic epidural tumours are probably larger than the classical ones.

With regard to radiotherapy alone, the nature of the primary tumour is certainly a factor far more important than for surgery. Myeloma, lymphoma, seminoma are highly responsive to radiation whereas melanoma, sarcoma and kidney tumours are considered to be radioresistant. The more encouraging results are observed among patients with highly sensitive tumours to radiation: one patient out of two with a spinal cord compression due to a lymphoma or a myeloma recovers sphincter control or is able to walk after treatment (Table 14)[23, 59, 62]. The wide range of response observed in different series reflects patients selection: in the Tomita series including only patients with a complete block, the best results were achieved with prostatic cancer, 8 out of 10 patients being ambulatory after treatment, compared to only 11 out of 21 women with breast cancer and only 2 out of 8 patients with a radiosensitive tumour such as lymphoma; in fact, the later group included 5 paraplegic patients. Results appear to be identical for the two types of treatment regardless of tumour type[62, 128].

The rapidity and the severity of onset of motor dysfunction directly influence both treatment results, surgery and radiotherapy. The probability of recovering a normal neurological status decreases with the severity of

Table 14. *Response Rate According to Tumour Type and Treatment*

	Bruckman**	Gilbert		Tomita*
		RT	Surg. + RT	
Lymphoma	76/147	4/5	2/3	2/8
Multiple myeloma	20/40	3/5	3/3	
Breast	26/79	17/26		11/21
Prostate	11/35	2/8	1/5	8/10
Lung	14/101	8/16	1/5	5/11
Kidney	2/21	6/10	0/2	5/16
Melanoma		1/5	0/2	

* Only complete block.

** Pooled data from 5 series treated mainly by Surg. and RT.

Table 15. *Influence of the Neurological Status Before Treatment on the Possibility of Ambulation After Radiation + Surgery*

	Neurological status pretreatment		
	Able to walk	Paraparesis	Paraplegia
Nubourg *et al.*	85%	43%	0%
Tomita *et al.**			
Slow progression	74%	14%	
Rapid progression	42%	9%	0%
Bruckman *et al.*	60%	35%	7%
Gilbert *et al.*	75%	44%	5%

* The series included only patients with complete block.

symptoms: in our own experience, none of the 16 paraplegic patients was able to walk two months after treatment compared to 21 out of 25 ambulatory patients (Nubourgh 1985). Gilbert *et al.* observed the same influence of the neurological status before treatment among patients with tumours considered to be sensitive or not to radiation. In the experience of Tomita *et al.*, slowly progressive symptoms are associated with a higher recovery rate than rapidly developing deficits (Table 15). This observation recalls the animal experiments carried out by Tarlov: in the case of acute and severe injury, recovery was only possible if the compression was relieved within hours but when the paralysis was induced over two days, it could be reversed by treatment within a week.

The comparison of a series of patients having the same primary tumour may give a better comparison of the modalities of treatment. Cobb *et al.* (1977) have analyzed a series of 44 patients with breast cancer: 26 were initially operated on, 12 of them receiving no postoperative radiotherapy, 18 patients were treated with initial radiotherapy. The two groups were rather homogenous, although the initial radiotherapy group was somewhat favored in an analysis of ability to walk. The conclusion of this study was that the two groups did not differe significantly in their outcome.

In 1982, we made the analysis of 21 cases of vertebral plasmocytomas[22]. One patient was only irradiated with a fair clinical result but this patient had no neurological deficit and only presented an osteolytic lesion of the spine with a block on myelography. Two other patients who presented a slow progressing paraparesis were initially irradiated but after 2 or 3 days of treatment, worsening of the paraparesis prompted us to operate. The other patients were initially operated on and thereafter were irradiated: gratifying results were obtained in 8 patients, a partial improvement was observed in 4 cases and no improvement in 4 cases; a postoperative ag-

gravation was noted in one patient. The analysis of this series is in favour of initial surgical decompression followed by irradiation.

Many other studies only concern lymphomatous tumours[58, 90, 119, 124, 152] and therefore the results of treatment have to be evaluated, taking into account the high radiosensitivity of this type of tumour.

All these studies illustrate the close dependance of the outcome, whatever the modality of therapy, with the nature of the primary tumour. By contrast with the better results for radiosensitive tumours, the distressing outcome of spinal metastases from pulmonary carcinomas is well demonstrated in all series.

Nearly all publications concern retrospective studies, which vastly reduce the quality of their analysis.

In addition, many studies lack one or another parameter (type of the primary tumour, clinical condition of the patient ...) which might have allowed a better appreciation of results with regard to the modality of treatment. The series that we have personally published do not completely escape this criticism.

Findlay (1984) made a particular effort to compare series of patients about whom accurate data were available. He thus collected from the literature 1,816 cases published since 1960 and divided them into three groups:

– one group treated by laminectomy alone without recourse to radiotherapy;

– a second group treated by immediate laminectomy supported by follow-up radiotherapy where appropriate (50% of the patients);

– a third group only treated by urgent radiotherapy, usually with steroids.

The histological make-up of each group was considered to be comparable. Findlay concluded from his study that "laminectomy as a decompressive procedure probably should be reserved for patients without vertebral collapse who have either had previous radiotherapy or who deteriorate during their initial radiotherapy treatment". However a close analysis of this paper leaves some data unclear. For instance, it is not easy to understand why the postsurgical results of laminectomy + appropriate radiotherapy are better than those of laminectomy alone with regard to percentage of postoperative deleterious effect on ambulation.

Stark *et al.* (1982) also produced a well documented retrospective analysis in 131 patients. They did not observe a significant difference between the patients treated by radiation alone and those submitted to surgical decompression with or without subsequent radiotherapy.

The prospective study of Young *et al.* (1980) is therefore worth considering even if the number of patients[29] is rather small. In a randomized clinical trial, Young *et al.* compared laminectomy followed by radiotherapy

to radiotherapy alone. All patients who were paraplegic before the onset of treatment in either group remained paraplegic. There were no deaths, nor specific complications related to the treatment in either series. The effectiveness of the two methods of treatment on pain relief, motor performance and sphincter function was not significantly different.

And so, because of the complexity of the problem, various and different opinions are expressed. We will quote a few of them as examples.

Bucy (1962, 1963) thought that surgery must prevail or precede the other forms of treatment when compression of the spinal cord exists.

Livingston and Perrin (1978) wrote that "the widely held view that surgical treatment of cord compression due to spinal metastases is ineffective is not justified".

Macedo *et al.* (1985) also wrote "early surgery prior to radiotherapy is indicated in selected patients since overall ambulatory rates are superior in those undergoing de novo surgery".

On the other hand, Gilbert *et al.* (1978) did not find a difference in outcome between those treated by surgery plus radiation and those managed by radiotherapy alone.

Levy *et al.* (1982) in a study of only those patients who were ambulatory preoperatively observed that patients treated with operation plus radiation have a better outcome in long term follow-up that patients only treated with radiation.

Patterson (1980) is of the opinion that "radiation therapy and the administration of high dose steroids seem to be as effective as surgery, if not more so". Black (1979) considers that "radiotherapy should be the primary mode of treatment and surgery should be reserved for situations in which radiotherapy fails or where there is bony compression or spinal instability".

The list of various opinions could be lengthened unprofitably, because the multifactorial outcome is not sufficiently analyzed.

Among the key factors which bear upon the outcome, are the nature of the primary tumour, the rapidity of the onset of neurological disturbances and the severity of the clinical condition at the time of the diagnosis.

The figures with regard to morbidity and mortality are somewhat variable according either to the series published or to the time when surgery or radiotherapy were performed.

White *et al.* (1971) and Patterson (1980) indicate worsening of the neurological status as a result of surgery in 10% of the cases and 30-day mortality rate 9%. Mullan and Evans (1957) observed worsening of the clinical presentation in 12 of 36 patients operated on. The complications following surgery are up to 30% (Gilbert *et al.* 1978, Livingston and Perrin 1978, Posner 1971 and 1977, Young *et al.* 1980).

In our own series[126] we noted a rate of survival at 6 months of only

29%; the rate was higher (41%) in patients treated by radiation alone; it was of 29% for patients operated on and irradiated postoperatively, and of 15% for patients only operated on. But such figures are worthless because, as it is often the case in other series, radiotherapy alone was usually reserved for patients having the best clinical presentation and at the same time a radiosensitive tumour; those patients only operated on had such poor clinical condition that postoperative radiation could not be applied. Patterson[135] has with reason stressed the point that "bladder involvement was an omnious prognostic sign, and if this was present at the start of treatment, only 27% regained ambulation".

Conclusion

Whatever the treatment applied to epidural metastases, the results – rate of improvement, morbidity and mortality – depend on so many factors that even now it still remains difficult to draw reliable figures. However, the general opinion is that radiotherapy without laminectomy is a reasonable measure for patients who have a rather slow progressive clinical evolution and above all who have a radiosensitive tumour. The histology of the tumour appears as the most prominent parameter in outcome. The rapidity of the outset of the disease is another key factor.

The results of any modality of treatment are better when it is applied initially rather than after relapse. Likewise, the results directly depend on the severity of the clinical signs whatever the treatment selected.

The level of spinal involvement, the multiplicity of spinal metastases, the extent of the spinal and paraspinal infiltration, the degree of instability of the spine, the general condition of the patient are other parameters which must be taken into account. We may state with confidence that the best way to improve the results of treatment, surgery and/or radiotherapy, is to diagnose the spinal involvement as soon as possible and in any case before the development of neurologic disorders.

Regarding surgical techniques, the results of tumour resection and decompression, associated with the correction of the spinal instability and angulation, are more promising than classical laminectomy, although the surgical anterior approach, except at cervical level, is a considerable therapeutic procedure which carries a high potential morbidity.

Our opinion, based on a large clinical experience, is that each individual patients has to be considered according to his own particularities and not according only to methodological considerations. We agree with Stark *et al.* (1982) when they write: "traditional clinical common sense together with knowledge and experience of the usual behaviour of spinal metastases will continue to be the key to the management of individual cases ... Overall, the published experience regarding spinal metastases provides little aid in

the management of individual cases". As suggested by Young *et al.*[192], a large prospective multicenter study should provide "sufficient numbers of patients within a reasonable time period to answer the perplexing question as to the most effective treatment of spinal epidural metastases".

The following guidelines represent our general strategy for the management of vertebral metastases:

– to obtain if possible the histology of the lesion prior to treatment.

– radiotherapy prevails over surgery as the first therapeutic attempt when the tumour is radiosensitive and when the clinical evolution allows time for the radiation to take effect;

Vice-versa, surgery prevails when the tumour is radioresistant or when the clinical evolution is extremely rapid;

– surgery is required in case of spinal instability and of spinal cord compression by the diseased vertebra;

– surgery is also recommended when a recurrence occurs after radiotherapy and in case of clinical worsening during radiotherapy;

– surgery has to be performed when the histological diagnosis of the tumour remains unknown, providing that a transcutaneous bone biopsy is not recommended;

– surgery followed by radiotherapy could be the best strategy when there is a large infiltration of the vertebra and paraspinal structures;

– radiotherapy is indicated when there are several active vertebral metastases;

– the addition of chemotherapy has to be considered in each individual case;

– the prospective duration of the patient's survival and the quality of his life must be taken into consideration. The surgeon has to be restrained from operation of patients totally paraplegic for over 24 hours for radiosensitive tumours and since over 6 hours for radioresistant lesions except after very slow development of neurologic disorders.

The systematic recourse to only one therapeutic modality in the management of epidural metastases, whatever the clinical situation, is philosophically and scientifically difficult to accept.

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Shunts and Shunt Problems in Childhood

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With 5 Figures

Contents

I. Introduction

Extra cranial shunting procedures (Cone *et al.* 1949, Matson 1951) were used to treat hydrocephalus before the work of Nulsen and Spitz (1952) and before the introduction of the Holter valve in 1956. However in most cases they were inefficient or even dangerous; they overdrained because they could not close and rapidly blocked due to tissue reaction to the constituent material.

Improvement came with the introduction of one way calibrated shunt systems, able to close at a certain differential pressure between their inlet and outlet and made of silicone rubber, a material which is biologically well tolerated. The first valves available were the Holter and the Pudenz valves (Pudenz *et al.* 1957). Both are unidirectional slit valves which work

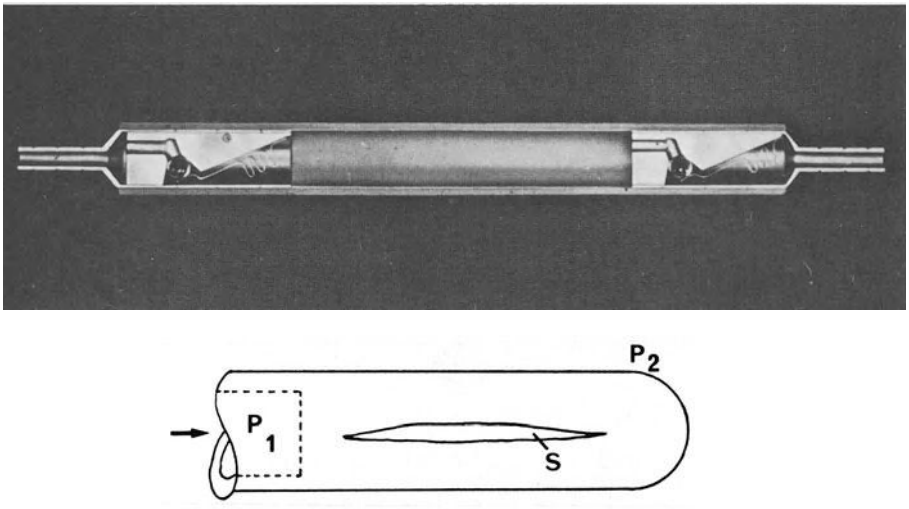

Fig. 1. Diagram showing a spring ball valve (top) and a slit valve (bottom). *P 1* Internal pressure, *P 2* external pressure, *S* slit

as follows (Fig. 1); calibrated slits in the catheter open when the pressure inside the tubing is higher than that outside. The area of the slit increases with the difference in pressure and the slit closes at a certain predetermined differential pressure. Both shunts include a reservoir which can be used as a pump to check the patency of the system. In the Holter valve, the slits in the cather are located inside the reservoir inserted behind the ear; in the Pudenz Valve, the reservoir is also placed behind the ear, but the slits are located at the tip of the distal catheter. Thus both systems include three parts: a ventricular catheter, a reservoir and a distal catheter. The difference is in the location of the slits, *i.e.* the valve.

Later, Hakim (Hakim *et al.* 1973) designed a second type of valve, the spring-ball valve in which a sapphire ball at the tip of a spring is located at the tip of a cone and pushed backwards by the difference in pressure between the inlet and the outlet of the cone (Fig. 1).

Many other valves, all based on the same principles, have been designed subsequently. All are differential pressure valves, the flow through the shunt system being related to the difference between the input and output pressure. They differ in the shape and size of the valve, the location of the reservoir, the possibility of self occlusion and in the number of parts in the shunt system (three, two or one as in unishunts).

Since all these valves are differential pressure valves, CSF flow rate through shunts is determined by the formula (Fig. 2).

$$F = \frac{\Delta P}{R}$$

(where F = flow, Δ.P. = difference in pressure and R = resistance of the shunt system)
In the upright position, ΔP increases by the difference in height between the inlet and the outlet of the shunt. Therefore in the upright position, all valves overdrain (*i.e.* drain more than CSF secretion rate) emptying the CSF volumetric reserve and resulting in very negative ICP values (McCullough and Fox 1974) when the possibility of brain reexpansion is exhausted (*i.e.* when the brain compliance is low). Several attempts have

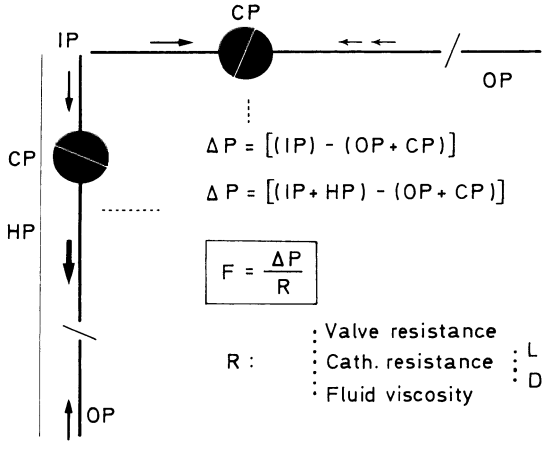

Fig. 2. CSF flow through shunts in the recumbent and in the upright position. *IP* Input pressure, *OP* output pressure, *CP* closing pressure of the shunt, *HP* pressure of the column of fluid due to upright position, *R* resistance, *L* length of catheter, *D* diameter of catheter

been carried out recently to remedy this drawback as overdrainage can eventually cause deleterious effects such as post-shunt pericerebral collections, slit ventricle syndromes or craniostenoses. Yamada (1982) increases the resistance of the shunt by inserting a throttle in series with the shunt. Another solution proposed is to use an externally adjustable opening pressure. The antisiphon device designed by Portnoy, Fox and Schulte (Portnoy *et al.* 1973) is inserted in series with the valve; closing, when ΔP is too high, such as in the uprigth position, it acts efficiently against overdrainage but carries a serious risk of underdrainage (McCullough and Fox 1974). The most recent solution proposed (Sainte Rose *et al.* 1987) is that of a variable resistance valve which acts as a flow regulator when the flow rate through the shunt tends to exceed the CSF secretion rate.

However the history of progress in extracranial shunt procedures should not be restricted to the history of improvement in shunt systems. For instance, the placement of the distal catheter, *i.e.* the place to which excess

CSF should be diverted and resorbed, has been a matter of discussion for some time. Although many sites have been proposed (Choux 1982), the debate has been rapidly restricted to a choice between two locations: the atrial cavity of the heart or the peritoneal cavity. The atrial cavity was the first choice when the new calibrated silicone shunt systems became available (Pudenz *et al.* 1957). Later on the peritoneal cavity was preferred (Jackson and Snodgrass 1955, Scott *et al.* 1955). The risks of obstruction, infection and overdrainage problems do not differ significantly in the two locations, but the peritoneal cavity allows the insertion of a long catheter, thus avoiding further procedures to adjust catheter position during the growth of a child. Therefore most authors now agree that the peritoneal cavity is the best location for the distal catheter. Insertion into the atrium through the jugular vein is limited to those cases in which, for some reason, the peritoneal cavity cannot be used.

Other advances have come from technical improvements and from the development of appropriate means to reduce postoperative infection. Transfontanellar echography and CT scans have led to an earlier diagnosis of hydrocephalus. However, in spite of these techniques, the final outcome is often far from satisfactory. It remains to be seen if these unsatisfactory results are due to late diagnosis, the rapidity of evolution of the disease or imperfections in the shunt systems now available.

Shunts in infancy and childhood are used under three circumstances: treatment of hydrocephalus, drainage of a cystic cavity under pressure and treatment of a subdural collection. In the two first cases the prosthesis is inserted, with some rare exceptions, for life. Therefore, knowing that many complications, mainly obstruction and infection, are possible, knowing that a certain number of operations per patient will be required and taking into account the fact that shunting systems do not accurately reproduce normal physiology, the decision to insert a valve should be taken only when absolutely necessary. It is always a simple procedure to perform, but a difficult decision to make.

Once the decision is taken the procedure should be performed in accordance with certain strict technical rules and these must be respected if postoperative complications are to be kept to a minimum.

II. Operative Techniques

A scrupulous surgical technique is the best way to prevent complications.

The patient is correctly placed on the operating table, *i.e.* the head is turned to the side opposite the site of insertion and a pillow is placed under the shoulders to straighten out the angle between the neck and the clavicle. The skin is scrubbed and three coats of antiseptic (iodine solution or betadine) are applied. The skin is then covered with an adhesive plastic drape and this is also wiped with antiseptic.

Ventriculoperitoneal Shunts

To insert the ventricular catheter, a small slightly curved incision (2 to 3 cm in length) is placed about 2 cm from the midline, at the level of the lambdoïd suture. A burr hole is made and the dura is opened: the dural opening should be small to prevent CSF leakage around the catheter. The catheter with its stylet is then introduced in the brain and aimed towards the midline of the forehead half-way between the nasion and the hairline; the tip of the catheter is placed in the frontal horn beyond the foramen of Monro, but at a distance from the anterior extremity of the ventricle. Preoperative careful measurements or intraoperative ultrasonography will help correct placement. To prevent postshunt pericerebral collections, CSF loss at the time of surgery should be kept to a minimum.

With the use of a long shunt passer, it is then usually possible to pass the inferior subcutaneous catheter directly down to the abdominal level without interposing incisions: the smaller the number of incisions the lower the rate of infection.

The ventricular catheter is led out of the burr hole and connected to the valve on the skull surface by means of a straight connector and then stitched to the periosteum to avoid secondary migration. Straight connectors are preferred to right angle connectors because, when such connections are used at the skull level, subsequent revisions are more difficult. The ventricular catheter is less accessible and can be easily lost. Actually the number of connections should be reduced as much as possible to lower the risk of disconnection; therefore one or two piece shunts are to be preferred.

The inferior catheter is introduced into the peritoneal cavity at the level of the umbilicus through the lateral border of the rectus abdominis muscle. This insertion is very simple when the catheter is introduced using the trocar of Portnoy. However some authors, fearing bowel perforation, prefer a classical approach to the peritoneal cavity. The whole tubing is then pushed into the peritoneal cavity (usually about 40 cm in infants), to avoid secondary adjustment procedures.

Ventriculoatrial Shunts

With ventriculoatrial shunts, the technique differs in the insertion of the inferior catheter, which has to be introduced through the jugular vein down to the atrial cavity.

The jugular vein is easily exposed at the anterior border of the sterno-cleido-mastoid muscle. Some authors introduce the catheter through the facial vein down to the jugular vein and the atrial cavity; some others insert it directly in the jugular vein which is tied off above the level of insertion.

The correct placement of the tip of the inferior catheter in the atrial cavity is of utmost importance. This can be achieved using simple intra-operative X-ray control; in infants the tip of the catheter should be placed facing the T 8 vertebra. However a more accurate placement is obtained under EKG control. A syringe (filled with hypertonic saline) is connected to the inferior catheter and is electrically linked to an EKG recorder. The

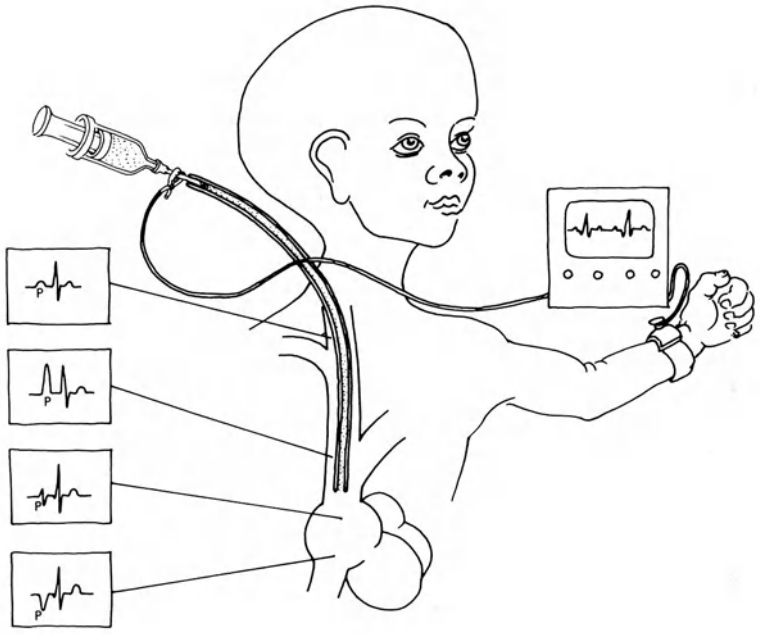

Fig. 3. Electrocardiographic determination of the optimum position for the tip of a ventriculoatrial shunt. Note that the P wave changes with the position of the tip

EKG between one arm and the tip of the catheter is then recorded. The syringe and the needle are isolated from the skin; the silastic catheter acts as an insulator and electrical activity at its open tip is recorded (Fig. 3).

When the catheter enters the jugular vein, the EKG is composed of a small P wave and a large QRS. As the catheter is pushed down the P wave becomes progressively as large as the QRS complex and then abruptly it becomes diphasic and small and then reverses its polarity. The correct placement is obtained when the P wave is diphasic.

Whenever possible ventriculoatrial shunts should be inserted on the right side as on the left side they take a "bayonet course" which makes subsequent revision surgery difficult.

Lumboperitoneal Shunts

Lumboperitoneal shunts are inserted when ventriculoperitoneal or ventriculoatrial shunts are contraindicated.

With the patient lying on the side, a narrow bore catheter is introduced into the lumbar subarachnoid space (either a simple tube through a needle or a T tube is inserted through a minor laminectomy approach). The tube should be anchored to the lumbar fascia. The tube is then fed through a subcutaneous tunnel to exit through a small skin incision in the loin. Here the valve with or without reservoir is connected. The distal catheter is fed through another subcutaneous tunnel to the paraumbilical area. Here it is introduced into the peritoneal cavity as described previously (the length of distal catheter lying within the peritoneal cavity need only be 20 cm).

Subduroperitoneal Shunts

Subduroperitoneal shunts are inserted in subdural haematomas. The entry orifice should always be large enough to allow a tangential direction of the intracranial catheter. It should be placed in the deepest part of the collection; the intracranial tube should be short.

In those shunts, a reservoir may be useful to check the patency of the system, but no valve is needed since the collection will be more efficiently drained with simple tubing.

Cystoperitoneal Shunts

Cystoperitoneal shunts are easily placed when cysts are large. With small deeply located cysts, it may be difficult and then intraoperative ultrasonography or stereotactic guidance become mandatory.

III. Problems and Solutions

In spite of early enthusiasm, it is now obvious that the overall morbidity and mortality from ventricular shunting is far from negligible. In our series, the overall mortality is 10.9%. This is not related to the immediate postoperative period but is in fact related to the numerous complications which may occur after shunting. They can be grouped under four headings: infection – misplacement – underdrainage and obstruction – overdrainage.

A. Infection

1.) Infection remains the main complication of shunt procedures for hydrocephalus, with an incidence of up to 20%, but most often in the range of 7 to 10% (Raimondi *et al.* 1977, Hirsch *et al.* 1978, Keucher and Mealey

1979, Alvarez and Mengual 1982, Haines and Taylot 1982, and Hoffmann *et al.* 1982). The perioperative infection rate in our series was 7.9%. However an appreciation of the individual factors that may cause infection is by far more important than this overall rate since such knowledge can lead to appropriate preventive measures. The following data comes from a study made in our service on a series of 1,174 consecutive operations for hydrocephalus performed between 1975 and 1982 in infants and children (Renier *et al.* 1984).

Age is the most important factor, the rate of infection being 11.1% before 6 months as compared to 4.2% after 12 months. In the group under 6 months of age, the relatively large number of gram negative infections is partially responsible for the increased risk. The condition of the skin is also important, those patients with dermatitis or open sores of the scalp have an infection rate of 13% as compared to 3.8% when the skin is normal. An intercurrent source of infection outside the CNS at the time of surgery increases the risk of infection.

The operative procedure is also important, the lowest infection rate being observed in revisions and the highest in reinsertions after previous shunt infection. The surgical team and the rapidity with which the operation is performed are certainly also important factors.

After surgery wound dehiscence or scalp necrosis increase the risk of infection. Therefore no pressure should be applied under or on the skin. Large reservoirs with hard sharp angles should be avoided and infants should be placed correctly in their bed after surgery.

The organism responsible for the infection is in most cases a staphylococcus, either epidermidis (in half of the patients) or aureus (in a quarter of them). Gram negative organisms are found in one fifth of the infected cases and these are mainly young infants.

Infection usually presents as an early postoperative complication. However it can also occur months or years after surgery. Post shunt septicaemia was sometimes a late complication but this is now rarely seen as ventriculoatrial shunting has been largely replaced by the ventriculo peritoneal technique. Late infection is not so common with ventriculo peritoneal shunts but peritonitis can develop when the distal catheter erodes through the bowel wall.

In our series, meningitis was observed in 62%, peritonitis in 19% and wound infection in 11% of the infected patients. Septicemia was found in 2% of them (ventriculo atrial shunts were only inserted in 5% of the cases). Different types of infection may be associated in the same patient. Staphylococcus epidermidis being the organism most often responsible for infection, the clinical features are often insidious and less overt than expected with the same complication due to other organisms. With septicemia or meningitis, the germ should be isolated at least once by repeated blood

cultures or lumbar taps before starting treatment. The diagnosis of peritonitis is often difficult. Besides the classical clinical and radiological signs two features are of interest: the inflammatory reaction of the skin over the distal catheter (1 case out of two in our series) (Lortat-Jacob *et al.* 1984) and the immobilization of the intraabdominal tip of the distal catheter on successive X-rays of the abdomen. In all cases, the diagnosis should be confirmed after surgery by culture of the infected material.

Peritonitis may be observed when the catheter erodes through bowel, but this is rare (one fifth of our cases). The diagnosis is usually made when the catheter protrudes out through anus. The delay between surgery and diagnosis varied in our patients between 8 days and 7 years. When death occurs it is always due to a gram negative meningitis: 10% of our patients, 8 out of the 35 reports in the literature (Wilson and Bertran 1966, Rubin *et al.* 1972, Sells and Loeser 1973, Grosfeld *et al.* 1974, Lee and Gwinn 1975, Schulhof *et al.* 1975, Azimi *et al.* 1976, Adeloya and Olumida 1977, Murtagh *et al.* 1980, Agha *et al.* 1983). In most cases, this complication is not the result of a perforation at the time of surgery, but of a secondary erosion through bowel probably due to a localized infection causing the catheter to adhere to the bowel wall.

2.) Prevention of infection is of utmost importance and relies on several strict rules.

– Surgery should be delayed, whenever possible, until the skin is in perfect condition and until any other intercurrent seat of infection is cured. When this is impossible, and if the hydrocephalus is communicating, a lumbo peritoneal shunt is indicated.

– Staphylococcus epidermidis being the organism most frequently encountered, it is very likely that in many cases infection comes from the skin of the patient. Therefore the skin area to be incised should be scrubbed before surgery and prepared very thoroughly with antiseptics. Adhesive drapes should also be wiped with antiseptics. Since the swear and sebaceous glands (Tanner 1979) may be colonized by the organism, quarter strength betadine should be poured into the operative wound at the beginning and at the end of the operation, an innocuous technique as long as the antiseptic does not reach the central nervous system. For the same reason, incisions should be as small as possible.

Silicone rubber being electrostatic, air born contamination is probably not negligible. As soon as removed from its pack, the shunt should be dipped in Betadine and remain in the antiseptic until insertion. However, the ventricular catheter should be washed in saline before insertion. For the same reason the asepsis in the operating theatre should be as thorough as possible, with a very low number of particles per square meter of air, and preferably a laminar flow. However we have shown that a more efficient

and less expensive method is the use of a surgical isolator (Hirsch *et al.* 1978). This technique, derived from the techniques used in the preparation of germ-free animals, allows strict asepsis and eliminates air born contamination. We have shown that it reduces very efficiently the infection rate especially when the operating room asepsis is not perfect.

The use of prophylactic antibiotics is nowadays less controversial as several studies seem to indicate that this reduces shunt infections (McCullough *et al.* 1980, Haines and Taylor 1982, Hoffman *et al.* 1982). They should be given during the operation and on the following day. They should of course be efficient against staphylococcus but, in very young infants they should also cover the gram negative risk.

As to the treatment of shunt infection, it is our belief that, it should always include the removal of the shunt. Although some authors (McLaurin 1973, Shapiro and Schulman 1982) favour in some cases the medical treatment without removal of the shunt, most agree (James *et al.* 1982) that the shunt itself is colonized and that it would be very difficult to sterilize it with antibiotics.

Two different protocols can be followed. In the first one, antibiotic therapy is started pending identification of the organism and its susceptibility. Later the most appropriate antibiotic is administered, the shunt is removed and external ventricular drainage instituted. The length of antibiotic therapy varies with different authors, 7 days in the patients of James *et al.* (1982), 15 to 21 days in most of ours; it also varies with the type of organism and with its resistance to therapy. Shunt reinsertion is decided when CSF cultures remain sterile after cessation of the treatment and when the CSF glucose level returns to normal. This protocol often results in a long hospital stay and carries a risk of infection through the external ventricular drainage. It has to be used however everytime the organism resists therapy and CSF sterilization requires prolonged treatment.

In the second protocol antibiotic therapy is given for five to six days; then the infected shunt is removed and a new one is inserted at the same procedure. Antibiotic therapy is then continued for three weeks. This protocol cannot be followed when, at the fifth day, in spite of antibiotic therapy, CSF cultures remain positive.

The appropriate antibiotics and the method of administration depend upon the organism, its susceptibility and the antibiotics available at the time of the infection.

– Septicemia, especially due to spaphylococcus epidermidis, is usually easily cured. Shunt nephritis, a rare complication of septicemia, does not need any extra therapy (Pierre-Kahn *et al.* 1982) and will regress spontaneously once the septicemia is cured.

– Prognosis in post shunt meningitis depends upon the organism responsible. Gram negative meningitis may be fatal in young infants.

– Peritonitis is usually cured by antibiotic therapy and removal of the infected catheter. However if the treatment is started too late and the clinical signs do not disappear within two days, a laparotomy may be indicated. This was the case in one third of our cases. This proportion is certainly lower now, due to earlier diagnosis and treatment. Abdominal ultrasonography is useful in decision taking.

Infection is the most dangerous complication of shunt insertion. Even when it can be cured, it is responsible for prolonged hospitalization which in the long term may be deleterious for the mental development of the child. The real treatment of infection is its prevention.

B. Misplacement

Primary misplacement of a catheter is a possibility which can and should always be avoided.

Misplacement of the intracranial catheter is rare in hydrocephalus since the ventricles are usually very dilated. However if the entry orifice is too lateral, the catheter may lie transversally, eventually crossing the midline; in such cases, the shunt will sometimes block when the ventricles shrink. In other cases, the catheter is in the temporal horn of the ventricle and will eventually be clogged by the choroid plexus. The correct placement of the intraventricular catheter is in the frontal horn, beyond the foramen of Monro, but at a distance from the tip of the ventricle so that the brain parenchyma does not block the catheter when the ventricular size diminishes.

Misplacement of a subdural catheter, in the treatment of a pericerebral collection, is also very rare. It may happen when the entry orifice is too small so that the catheter does not enter in the desired tangential direction. In such a case the tip of the catheter will be found in the brain parenchyma or even in the ventricles.

Misplacement of an intra cystic catheter is more frequent especially when the cyst is small and deeply located.

In difficult cases (small ventricles at a reoperation – small cyst), intraoperative ultrasonography through the fontanelle or through a correctly placed burr hole will avoid misplacement. In some rare cases, stereotactic guidance may be helpful.

Misplacement of the peritoneal catheter is more often seen. Perforation of viscera at the time of surgery has been observed in two cases in our series; in one case the colon and in the other case the bladder were inadvertently penetrated. The latter should have been avoided with a correctly placed incision and by emptying the bladder before surgery. Besides these primary misplacements, secondary misplacements can occur. Catheters in the peritoneal cavity can erode into various viscera and have been found

in the large intestine, protruding out through the anus or even in the stomach. They can migrate through the inguinal canal and cause a hydrocele. Shunt systems can also migrate into the peritoneal cavity, totally or partially, when they have not been correctly fastened to the skull or when they rupture during growth. These lost catheters should be removed only in infected cases.

Catheter coiling around the intestine is a very rare but dangerous complication. It results in intestinal obstruction and requires a laparotomy with perhaps an intestinal resection.

Misplacements are also possible with ventriculoatrial shunts. When the catheter is in the subclavian artery, a diagnosis easily made on X-ray controls, it blocks more or less instantly. When it is too low, in the ventricular cavity, it does not work because the mean pressure of this cavity is too high.

To prevent misplacement in the heart good intraoperative control is required. In our experience, the EKG control is the most accurate method.

When there is a disconnection, the distal catheter can migrate either into the ventricular cavity or into the pulmonary artery. These lost catheters should be removed.

C. Underdrainage and Obstruction

1.) Shunt failure can be due to total or partial obstruction of the valve, of the ventricular catheter or of the distal (peritoneal or atrial) catheter. Obstructing tissues are sometimes tissues normal to the region such as choroid plexus, connective tissue, brain tissue, meninges, ependyma or mesothelial cells; in other cases they are pathological tissues (inflammation – necrosis – haemorrhage, fibrin, tumour, calcium) or foreign material such as hair, talc powder, or cotton (Sekhar *et al.* 1982). In ventriculoatrial shunts, the membrane which normally surrounds the catheter can obstruct the tip of the distal catheter.

– Shunt failure can be due to a disconnection: it can also be due to the development of an intraabdominal cyst around the tip of the catheter; in such a case ultrasonography will lead to the correct diagnosis.

Shunt failure is easily diagnosed when shunt obstruction is total. In infancy, signs of hydrocephalus will resume; in childhood, signs of increased ICP are more or less rapidly observed. In most patients, symptoms evolve over several days. In rare cases, this may develop rapidly and be fatal within one day. Therefore shunt failures should always be treated as emergencies.

Pumping the reservoir may help to establish the diagnosis. If when being pressed the reservoir remains flat, the obstruction is located in the ventricular catheter. If it cannot be depressed obstruction is at the level of the

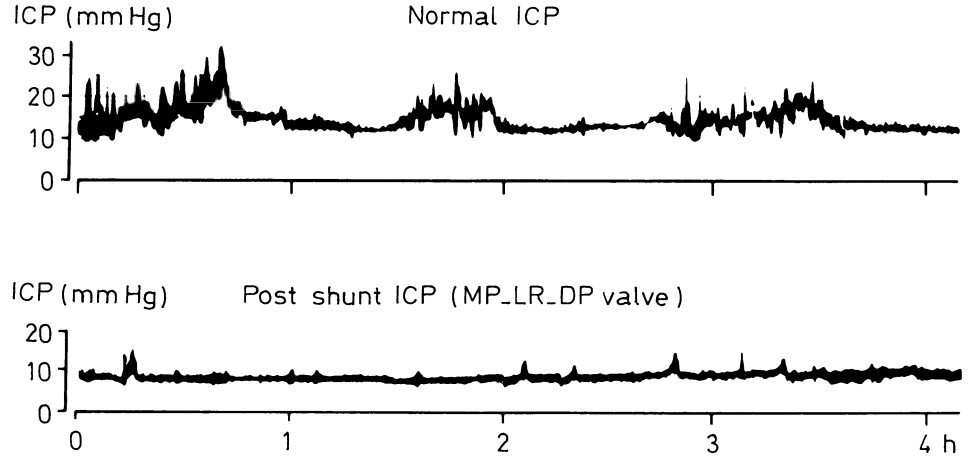

Fig. 4. Intracranial pressure recording of a normal child showing peaks during REM sleep (top). These peaks are lost when a shunt is inserted to treat hydrocephalus (bottom)

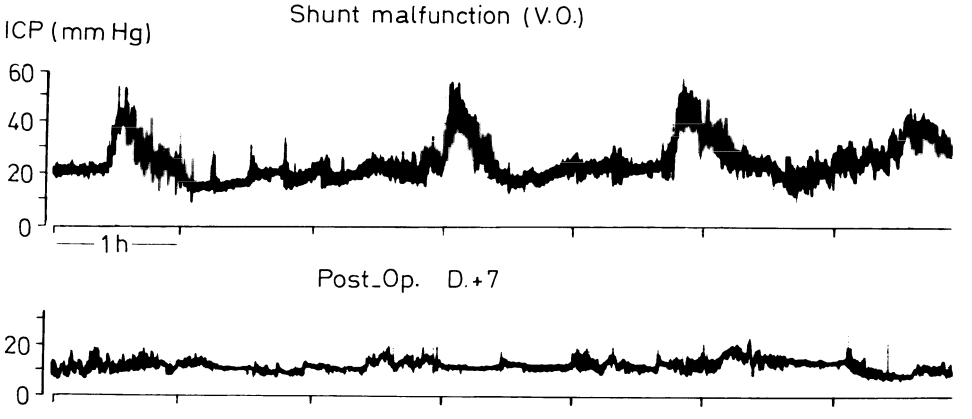

Fig. 5. Intracranial recording in shunt malfunction showing sustained pressure changes during REM sleep (top). One week after surgery, these peaks have disappeared

distal catheter. Plain X-rays of the shunt may demonstrate a shunt disconnection.

A CT scan will always show ventricular enlargement (which can be slight in cases of periventricular gliosis).

Partial shunt failure is frequently encountered: more often it is an intermittent failure such as can be observed in shunt disconnection, in intraabdominal cysts and slit ventricles. In our series, the risk of shunt obstruction is doubled from 8.4 to 21.3% in patients showing slit ventricles. These intermittent shunt failures are characterized by recurrent signs of

increased ICP. When the diagnosis is difficult, long duration ICP recordings (Figs. 4 and 5) and CT scans help; the estimation of the ratio of the ventricular surface to the total surface of the cranium on a CT scan cut through the ventricle allows accurate comparisons before and after suspected shunt failure. In vivo measurements of CSF flow through shunts is rarely performed (Rougemont *et al.* 1970, Sato *et al.* 1982). MRI might become of interest in the future.

In aqueductal stenosis, partial shunt failure results sometimes in the very peculiar aqueductal syndrome, characterized by the progressive development of Parinaud's Syndrome, nystagmus retractorius, memory disturbances and eventually cranial nerve palsies and coma. ICP monitoring demonstrates a slight ICP increase as compared to the expected value in a shunted patient. Even though the shunt is not completely obstructed, the only efficient therapy is shunt replacement. The increased difference in pressure between the supra and infra tentorial compartments distorts the upper brain stem and is responsible for the syndrome.

Aqueductal stenosis is in some patients secondary to shunting (Raimondi *et al.* 1969). When it occurs in patients whose fourth ventricle orifices are closed, as in the Dandy Walker malformation, the fourth ventricle is trapped and progressively enlarges, resulting in cerebellar and brain stem compression. In such a case a shunt has to be inserted in the fourth ventricle. To avoid this complication, shunts in Dandy Walker malformations should always be initially inserted in the fourth ventricle, rather than in the lateral ventricles. Trapped fourth ventricles have also been observed in patients presenting with primary aqueductal stenosis and with secondary postmeningitis closure of the fourth ventricle's orifices.

CSF underdrainage can occur in the peritoneal cavity. However CSF ascites is rare; this has been found in 4% of the patients in our series. The seeding of an intra cerebral tumour to the peritoneum through a shunt has been reported in some cases (Triolo and Schulz 1980). In other case, the CSF proteins might be responsible for the ascites (Adegbite and Dhan 1982, Weidmann 1975). The CSF protein content was elevated in all our patients presenting with ascites. In these patients, the ventriculoperitoneal shunt should be replaced by a ventriculoatrial shunt.

Systematic X-ray controls sometimes arouse suspicion of shunt obstruction whereas patients are doing well (the ventricular catheter may have dislodged into the brain parenchyma, the distal catheter may be outside the superior vena cava or the peritoneal cavity, or there may be a disconnection). Before concluding that these patients do not need a shunt any more, one should be very careful as CSF often continues to flow around the catheter or in a channel that has developed between the two disconnected parts of the shunt. In order to ascertain if shunt removal is possible, the clinical effects of a total surgical occlusion of the distal catheter should be studied

for at least two weeks. In cases of disconnection, metrizamide injected in the reservoir will eventually demonstrate the persistence of a natural channel between the two disconnected parts.

2.) Knowledge of causes of shunt obstruction is helpful in deciding how best to prevent this occurring: correct placement of the ventricular catheter, strict asepsis, choice of the valve which will avoid the development of slit ventricles. The number of connections should be reduced as much as possible in order to decrease the risk of disconnection. Since ventriculoatrial shunts often block when blood flow is low at their tip, atrial catheters should be systematically lengthened when they are out of the superior vena cava, *i.e.* when their tip is at the T 4 level on a correctly centred X-ray.

3.) Shunt revision for obstruction always begins by identifying the part of the shunt which is blocked. Then the ventricular catheter, the valve or the distal catheter is changed or replaced in the correct position. Atrial catheters can be lengthened if they are on the right side whereas this is impossible on the left side because of their "bayonet" course. The risk of infection is lower in revisions for shunt failures than it is in primary insertions and the risk is lower in revisions of the peritoneal catheter than it is in revisions of the ventricular catheter (Renier *et al.* 1984).

Total or partial shunt obstructions are frequent and responsible for a high proportion of reoperations.

D. Overdrainage

1.) As already stated, CSF flow through a differential pressure shunt is related to the difference between input and output pressure ($\triangle P$) and to the resistance of the shunt (R). Overdrainage can be considered as constant with conventional differential pressure valves when patients are in the upright position since $\triangle P$ increases whereas shunt resistance and CSF secretion remain practically constant; it can also occur in other circumstances characterized by temporary physiological ICP increases (REM sleep, exertion, etc. . . .). Overdrainage is more important with low resistance valves (spring-ball type: *e.g.*, Hakim or silicone rubber diaphragm type: *e.g.*, Heyer Schulte) than with high resistance valves (silicone-rubber slit valves: *e.g.*, Holter). Overdrainage becomes an important problem when children reach a certain size and are able to walk, *i.e.* roughly around two years of age.

With ventriculoatrial shunts, in the upright position, $\triangle P = ICP + H - CP$ (CP = closing pressure of the shunt − H: distance between cerebral lateral ventricle and atrial cavity of the heart). With ventriculoperitoneal shunts, in the upright position, H is the distance between the cerebral lateral ventricle and the xiphoid process (the distance between the intraabdominal tip of the tubing and the xiphoid process being

annulled by the difference in pressure at the end of the catheter and at the upper part of the peritoneal cavity). Therefore in a given patient, if the closing pressure and the resistance of the shunt are known, the amount of overdrainage in the upright position can be estimated. However there is no simple solution to overdrainage since a conventional differential pressure shunt which would not overdrain in the upright position would underdrain in the recumbent position.

2.) Overdrainage can be prevented by the antisiphon device of Portnoy *et al.* (1983). This system closes when $\triangle P$ becomes too high, as in the upright position. However it might carry a risk of underdrainage in this position (McCullough *et al.* 1982).

Another solution, that of the orbis-sigma valve, relies on a CSF flow control not on a primary regulation of ICP which is a highly variable parameter. This valve is a variable resistance valve with three stages. As long as the CSF flow through the shunt is smaller than the CSF secretion rate (between 20 and 25 ml/h), the shunt acts as a low resistance shunt with a low opening pressure. When the CSF flow reaches 20 ml/h, the resistance of the shunt increases so that it becomes a flow regulator. The third stage is a safety device: at that point, the shunt is again a low resistance shunt but with a high opening pressure. This third stage avoids any risk of intracranial hypertension.

3.) Preventing overdrainage is essential to reduce the risk of postshunt pericerebral collections, slit ventricle syndromes, postshunt craniostenoses and probably other deleterious effects which are at the moment unknown.

About 3% of the patients in our series developed postshunt pericerebral collections (Hoppe-Hirsch *et al.* 1987). This incidence is four times higher in children over two than in those under two years of age, a fact which demonstrates the relationship between this complication and overdrainage since the main difference between the two groups is the upright position. It should also be pointed out that these postshunt pericerebral collections are slightly more frequent in non communicating than in communicating hydrocephalus.

These collections are symptomatic in about half of the cases, but an asymptomatic collection may become symptomatic at a later stage. They should therefore always be treated. The principle of treatment is to reestablish a negative difference in pressure between the subdural space and the ventricles. This is carried out by inserting a valveless tube between the subdural space and the peritoneal cavity. Although half of these pericerebral collections are bilateral, one subduroperitoneal shunt is sufficient since they communicate. Eighty percent of these collections are cured by this simple technique. Moreover in our patients, clinical deterioration has never been observed after this treatment.

Slit ventricles are frequent; their incidence is 18% in our series. However

they are in most cases asymptomatic. The slit ventricle syndrome, characterized by the recurrence of signs of increased intracranial hypertension, is on the contrary rare. In some cases, it is due to the intermittent obstruction of the shunt by the walls of the ventricle; in these cases, the ventricles are slightly larger on a CT scan performed during intracranial hypertension than before. In other cases, increased ICP is due to loss of the CSF volumetric buffering reserve necessary for instance in the case of vasodilatation. Prevention of the slit ventricle syndrome lies obviously in the choice of a shunt which does not overdrain. The treatment tends in all patients to restore a minimal volume. This can be achieved by performing an operation which will open the skull or enlarge the cranial cavity. These operations are especially indicated when the head circumference and the volume of the cranial cavity are reduced. In other patients, the restoration of a ventricular volume is obtained by inserting a valve with a higher opening pressure or a higher resistance. Actually the antisiphon device and the orbis-sigma valve are in these slit ventricle syndromes a better solution. In some children both types of operation (valve replacement and enlargement of the cranial cavity) have to be performed either simultaneously or successively.

Post shunt craniostenoses (Strenger 1963, Anderson 1966) are also a consequence of overdrainage. In most cases, they are charcterized by a premature fusion of the sagittal suture. In those patients the deformation is of the scaphocephalic type: the cranium is lengthened and narrowed.

Post shunt craniostenoses are usually a pure dysmorphic problem. Sometimes however these craniostenoses result in a reduction of the volume of the cranial cavity and in a slit ventricle syndrome. In these cases, enlargement of the cranial cavity together with reshaping of the skull and replacement of the shunt become mandatory.

Although percutaneous ventriculocisternostomies may be of help in some non communicating hydrocephalus (Hirsch *et al.* 1982, Jaksche and Loew 1986) shunting remains in most cases the only therapeutic solution for hydrocephalic infants and children. However the enumeration of its complications demonstrates that it is far from a perfect solution. Shunted children will have to be followed up for years and will often be operated on several times. Long term results will be unsatisfactory in nearly half of the cases.

Therefore the decision to insert a shunt should be taken only when absolutely necessary, *i.e.* in children where hydrocephalus is active and progressing.

Infection and obstruction remain serious complications though strict attention to detail will reduce this occurrence. Overdrainage is responsible for pericerebral collections, slit ventricles and thus shunt obstructions and craniostenoses and this will be diminished by the choice of an appropriate

shunt. The efficacy of these improvements will have to be determined in future years.

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