VASCULAR FACTORS AND BLOOD FLOW IN THE NORMAL AND DISEASED SPINAL CORD

(with particular reference to the myelopathy caused by disc protrusions in the dog)

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INDEX OF CONTENTS

Section I/

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GENERAL INTRODUCTION

Spinal cord diseases are a common cause of disability in man and domestic animals. The signs range from mild discomfort or pain, to total paralysis of limbs and loss of sensation and bladder control. Intervertebral disc protrusions represent one of the main causes of spinal cord damage in dogs and they are no less important in man. An improved understanding of this disease would, therefore, be of great veterinary and comparative interest.

The pathogenesis of disc degeneration, rupture and protrusion have been investigated in some detail. However, once neurological signs are present it is the damage to the spinal cord or nerve roots that must be treated.

Treatment is usually defined as conservative, involving rest, drug therapy and various manipulative procedures or surgical. Although both forms of treatment are successful in some cases, the reasons for recovery or failure to recover are not understood. This is because the pathogenesis of the myelopathy is still uncertain. If the pathogenesis of the cord lesions can be determined then treatment can be placed on a more rational basis.

The aim of this study was to define the spinal cord pathology in cases of disc protrusion and from this to attempt to establish the pathogenesis of the myelopathy. The results of this investigation,which are presented in Part I, suggested that disturbances of blood flow are important in the pathogenesis. Accordingly, a study was made of spinal cord blood flow and the physiological factors which control flow. The results of this investigation are presented in Part II.

PART I

The naturally occurring myelopathies of disc protrusion with special reference to the part played by disturbances in blood flow.

INTRODUCTION

In 1895, Dexler described pathological changes in the vertebral column of dogs which were later recognised as intervertebral disc protrusions. Since then a great literature has accummulated on various aspects of the topic. It is appropriate to divide disc protrusions into orthopaedic aspects, dealing with changes in the disc and the mechanics of protrusions and neurological aspects, dealing with the myelopathy and signs resulting from cord damage.

The histology of the normal canine intervertebral disc and changes occurring with maturation and degeneration have been investigated in detail. Hansen (1952), King (1956) and Olsson (1951) have provided illuminating details of the orthopaedic aspects of disc protrusions. Far less, however, is known about the cord lesions and the manner in which they are produced.

It has been shown that both clinically and pathologically the myelopathy can be divided into two forms (Funkquist 1962: Hoerlein 1971). The more common is the localised myelopathy involving the segments immediately adjacent to the protruded disc. The second form is a more extensive lesion involving many segments of the cord and is known as "the ascending syndrome", acute disc protrusion or haemorrhagic myelomalacia.

The clinical signs relating to thoraco-lumbar disc protrusions have been presented by Hoerlein (1971), McGrath (1966) and Palmer (1964).

The localised myelopathy:- Only a few satisfactory reports are available concerning the pathology of this localised myelopathy.

Palmer (1970) described the pathology of cervical and thoraco-lumbar disc protrusions. He summarised the changes as Wallerian type degeneration of the white matter (W.M.) with increase in glial fibres. In the grey matter (G.M.) there were varying changes from chromatolysis to partial malacia. Partial malacia of the W.M., was also observed. Most cords showed hyalinisation of blood vessels, in particular small veins and capillaries. He also demonstrated compression and degeneration of the nerve roots as a result of dorso-lateral disc protrusions. Palmer (1964) and Wright & Palmer (1970) presented cases of intervertebral/

intervertebral disc protrusion and described malacic changes in the white and grey matter. They discussed the role of vascular factors in the production of these lesions.

Further investigation of the arterial and venous supply to the cord in cases of disc protrusion was performed by Lindblad et al (1961), using radiographic contrast studies.

Hoerlein (1971) has given a limited account of the cord pathology describing demyelination, resulting in a "moth eaten" appearance of the W.M., with numerous lipid phagocytes. He also mentions gliosis and hyalinisation of blood vessels.

It is apparent, therefore, that there is a variation in the pathology between individual cases but at least two basic changes are present:-

1) Malacia of the W.M., or G.M. ; and,
2) Wallerian type of degeneration with resultant gliosis and hyalinisation of blood vessels.

The Ascending Syndrome

Surprisingly, more information is available about the pathology of this extensive form of cord damage. Funkquist (1962) described this syndrome developing in 21 of 67 dogs with thoraco-lumbar protrusions, that were examined at autopsy. She drew attention to the association between Type III protrusions and the ascending syndrome (20 of 21 dogs with ascending syndrome had Type III protrusion). She also discussed the role of circulatory disturbances in the pathogenesis of the myelopathy. Hoerlein (1953 & 1971) described the changes in more detail. There was extradural necrosis and haemorrhage and extensive subdural haemorrhage. The cord was diffusely softened with concurrent haemorrhage and extensive demyelination. Cavitations were present and many neurones were degenerate. Neutrophil infiltration had occurred in many cords.

Palmer (1964) described this extensive necrosis in 3 cases of disc protrusion and suggested it was "a reflection of some vascular peculiarity of the dog cord". Lindblad et al (1962) and Olsson (1960), in arteriographic studies, demonstrated the absence of arterial filling in cords showing this extensive myelopathy.

The/

The cord in the ascending syndrome shows extensive necrosis and marked meningeal haemorrhage. There is general agreement that vascular factors are important in the pathogenesis but their exact role is not determined.

Cervical disc protrusions in the Human

It would seem appropriate to briefly examine the literature regarding disc protrusion in the human and compare the pathogenesis of the myelopathy with that in the dog. The condition most studied in man is cervical spondylosis, which, in a proportion of patients, results in a myelopathy. A large amount of literature has accummulated regarding the pathogenesis of this myelopathy. The disagreements are whether ischaemia or mechanical factors play the major part in the pathogenesis.

Wilkinson (1960) summarised the necropsy findings in 17 cases of cervical spondylosis. Twelve patients had distortion of the cord due to spondylotic bars on the dorsal aspect of the discs. Neuronal degeneration (11 cases) and cavitation of the G.M., (3 cases) were observed at the site of maximal damage. Rostrally and caudally there was the usual Wallerian degeneration. There was no evidence of anterior spinal artery thrombosis. Payne & Spillane (1957) state, however, that the indentations of the cord found after fixation "in situ" are artefacts, as the cord will adapt to any surface upon which it rests, during fixation.

Stoltmann & Blackwood (1964) demonstrated an in-folding of the ligamentum flavum during extension of the neck and suggested that in cervical spondylosis the cord was compressed between the ligament and the spondylotic burr.

Stenosis of the vertebral canal has been implicated in the pathogenesis. (Burrows 1963; Hinck & Sachder, 1966) Stortebecker (1962) suggests that the protrusion may cause root sleeve fibrosis with resultant radicular artery compression and cord ischaemia.

In 1953 Mair & Druckman reported 4 cases of cervical disc protrusion and described the histology of the cord. At the level of the protrusions they showed that the major changes were in the ventral horns, lateral and ventral portions of the dorsal columns. They suggested this corresponded to the ventral spinal artery (V.S.A.) supply zone,with the exception of the anterior columns. They also stated/

stated that the histology was suggestive of ischaemia. Taylor (1964), in a summary of cervical spondylosis, advanced the theory that vascular factors play the major part in the pathogenesis and suggested that compression of radicular vessels at C5/6/7 was the cause. Taylor illustrated the periarterial fibrosis that can occur in the intervertebral foramen and suggested that either this or the osteophytes, or a combination, are responsible for the compression. He also stated that laminectomy combined with facetectomy, to decompress the roots and vessels, gives superior results to laminectomy alone.

Brain (1948) suggested venous compression, either in the drainage of the cord or in the intervertebral veins, as part of the pathogenesis.

This brief selection of reports from the literature demonstrates the various theories concerning the pathogenesis. It is apparent that there is reasonable evidence to incriminate vascular factors, arterial, or venous, but it would not be safe to assume that mechanical factors do not operate.

Before more detailed investigation of vascular factors, it is useful to consider some aspects of experimental and clinical ischaemic cord disease.

Ischaemia of the Spinal Cord

Ischaemic disease of the spinal cord is being recognised more commonly than previously. The causes are numerous e.g., thrombosis or thromboembolism of intrinsic or extrinsic vasculature of the cord, syphilitic arteritis, trauma or iatrogenic damage to the aorta or its branches which supply the cord. The pattern of the cord lesion varies with the site or the vascular interference. Wolman & Bradshaw (1967) describe 2 cases of probable spinal cord embolism. In case 1 necrotic areas were present from segment T2 to T10. The shape and position varied between segments. At T2 there was a wedge shaped infarct in the right ventro-lateral column from the cord surface to the ventral horn. At T4 the centre of the dorsal columns was involved. At T7 there was a wedge shaped infarct in the right ventro-lateral column and in the dorsal column, left lateral column and left dorsal horn, there was a crescentic infarct separated from the surface by intact W.M. The patient had atheromata/

atheromata of the aorta and cerebral vessels. They suggested that the crescentic infarcts occurred at the border zone between the anterior spinal artery territory and the penetrating branches of the pial vessels.

Garland, Greenberg & Harriman (1966) presented spinal cord infarction of different aetiologies. They divided their cases into four categories:-

(1) Venous infarction. This case showed thickening of the intra-spinal vessel walls and a tendency to cystic change. The meningeal veins showed evidence of long-standing thrombosis and the extent of cord softening was variable.

(2) Softening in arterial territories. They suggest the territory of the V.S.A., is the commonest due to the lack of reinforcing medullary vessels and lack of collateral supply.

(3) Softening in intermediate arterial zones. This occurs with a simultaneously reduced blood flow in several radicular arteries and results in an infarction of central distribution. They suggest this may occur following certain aortic lesions e.g., aneurisms.

(4) Spinal cord malacia. The chief alterations are in the central G.M., which is in a patchy lacunar state.

Spinal cord infarction, due to aortic damage, has been reported by Hughs (1964) where the infarct involved the whole diameter of the cord. Following an aortoplasty, during which the aorta and lumbar origin of the artery of Adamkiewicz were clamped for 3 hours, Hogan & Romanul (1966) describe the infarction of the cord which was centrally situated in the G.M., and the surrounding W.M. The infarct extended from T12 - S5 and was maximal at about L5.

Woodard and Freeman (1956) ligated extradurally, 6 pairs of nerve roots (T6 - T11) together with accompanying blood vessels in dogs. Their histological findings were as follows:- Consistent loss of dorsal horn neurones, especially those of Clarkes column. Cavities appeared in threequarters of the cords, with/

with the dorsal grey commisure always being involved at some level. The larger cavities sometimes included the dorsal horns and adjacent W.M., of the dorsal and lateral funiculi. Lipid phagocytes were present when there was destruction of the fibres in their areas and the cavities were bordered by hypertrophied astrocytes. They state that this cavitation is an early feature of cord ischaemia but does not appear to represent insufficiency of supply from any one vessel but is due to impairment in the general circulatory state of the cord. They appear undecided whether arterial or venous obstruction is the major factor in producing the cavities.

Tauber & Langworthy (1935) attempted to produce cavities in the cords of cats by ligation of the dorsal and ventral halves of the cord with a silk ligature. Only ligation of the ventral half produced a cavity which was always situated in the base of the dorsal columns. They suggested this was due to occlusion of the ventral spinal artery.

Hughs & Brownell (1966) described ischaemic changes in patients with arteriosclerosis. The pathological findings in the W.M., were:-

1. small areas of necrosis;
2. large spongy areas of diffuse degeneration;
3. Wallerian degeneration of long tracts; and,
4. thickening of walls of capillaries and small arteries by hyaline change and connective tissue proliferation,

and in the G.M.:-

1. small focal areas of necrosis;
2. depletion of neurones with gliosis;
3. "ischaemic" changes in surviving neurones; and,
4. similar changes in vessels to those seen in the W.M.

Hughes (1970) also described the syndrome due to thrombosis of the posterior spinal arteries. The lesion was confined to the dorsal columns and the dorsal grey horns. The infarction extended from T5 - T6 and the thrombosed vessels were present at the same segments.

Having/

Having reviewed some of the relevant literature, it is now appropriate to study the naturally occurring myelopathy due to disc protrusion in dogs. This will be presented in two sections:-

Section I The localised myelopathy.
Section II The ascending syndrome (or extensive myelopathy).

In each section the part played by vascular factors will be considered in detail.

SECTION I

The Localised Myelopathy

Materials & Methods

The material for this investigation was obtained from twenty-three dogs with myelopathy due to disc protrusions. These dogs had been admitted to the Surgery Department of the Glasgow University Veterinary Hospital. Two dogs had been previously treated successfully for protrusions of another disc and, therefore, the number of lesions studied was twenty-five.

Eighteen cases were destroyed after conservative treatment and one died following a urinary tract infection. Four cases were treated surgically, one dying under anaesthesia and three being destroyed subsequently after failing to recover.

Most cords were removed from the vertebral canal for fixation, although in a few cases the entire vertebral column was removed and fixed in situ to study the compressive changes resulting from the protrusion. Samples from three cords were fixed in formol ammonium bromide for 7 days, when frozen sections were cut for staining with Cajal's gold sublimate. The remainder were fixed in 10% formol saline for two to three weeks, when representative samples were embedded in paraffin wax. The stains employed were Haematoxylin and eosin, van Gieson, Mallory's phosphotungstio acid Haematoxylin, cresyl violet, Holzer, Martius Scarlet Blue, Marchi, Weigart Pal and Glees silver impregnation.

RESULTS

The site of the disc protrusion, together with the rostro-caudal extent of the cord damage is illustrated in Fig.1.

The examination of the cords suggested that three broad classifications of lesion could be made.

1. Compressive change:- This was estimated at surgery or at necropsy, after fixation of the cord in situ or after removal for fixation, and was recognised by indentations or flattening of the cord. (Fig.2) These distortions of cord shape could then be assessed microscopically.
2. Malacic areas:- These were localised areas of necrosis of the nervous tissue, often with preservation of the vasculature and the mesenchymal elements. (Figs. 3a & b) In lesions of short duration phagocytic cells were present but cystic spaces were the eventual result.
3. A diffuse demyelination of the white matter (W.M.) which varied in severity from area to area. The term demyelination is used to indicate a myelinoclastic process as defined and illustrated by Wright & Palmer (1970). The degeneration involved both the axons and myelin sheaths and was accompanied by a glial reaction. (Figs. 4a & b)

It was found that one cord might show mainly one type of appearance, or a combination of all three. The three processes might be present at the same segment or in different segments. The frequency of each process is shown in Table I.

Compressive change:-

As would be expected, maximal compression occurred at the level of the protrusion. It was most marked in those "button like" protrusions classified as type I by Funkquist (1962). Where the protrusion had spread out along the epidural space as in Funkquist's type III, the compression was minimal or could not be demonstrated. When the protrusion remained in the mid-line the compression was usually bilateral, whereas a dorsolateral protrusion produced mainly unilateral compression. The compression caused dorsoventral flattening of the cord with an increase in the transverse distance of the lateral columns. In 4 specimens it appeared as if the cord was/

was anchored laterally to the dura by the denticulate ligaments which prevented any displacement of the cord (Fig. 2). This anchoring effect was either unilateral or bilateral, depending on the position of the protrusion. This feature was not found in all cords with obvious compression. In conjunction with this anchoring effect, small radial fissures could sometimes be found running from the grey matter (G.M.,) towards the pial attachment of the ligament. (Fig. 2) Whether these are true pathological "lines of stress" or an artefact produced by section of previously damaged tissue, is not certain, but they were present when the dura was removed prior to section and lipid phagocytes were found along these fissures.

In the majority of compressed cords the anatomical divisions of grey and white matter could be distinguished but, in a few, total disruption of structure had occurred. The W.M., was usually more severely affected than the grey. The lateral columns showed more damage than the ventral with the dorsal columns usually being least affected.

In transverse section many of the axons were swollen, staining pink in H. & E. sections with occasional axons showing basophilic stippling. In longitudinal sections, some axons showed irregular swellings along their length and ended in large retraction balls, a feature best demonstrated in silver impregnations. The number of retraction balls decreased as the period of survival increased.

Some of the myelin sheaths were swollen and contained myeloclasts. These cells contained little cytoplasm and the mature lipid phagocytes, with swollen foamy cytoplasm, were seldom found. The microglia appeared to be the earliest cell to react and their response was limited mainly to the perivascular areas where they were found in small clumps around the intramedullary vessels. Very little evidence of phagocytosis could be seen in these cells. In the areas between the vessels only an occasional myeloclastic cell could be found. The perivascular accummulations of microglia were still present one year after onset.

Irregular patchy demyelination could be demonstrated by myelin stains and appeared to proceed slowly. This was compatible with the/

the presence of a few actively phagocytic microglia. With the swelling of the myelin sheaths and removal of degenerate myelin, spaces and fissures of various sizes developed, giving the W.M., a slightly "moth eaten" appearance. The astrocytic response in the W.M., varied but in most cords a general increase in astrocytic nuclei could be seen in H. & E., sections. The nuclei appeared slightly swollen and often small groups of astrocytes could be found, suggesting proliferation. Slight swelling of the cell body was also seen. Sections stained for astrocytic fibres failed to demonstrate any degree of neuroglial sclerosis.

A striking feature encountered in all but one of the cords showing compression, was a marked increase in blood vessels in the W.M., and this was greater in the areas showing the most damage. It was, therefore, usually most marked in the lateral columns and least in the dorsal. The increase could be marked at $2\frac{1}{2}$ weeks and was still present at one year after onset.

The new vessels were mainly precapillary arterioles. Many of these anterioles, together with the veins, had thickened adventitia, due to an increase in collagen. The earliest increase in adventitial collagen appeared about 2 weeks, with a very thin layer around some vessels. The amounts increased, till in long-standing lesions the adventitia became markedly thicker. (Fig.5a & b) In some instances, thickened vessels could be seen invading the cord from the meninges. It is interesting to note that in the compressed cords with these vascular changes, the compression was gradually increasing as judged from the clinical history and signs, whilst in one case where the compression was acute, the increase in vessels was minimal with very little increase in the adventitia.

Malacia:-

Most of the cords with malacia had little evidence of compression. The malacic areas were not always maximal at the level of the protrusion and in some cords were not even present at the site of the protrusion. The malacia was mainly in the W.M., with only the periphery of the G.M., being affected.

The/

The position of the malacic areas varied from cord to cord and between segments in a cord. The characteristic sites were in the dorso-lateral funiculus, the lateral funiculus, the base and central area of the dorsal funiculus and the ventral funiculus. (Fig. 3) Figs. 6a & 6b show how the position of the malacia may vary within one cord. The shape varied from circular to triangular with the base of the triangle being to the periphery. There was, in many instances, a strip of non-malacic W.M., between the malacic area and the pia, whilst in other sections the malacic area extended to the meninges, causing outward bulging of the pia. Adjacent areas of malacia could fuse to cause large crescentic shaped areas of necrosis (Fig. 7) which might involve the tips of the dorsal horns.

In two cords the area of malacia varied from this. In these cords there was involvement of the whole lateral and ventral column with the exception of a thin strip of W.M., adjacent to the pia. The base of the dorsal column was involved together with the G.M., (Fig. 8). One case was of a few days duration, whereas the other had survived for over a year. The more recent case showed necrosis of the areas mentioned with numerous lipid phagocytes. There was also marked proliferation of astrocytes, especially in the G.M., with some swelling of their cell bodies. There was a marked increase in blood vessels throughout the malacic area in both cords.

The character of the border with the non-malacic tissue varied with the stage. In the case of shortest duration (8 days) there was a well established triangular area of malacia in one dorso-lateral funiculus. The borders were ragged and ill defined with capillary proliferation, whereas with longer duration the borders were clear cut and well defined and the vessels were surrounded by a thin sheath of collagen.

Within the malacic areas, necrosis of all neural elements had occurred with phagocytosis of breakdown products by numerous lipid phagocytes. Lesions of longer standing contained eosinophilic fluid. Trabeculae of blood vessels and connective tissue crossed the malacic areas, often surrounded by lipid phagocytes. An increase in microglia in the bordering areas was noted. Astrocytes were increased in the border zone and showed slight swelling. Stains for neuroglial fibres demonstrated a fine sclerosis around the malacic areas.

Cords showing diffuse demyelination:-

Cords showing diffuse demyelination often had no evidence of compression but demyelination was frequently present at the same level as malacic areas. The demyelination in the W.M., might affect all columns or only small areas of one column. There appeared to be no obvious preferred site. In two cords, small, irregular malacic areas were present in the centre of the vacuolated W.M. These areas did not resemble the previously described malacia in appearance, being smaller, slowly developing and with poorly defined borders (Fig. 4). The demyelinated areas contained numerous swollen myelin sheaths, some of which contained swollen or fragmented axons. In lesions of short duration, retraction balls were present but their numbers decreased with longer periods of survival. There was considerable variation in the size of the swollen myelin sheaths and lipid phagocytes in various stages of development were present. There was an increase in microglia in the W.M., with small clumps either in the vacuolated area or surrounding vessels. Holzer's stain demonstrated a neuroglial sclerosis, the fibres being displaced by the swollen myelin sheaths. The appearance was, therefore, of swollen degenerating fibres being supported on a fine network of neuroglial fibres (Fig. 9).

There was a moderate increase in small vessels, especially in the demyelinated areas. These vessels, which were mainly veins, were also surrounded by a sheath of collagen of varying thickness. The increase in vessels, however, was not usually as marked as in the compressed cords, nor were the adventitial sheaths so thickened. No fibrin was demonstrated in or around the vessel walls in any cord.

The changes in the Grey Matter:-

Malacia was only present occasionally when the periphery of a dorsal horn was involved. Loss of neurones was common to all cords. The severity varied but dorsal, intermediate and ventral areas of G.M., were involved. The cell loss was often marked and in longer standing lesions the G.M., had a fenestrated appearance, due to loss of neurones and fibres. This fenestrated appearance was most marked in those cords with malacic areas in the W.M. Degeneration of the neurones was found in every case, the commonest change being chromatolysis. Both central and peripheral chromatolysis/

chromatolysis was present, often in the same area of G.M. Some cells showed a diffuse loss of Nissel's granules throughout the cytoplasm. In many instances the type of degeneration could not be categorised. Many cells were shrunken and distorted and a few showed eosinphilia of the cytoplasm, although they did not resemble the type seen in acute ischaemic necrosis. In all cases the severity of neuronal degeneration was irregular and markedly shrunken cells could be present with those showing minor degrees of chromatolysis. (Figs. 10a, 10b, 10c, 10d)

The glial response varied markedly but both microglial and astrocytic proliferation occurred. Microgliosis was never as marked as in the W.M., and apart from the two cases showing necrosis of the G.M., lipid phagocytes were very infrequent. Astrocytic proliferation was common and was seen in H. & E. and Cajal sections. (Figs. 11a, 11b) Astrocytic gliosis could lead to quite marked sclerosis of the G.M.

Changes in the Nerve Roots & Meninges:-

These tended to occur late and progress slowly. There was an extremely variable rate of onset and development. There could be remarkably little change at 2 months or marked change at 3 weeks. Degeneration of the fibres was patchy, normal and degenerating fibres being present together in the same root. In general, the ventral root fibres were affected before the dorsal root but this was not constant. Swelling of axons and myelin sheaths was the initial change, followed by an increase in Schwann cells and macrophages, which could be demonstrated in the swollen myelin sheaths. In cords with malacic areas the changes in nerve roots occurred early and progressed rapidly. The affected fibres showed pallor of staining, with marked breakdown and phagocytosis of myelin.

In older lesions fibrosis occurred. This could be seen, occasionally, as early as one month after onset and the amount of collagen increased with the duration of the lesion. It appeared initially as an increase in the endoneurial connective tissue. Concurrent with the fibroplasia was a loss of nerve fibres and at a year there was a marked loss of fibres. (Fig. 12)

There/

There was an increase of collagen in the pia and arachnoid and also thickening of the adventitia of many of the arteries and veins supplying the cord.

Changes at segments not associated with the protrusion:-

Lesions were present in several cords in the dorsal funiculi caudal to the main lesion. These consisted of small areas of demyelination or malacia in the base of the funiculi which sometimes coalesced to form a single lesion.

In the base of the ventral funiculi, small malacic foci were sometimes found, separated from the main lesion by one or even two non-malacic segments. (Fig. 13)

In the lateral, dorsolateral and ventrolateral funiculi, scattered areas of degenerating fibres were present, with an accompanying microglial reaction. Blood vessels with thickened adventitia were present in these areas. The swelling of the myelin sheaths was greater than that usually associated with Wallerian type degeneration but these degenerating fibres usually extended only one or two segments cranial and caudal to the main lesion.

Wallerian degeneration was best demonstrated in the spinocerebellar tracts and the dorsal column fibres which eventually form the fasciculus gracilis. (Fig. 14) With appropriate stains, the degenerating fibres could be traced into the caudal medulla but no attempt was made to localise their terminations.

Cords and meninges were examined for evidence of haemorrhage, either recent or longstanding, as indicated by the presence of macrophages containing haemosiderin. Extradural haemorrhage was present in 8 cases, subarachnoid haemorrhage in one case and intramedullary haemorrhage in five cases. The intramedullary haemorrhage was always slight and usually present in the G.M., around congested blood vessels.

DISCUSSION

Many cords show no evidence of compression by the protrusion and those with severe compression often have less severe lesions than those with no compression. The site of maximal cord damage is not always opposite the protrusion and many cords show lesser changes several segments from the site of maximal damage. These latter findings suggest a probable vascular factor in the pathogenesis.

Based on the pathological findings presented in this paper, it is suggested that vascular factors play an important role. A large number of cords have malacic areas which show a consistency in both distribution and appearance. The typical areas are in the W.M., in the dorsolateral, lateral and ventral funiculi and in the base of the dorsal columns. The appearance is often wedge shaped and in many cases there is an area of relatively normal W.M., between the malacic area and the pia. In the older lesions the border is well defined. It is suggested that these are infarcts of the W.M., occurring in the area supplied by distal ramifications of the V.S.A., probably in the border zone with vessels penetrating from the pia. These infarcts correspond in shape to those described by Wolman & Bradshaw (1967) in their cases of spinal cord embolism. A crescentic infarct found in one case in this series (Fig. 7) is also described by these authors and attributed by them to ischaemia of the watershed area between the V.S.A., territory and pial branches. The cavities in the base of the dorsal columns resemble those produced experimentally by Woodard & Freeman (1956) after ligation of the nerve roots and blood vessels from T6 - T11 in the dog. It is interesting to note that the G.M., is spared from these infarcts with only the periphery of one horn being involved at the most. The two cases which showed necrosis of the G.M., and surrounding W.M., probably represent another form of ischaemic damage. The area of the lesion did not include the dorsal portions of the dorsal columns or the periphery of the lateral and ventral columns and, therefore, corresponds, to what is almost certainly, the territory of the V.S.A., in the dog.

The/

The origin of these infarcts is most probably a reduced blood flow through the intramedullary branches of the V.S.A., and possibly those derived from the pial vessels. The cause of the reduced flow is not certain in every case but there are three possibilities:-

a) Compression by the disc material of the branches of the V.S.A., in the cord tissue:-

> Brieg, Turnbull & Hassler (1966) suggested from a study of human necropsy material, that in spondylosis during flexion of the neck, there is a decreased blood flow through the vessels in the lateral columns, due to the mechanical stresses placed upon them;

b) Compression of the V.S.A., itself; and,

c) Compression of a major medullary artery in the intervertebral foramen before it can supply the V.S.A.

Obviously a combination of a, b and c could occur.

Whether a localised peripheral infarct or destruction of the whole territory of the V.S.A., is produced, probably depends on the degree of reduction in flow, being far more severe in the latter. A diminution in flow will first affect the areas supplied by the terminal branches of the system. The fact that no marked pathological changes have been found in the majority of these vessels suggests that compression of the vessels, rather than obstruction by thrombi etc., is the major factor and that the infarcts are usually a result of chronic, rather than acute, ischaemia. The suggestion of a decreased blood flow, rather than complete ischaemia, is also supported by the differential vulnerability of the tissues, in that the mesenchymal components survived, while the neural elements became necrotic.

The rostro-caudal extent of the malacic lesions and the foci of malacia which occurred one or two segments from the primary lesion, are probably also governed by similar factors. The V.S.A., does not receive a supply from every radicular vessel but is reinforced by a number of medullary arteries at various levels. It is known in man (Schneider & Crosby (1959); Garland et al (1966)) that damage to the V.S.A., or its contributory branches at one level/

level, can cause ischaemia at a different level. These secondary levels are in the intermediate areas between the reinforcing branches of V.S.A., and are, therefore, governed by the position of these reinforcing arteries and the direction of flow in the V.S.A. These anatomical details have not been investigated in the dog but the variation in the rostro-caudal extent of the malacic areas in some of these cases is probably also determined by a decreased longitudinal flow in the V.S.A., causing ischaemia in the water shed areas. In the other cases the malacic areas are related to those segments immediately overlying the protrusion.

The histology of these malacic areas is almost identical to those described by Woodard and Freeman in their experimental cord ischaemia and by Garland et al (1966) in the human. The only variation appeared to be the lesser degree of astrocytic response in the present cases. Fine neuroglial sclerosis occurred around the border of the infarct but was not marked and only progressed slowly. Any swelling of the cell body was slight and only a few astrocytes were involved.

Some cords showed neither malacic areas nor compressive changes and in these the major damage was in the W.M. This has been described, morphologically, as a vacuolated appearance, with degeneration of both axons and myelin sheaths.

Wright & Palmer (1970) have suggested that this non-malacic lesion, which primarily involves the W.M., is possibly due to venous obstruction.

Barron et al (1959), in a series of extramedullary spinal cord tumours, demonstrated that changes occurred mainly in the W.M., and that there was no correlation between cord compression and histological damage. They suggested that the myelopathy was due to venous obstruction caused by the tumour. The small irregular malacic areas found occasionally in the vacuolated W.M., in this series, are probably also infarcts, and appear similar to those described by Barron et al.

Woolf (1954) has shown that in experimental obstruction of the saggital vein in cats, the major changes occurred in the W.M. He/

He further showed that the histological changes consisted of beading and swelling of the myelin sheaths progressing to formation of globules which became phagocytosed by myeloclasts. There was degeneration and loss of axons and a resultant diffuse spongy gliosis. The astrocytes in these areas were "bloated". This histological description resembles that seen in these cords, with the exception of the "bloated" astrocytes. The astrocytes in these cords did not tend to show marked hypertrophy.

Gillilan (1970), in a study of spinal veins in the human, has suggested an anatomical basis for the localisation of the lesions in the W.M., in cases of disc protrusion. This theory is based on obstruction of venous drainage from the affected areas of the lateral and dorsolateral funiculi.

In the cords with the diffusely demyelinated W.M., the pathology differed from both the compressed and malacic cords and it would appear, therefore, that in these cords showing minimal signs or no signs of compression and with the demyelination of the W.M., there is a reasonable possibility that venous obstruction may play a part in the pathogenesis.

In cords where marked compression was evident, it is more difficult to decide on the pathogenesis. As the majority of cases were not operated upon, compression was judged on the appearance at post mortem, either fresh, or after fixation in situ. The possibility of artefactual indentations being produced (Payne & Spillane 1957) has been discussed. The present author was satisfied that the majority of cords which showed indentations after fixation in situ were, in fact, compressed in vivo, as in most cases the protruded mass occupied over half the diameter of the vertebral canal. In addition, similar but smaller indentations could be found after the cord was removed for fixation with the dura intact.

Kahn (1947) has suggested the deticulate ligaments anchor the cord and prevent dorsal displacement during compression. He suggests that the primary pressure is on the ventral funiculus and a secondary force via the denticulate ligaments is exerted on the dorsolateral funiculus. This theory seems to have fallen into disrepute/

disrepute but in four cords I have noted that the compressed cord appeared to be anchored by the ligaments. The cords showing this feature were all severely flattened. It is hard to determine the exact role that they were playing, as in other cords with similar degrees of compression, the ligaments could be seen to be not anchoring the cord. It is possible that in certain cases the ligaments accentuate the damage caused by compression. The vascular changes, consisting of hyperplasia and adventitial fibrosis, are of interest. Hughes & Brownell (1966) describe similar thickenings around capillaries and small arteries in their cases of spinal cord ischaemia. They state, however, that the spinal veins were normal, whereas in this series veins also showed thickening. Garland et al (1966) mention the thickening of intraspinal vessels in cases of venous obstruction. Mair and Druckman (1953) and Wilkinson (1960) both mention the fibrous thickening of blood vessel walls in cervical spondylosis. This fibrous thickening of the vessels is identical to the "hyalinisation of small vessels" mentioned by Wright & Palmer, who found that the veins and capillaries were mainly affected. The present author would agree with their statements that this change is more common in the W.M., and is closely correlated to the occurrence of demyelination. These latter authors suggest that the hyalinisation may be a result of an increased vascular permeability to plasmatic constituents. In this present series no evidence of a fibrin "leak" from the vessels was found. The adventitial fibrosis may be a result of a chronically decreased blood flow, as subendothelial proliferation of connective tissue has been found in cerebral arteries following ischaemic episodes (Romanul & Abramowicz 1964) and the changes seen in the much smaller cord vessels may be of a similar nature. The vascular permeability in the acute stage of the myelopathy has yet to be established. Whatever the origin of this vascular thickening, it will decrease diffusion rates across the vessel walls.

It is well-known that if spinal cord ischaemia is produced experimentally by occlusion of the aorta, the principle histological changes are found in the G.M., particularly the intermediate and ventral areas. (Tureen 1936, Van Harreveld & Marmont 1939) This effect may also be seen following aortic surgery in man. (Adams & van/

& van Geertruyden 1956) and aortic aneurism (Thompson 1956).

Tarlov (1957) has suggested on this and other evidence, that the clinical signs of cord compression are not due to ischaemia but to mechanical deformation. The present author suggests that the two situations cannot be compared, as in cord compression only a small part of the spinal circulation (V.S.A., its branches or a medullary artery) is being occluded, so decreasing the flow in certain areas of the cord, mainly the W.M. In aortic occlusion there is a sudden decrease in flow to all parts of the cord and, therefore, those areas with the highest blood flow and highest oxygen demand (i.e., the G.M.) will be affected first. (In Tarlov's publication there are illustrations of cords with malacic areas in positions corresponding to those described in this publication). Infarcts in the W.M., have been well documented, both clinically (Hughs & Brownell 1966, Wolman & Bradshaw, 1967) and experimentally (Woodard & Freeman 1956) after atherosclerosis, arterial embolism or ligature.

SECTION II

The Ascending Syndrome (extensive myelopathy)

Material & Methods

Eight dogs with clinical evidence of the ascending syndrome were destroyed because of a poor prognosis. The duration of signs varied from one day to two weeks. Immediately after death the spinal cords were removed and fixed in 10% formol saline for three weeks. Representative blocks of cord were embedded in paraffin wax and stained with Haematoxylin & Eosin (H/E), Haematoxylin van Gieson, Martius Scarlet Blue (M.S.B.), Mallory's phosphotungstic acid haematoxylin, Holzer, Loyez and Marchi.

Results:

Seven of the disc protrusions were classified as Type III and one as Type II (Funkquist 1962). In a Type III protrusion the disc substance spreads along the epidural space for a distance of one or more vertebrae and may completely encircle the dura. The Type II protrusion combines a localised "button shaped" mass over the disc with some extension along the epidural space.

In all specimens there was a considerable epidural haemorrhage around the protruded material, together with epidural fat necrosis. There was also marked meningeal and intramedullary haemorrhage extending for varying distances rostral and caudal to the protruded disc. Details of these findings are presented in Table 2.

The severity of cord damage at various representative levels was classified as:-

1. Areas of total transverse necrosis;
2. Areas of sub-total transverse necrosis;
3. Areas of lesser damage; and,
4. Changes in extramedullary vessels and nerve roots.

The extent of each process is presented in Table 2.

In no case was there any evidence of cord deformation by the extradural mass.

1. Areas of Total Transverse Necrosis

There was total necrosis of both neural and mesenchymal elements of the cord. The disruption of structure was occasionally so marked/

marked that the anatomical divisions of G.M., and W.M., could not be distinguished. The majority of intramedullary blood vessels were necrotic and there was often severe haemorrhage which was usually more marked in the G.M. In addition, neutrophils were found in many areas, especially around necrotic neurones (Fig.15). The ventromedian septum often contained a dense accumulation of neutrophils which were not related to any haemorrhage. There was a marked lack of reaction to this necrosis and no lipid phagocytes were found in these necrotic areas, even after a ten day survival. In many segments the neurones showed ischaemic cell change (I.C.C.) in varying degrees of severity. In the less severely affected neurones there was shrinkage, loss of Nissl granules and a prominent nucleolus inside a faint nuclear outline. The cytoplasm of more severely ischaemic neurones was homogeneously pink (H. & E.) and the nucleus pyknotic. Small irregular basophilic dots, representing the degenerate boutons terminoux were found around some neurones. Eventually only a faint cell outline (ghost cells) could be identified (Figs. 15 & 16).

2. Areas of sub-Total Transverse Necrosis

This term is used to denote necrosis of a considerable transverse area of the cord but with sparing of certain structures. Two patterns were seen in the first of which there was necrosis of neuroectodermal structures and sparing of blood vessels and microglia i.e., the mesenchymal elements. In certain segments, surviving capillaries in the G.M., showed marked endothelial hyperplasia and were accompanied by an occasional lipid phagocyte (Fig. 17). In other segments there was a marked accumulation of lipid phagocytes and at some levels preservation of a thin strip of W.M., on each side of the ventromedian fissure. (Fig. 18) There was an increase in the number of intramedullary vessels, both arteries and veins having thickened hyalinised walls. This collagen formed rapidly and was well developed by 14 days.

In the second form of sub-total necrosis there was survival of both neural and mesenchymal structures in certain transverse areas of the cord and necrosis in others. (Fig. 19) The G.M., was more commonly affected than the W.M., the necrosis being accompanied often by marked haemorrhage and loss of normal architecture. Any neurones present were degenerate, many showed I.C.C., and others were vacuolated. Many blood vessels were necrotic/

necrotic and migrating neutrophils were present, both in the vessel walls and surrounding tissue. (Fig.20) Deposits of fibrin around necrotic vessels were demonstrated in both intra-medullary and meningeal vessels but not around non-necrotic vessels. (Fig.21)

3. Segments with Lesser Damage

Bordering the sub-totally necrotic areas, were segments showing lesser degrees of damage. Localised infarcts of the W.M., were not uncommon. (Fig. 22) They were often triangular in shape with the apex to the periphery and were found in the dorsal, lateral and ventral funiculi. The infarcts contained numerous lipid phagocytes, and slightly hypertrophied astrocytes were found around the borders. Around the more recent infarcts there was capillary endothelial proliferation and a microgliosis.

Other areas of W.M., showed a patchy demyelination with swelling of the axons and myelin sheaths and phagocytosis of the debris by microglia. (Fig. 22)

The neurones of these segments showed severe chromatolysis but I.C.C., was not usually seen.

The lesion was often increased by a rostral or caudal extension of haemorrhage and necrotic tissue. This was seen either in the base of the dorsal funiculus or in the region of the central canal and rostral extensions were the more common. The reaction to this necrotic "plug" varied but there was often capillary endothelial hyperplasia. In other areas there was neutrophil infiltration and evidence of further I.C.C., in the G.M., around the "plug".

4. Changes in Extra-medullary Vessels and Nerve Roots.

Evidence of severe extramedullary vascular damage was present in all cords, many of which contained thrombosed arteries and veins. There was no consistent pattern of thrombosis. (Fig.23) Many other vessels were necrotic with extravasation of erythrocytes into the meninges and infiltration of their walls with neutrophils. Numerous vessels were markedly congested, the veins being affected to a greater degree than the arteries, and strands of fibrin representing early thrombosis were sometimes found in the lumena of the veins. (Fig. 24) Many congested vessels had ruptured, resulting in severe sub-dural and sub-arachnoid haemorrhage, which could extend from the sacral to the anterior thoracic or cervical segments./

segments. The vascular congestion was more prominent in the lumbar and sacral areas. In the sacral areas the haemorrhage extended between the nerve roots. The pattern of extramedullary vascular damage at a given segment did not appear to be directly related to the severity of the myelopathy at that segment.

The nerve roots also showed a wide range of changes. Intra-radicular haemorrhage was not uncommon, particularly in the sacral area and cauda equina. Many of these nerve roots showed pallor of staining and loss of Schwann cell nuclei. Other nerve roots showed Wallerian type degeneration with swelling of axons and myelin sheaths and phagocytosis of debris by histiocytes. (Fig. 25)

Discussion:

In 87% of cases, the protrusion was Type III and no Type I protrusions were present. Funkquist (1962) found twenty Type III protrusions (95%) in a series of twenty-one cases of the ascending syndrome. This distribution is in contrast to the localised myelopathy of disc protrusion, where a large proportion are Type I. (Funkquist 1962)

The speed of onset, as judged clinically, was less than 12 hours in six of the seven cases with Type III protrusions. (There is no information available with the seventh). None of these cases had prodromal signs for more than a few hours, which supports Funkquist's suggestion that Type III protrusions are a result of disc material being forced into previously intact parts of the epidural space. In the case with Type II protrusion, the onset of paraplegia was gradual and there was a previous disc protrusion at the adjacent rostral disc. These factors probably prevented the spread of the protruded material in the epidural space.

Another variation from the localised myelopathy is the marked extra and intradural haemorrhage. The extradural haemorrhage, together with an accompanying inflammatory reaction, often comprises a large proportion of the extradural mass as shown by Hansen (1952).

The cord pathology indicates severe ischaemia of the segments. Blackwood (1967) states that neutrophil infiltration indicates some blood flow in the region, although in many areas containing neutrophils, all the blood vessels were necrotic. There was also variation in the severity of the neuronal ischaemia between necrotic/

necrotic segments. These facts suggest that the onset of ischaemia and tissue damage were not simultaneous in all segments. The severity of the damage is further emphasised by the complete lack of microglial reaction to the necrotic tissue. The infarction of the G.M., is typically haemorrhagic as in the brain (Blackwood 1967) and erythrocytes in the W.M., were usually related to necrotic blood vessels.

The areas of sub-total necrosis with vascular and microglial survival, probably represent incomplete ischaemia. The mesenchymal structures survive, as they are less vulnerable to anoxia and this results in the numerous lipid phagocytes found in these segments. The numerous wedge shaped infarcts found in the W.M., in segments with lesser damage probably result from a decreased blood flow in the terminal branches of the V.S.A., causing ischaemia in the "watershed areas" between the V.S.A., territory and that of the pial vessels. Similar lesions have been demonstrated in the localised myelopathy of disc protrusions (Section 1).

The suggestion that ischaemia is prominent in the pathogenesis of the ascending syndrome is not new but it is uncertain how the ischaemia is caused. The most severe infarction covers the transverse area of the cord and is not, therefore, related to the territory of any spinal artery. It is unlikely, therefore, that the arterial thrombi are the cause of the ischaemia, through obstruction of blood flow.

Funkquist (1962) suggests this myelomalacia is a result of circulatory disturbance and quotes experiments by Woodard & Freeman (1956) to support this. Woodard & Freeman (1956) bilaterally ligated the nerve roots and accompanying blood vessels from T6 to T11 in dogs. The pathological changes were small cavities in the dorsal grey commissure extending into the adjacent W.M., loss of dorsal horn neurones, in particular, those of Clark's column and varying degrees of gliosis in the G.M. These changes do not resemble those seen in the ascending syndrome and it is unlikely that loss or obstruction of radicular or medullary vessels could produce the extensive cord necrosis. Indeed all the intercostal arteries can be ligated in the dog without any evidence of locomotor defect (Killen & Adkins 1965).

It would appear that mechanical obstruction or compression of medullary/

medullary vessels by the extradural contents is not the cause of the ischaemia.

Factors that have to be taken into account in considering the pathogenesis of the ischaemia are:-

1. The predominance of Type III protrusions;
2. The acuteness of onset;
3. The marked extra and intradural haemorrhage; and,
4. The presence of thrombi.

Type III protrusions would appear to be associated with the ascending syndrome, as shown in this study and by Funkquist (1962). However, up to 50% of cases with localised myelopathy may have Type III protrusions (Funkquist 1962).

In the majority of dogs with the ascending syndrome, the development of signs is rapid as judged clinically. Olsson (1958) has introduced the "dynamic factor" to explain apparent discrepancies between the size of protrusions and the severity of cord damage. He suggests that a "sudden powerful protrusion may momentarily give rise to irreversible changes" whereas the "cord can endure slowly increasing or large stable compression". Whilst the speed of development is undoubtedly of importance, there must obviously be other factors operating. Many localised myelopathies are caused by protrusions which are of sudden onset, and in disc explosions there is usually no evidence of multi-segmental necrosis (Griffiths 1970).

Palmer (1964) suggests that temporary vasospasm occurs as a result of the mechanical trauma. This is possible, but Kelly et al (1970) could not demonstrate vasospasm of the dorsal cord vessels after subjecting the cord to experimental trauma of 400 gram centimetre force. However, they showed that local cord hypoxia developed rapidly after the injury. This hypoxic area only extended for approximately one centimetre in either direction. Vasospasm can also be induced as a result of subarachnoid haemorrhage. This is known to occur in man and Wilkins & Levitt (1970) have shown a similar phenomenon in the circle of Willis in experimental dogs. They demonstrated arterial spasm occurring shortly after injection of whole blood, or serum from incubated whole blood, into the cisterna magna and this arterial spasm persisted for several days. They suggest vasoconstrictor substances are liberated during haemolysis. A similar situation is/

is known to occur in cats with thrombo-embolism of the caudal aorta. The resulting ischaemia is not due to vascular obstruction but rather to failure of any collateral circulation. Butler (1971) reproduced the syndrome by injection of supernatant from lysed erythrocytes into an aortic space between double ligatures. He also produced evidence to suggest that 5 - hydroxytryptamine may be implicated in the pathogenesis of the collateral circulatory failure.

The ascending syndrome is often accompanied by marked subanachnoid haemorrhage and thrombosis of the cord vessels. There are present, therefore, factors which are known to be capable of causing vasospasm and reduction of collateral circulation. It is possible that these factors operate in the pathogenesis of the segmental necrosis. Lindblad et al (1961) have demonstrated, microangiographically, the marked decrease in arterial filling that occurs in the ascending syndrome.

It would be erroneous to suggest that only arterial factors operate. A noteable feature of the pathology was the marked venous congestion, especially in the caudal cord, often leading to venous rupture. These ruptured veins, together with diapedesis from necrotic vessels were probably the source of the marked meningeal haemorrhage. Early venous thrombus formation was probably the result of a decreased blood flow.

In support of venous factors being implicated in the pathogenesis of the necrosis, the work of Denny-Brown et al (1956) should be considered. These workers produced a sudden retrograde distension of a cerebral vein by injection of warm saline. At a critical pressure a blanching of the area occurred, caused by arterial spasm. There was a partial restitution of circulation followed by distension of the capillaries and veins and vascular stasis. This is followed by capillary rupture and perivascular haemorrhage and plasmatic leakage from degenerating and necrotic vessels. Neutrophils and microglia were found in the infarcted area. Indian ink injection of the main arteries demonstrated complete lack of filling of the infarct with no collateral circulation.

The histological features of this experimental lesion, closely resembles the cord damage in the ascending syndrome. It is likely that in the cord there is a sudden rise in pressure and distension/

distension of the venous sinuses and medullary veins. This stasis has been demonstrated radiographically by Lindblad et al (1961). This could well result in arterial spasm and the syndrome described by Denny-Brown et al. It is almost certain that in these cords there is failure or severe impairment of a collateral circulation. The circulatory disturbances in the cord are complex and it is unlikely that total ischaemia occurs simultaneously, even in the eventually necrotic segments. In the sub-totally necrotic areas, small islands of damaged but living tissue can be present in the midst of a necrotic area.

The rostral extension by the necrotic, haemorrhagic plug, probably occurs due to the displacement of tissue which is prevented from moving laterally by the inelastic dura. McGrath (1966) makes this suggestion, which would appear reasonable. The present author has often observed a similar phenomenon in cords damaged through vertebral fracture or sub-luxation. This "plug" of tissue which occurs in the base of the dorsal columns or central canal is also seen in traumatic lesions of the spinal cord in man. (Greenfield & Russel 1967)

PART II

An experimental study of spinal cord blood flow, with particular reference to the physiological parameters controlling the flow.

INTRODUCTION

In Part I histological evidence was presented which suggested that ischaemia was involved in the pathogenesis of the myelopathy caused by disc protrusions. In the localised myelopathy a reduction in blood flow in certain areas was suggested, whereas in the ascending syndrome a much more severe, and, in some areas, a total ischaemia was present. It would be useful to be able to measure the blood flow in the cord to confirm these suggestions and to evaluate treatment.

The blood supply to the thoraco-lumbar spinal cord in the dog, in relation to the measurement of spinal cord blood flow. (S.C.B.F.)

The blood supply to each segment is derived from three arteries, the single ventral spinal artery (V.S.A.) and two dorsal spinal arteries. The V.S.A., is a constant structure running the entire length of the cord, although varying in diameter in different regions. The dorsal spinal arteries are not constant and may be absent, especially in the thoracic cord or may be plexiform channels.

The V.S.A. is supplied by a varying number of medullary arteries which are usually unpaired. The largest medullary artery usually accompanies the ventral nerve root of either L5 on the right or L4 on the left. In the lower thoracic and rostral lumbar cord, there are a number of smaller medullary arteries (Fig. 26

A review of techniques for repetitive recording of blood flow.

The appreciation of the anatomy of the cord's blood supply allows the various techniques of flow measurement to be studied briefly for their applicability.

(1) Blood Flowmeters (Electromagnetic & Ultrasonic)
These allow an assessment of blood velocity rather than flow and are applied to the arterial trunk supplying an organ. Their use is obviously precluded in the cord where each segment may be supplied from three main arteries, which are relatively/

relatively very small in diameter and not suitable for this form of measurement.

(2) Heat Clearance Techniques Betz (1968) has reviewed heat clearance techniques, for use in the measurement of local blood flow. They are quite suitable for use in the spinal cord as demonstrated by Wullenweber (1968) and Palleske & Herrman (1968), but have the disadvantage of only allowing qualitative measurements. The effect of blood gases etc., on S.C.B.F. can be assessed but no valid comparisons between different dogs can be made.

(3) Diffusible Indicators The techniques employing these indicators make use of their rapid diffusibility between blood and tissue and are all based on the Fick principle (v.i.)

(a) The Kety-Schmidt Method

This method was introduced in 1945 by Kety and Schmidt to measure cerebral blood flow. The indicator used was nitrous oxide which was inhaled for a period of ten minutes or more. Intermittent samples are taken from the main artery and vein supplying the organ under study and the concentration of N_2O measured. This is continued until a state of equilibrium is reached. From the integrated arterio-venous difference in N_2O content, the blood flow can be calculated over the inhalation time. The N_2O can be replaced by other indicators such as the inert radioactive gases Xenon ^{133} (Xe^{133}) or Krypton ^{85} (Kr^{85}) (Lassen & Munck 1955).

This basic technique and its modifications require a main artery and vein from the organ for the collection of samples. It is, therefore, unsuitable for the spinal cord/

cord where there is a multiple arterial and venous supply. It would be impossible to obtain samples of blood wholly or even chiefly supplying or draining the cord.

(b) Intra-arterial Injection Techniques

The Kety-Schmidt method has been largely replaced by intra-arterial injection of the radioactive indicator followed by external monitoring of the tissue desaturation process. There are two basic isotope counting methods depending on the indicator chosen. These are beta (B) and gamma ( ) counting. The latter will be discussed first as it is more commonly used. The usual isotope employed is Xe^{133}. It would be possible to inject Xe^{133} in saline into the aorta and obtain saturation of the spinal cord but the Xe^{133} would reach the other tissues in the vicinity, such as muscle, bone and even abdominal viscera. The range of the emissions would result in the desaturation process of all these organs being recorded. Attempts to limit the recording to the spinal cord by use of lead shielding would be excessively traumatic. Injection into one of the medullary arteries, besides being technically difficult, would also be traumatic and might result in arterial spasm. For these reasons it is necessary to place the Xe^{133} in the cord tissue by direct injection to ensure that only emissions from the cord are recorded. A more detailed study of the theory will be presented below.

Techniques involving B counting usually use Kr^{85} as an indicator (Lassen & Ingvar 1961).

The/

The intra-arterial injection is similar to that used for Xe^{133} but the B emissions have an average range of about 0.7 mm., in tissue (Glass et al 1961). It would, therefore, be feasible to record from the spinal cord without interference from other tissues. Initial studies confirmed these impressions but there are technical difficulties. It is difficult to obtain a high initial Kr^{85} concentration in the thoraco-lumbar cord following aortic injection. This is due to the loss of Kr^{85} to abdominal organs and limbs. This could be overcome by cannulation of the intercostal or lumbar vessels from which the medullary arteries arise. These vessels would first have to be identified angiographically and this technique has not been developed in the dog to date.

It is also necessary to drain C.S.F. and prevent its accummulation at the recording site. If this is not accomplished, the count rate from the cord diminishes markedly. Blood seeping onto the cord surface acts in a similar manner and therefore strict haemostasis accompanied by continuous removal of fluid (C.S.F. and blood) is necessary throughout the recording period. These technical difficulties make the method less useful for measuring S.C.B.F. over periods of 6 to 8 hours as required in these experiments and Xe^{133} direct injection technique has therefore been adopted.

Theoretical considerations of the method.

The/

The method is based on the Fick principle which states that in the steady state the quantity of an indicator taken up or given out by an organ in a specific time is the product of the blood flow and the arterio-venous difference for the indicator.

It has been shown by Kety (1951) that freely diffusible indicators can be used to measure local blood flow as their clearance is determined solely by blood supply.

Xe^{133} is an inert radioactive gas which emits rays of 81 Kev., and is suitable as an indicator for several reasons. It is inert and freely diffusible through tissues and is also far more soluble in air than blood. On circulation through the lungs, a high proportion will be exhaled and any remaining isotope will be diluted, so that there is no effective arterial recirculation.

Following the injection of a small amount of Xe^{133} into the tissue, there will be diffusion into the peri-injection site tissues, and the partial pressure of Xe^{133} at a given point will be governed solely by solubility and diffusion. Initially, following injection, the Xenon tension in the capillaries will be low or zero. Diffusion into the capillaries will occur and as long as there is a blood flow present, there will be continuous diffusion into the capillary and clearance by the bloodstream. It follows that the greater the blood flow the faster is the clearance.

If the tissue under study is uniformly perfused, i.e., homogeneous, the clearance curve is likely to be a simple monoexponential function. Gillespie (1968) has outlined the theoretical conditions which have to be met for a monoexponential clearance. In a heterogeneous tissue, different areas will be clearing at varying speeds and the clearance curve will, therefore, be biexponential or multiexponential, depending on the tissue. The types of clearance curve recorded from the spinal cord and their origin will be discussed later.

The derivation of the formula for the calculation of S.C.B.F. using this technique, is identical to that which was used by Lassen et al (1964) for the measurement of muscle blood flow by direct/

direct injection.

Review of the literature on S.C.B.F.

Only a brief review of previous work is presented here. The cited literature is discussed in detail under the appropriate section of the study.

In comparison to the brain, relatively little work has been devoted to the blood flow in the spinal cord. Field et al (1951), using a thermocouple technique, were early workers in this field but certain of their results are at variance with current concepts. Several workers (Otomo et al 1960, Margolis et al 1957) have used direct observation of the response of spinal pial vessels to various agents or measurement of the velocity of the flow using intra-vascular indicators. More recently Palleske and Herrmann (1968) in pigs and Wullenweber (1968) in the human, have used heat clearance techniques to obtain qualitative information regarding spinal cord blood flow (S.C.B.F.). Landau et al (1955) and Flohr et al (1969) have developed quantitative techniques for single measurements of cord blood flow. Smith et al (1969) using an inert gas radio-active isotope clearance technique measured the flow in goats.

Two of the main physiological parameters which alter cerebral blood flow (C.B.F) are the blood gases carbon dioxide (CO_2) and oxygen. (Harper 1965, 1969) It is accepted that the cerebral blood flow (C.B.F) is increased in hypercapnia and decreased in hypocapnia. Hypoxia also increases C.B.F. (McDowall 1966). The effect of these blood gases on the S.C.B.F. has been studied by relatively few workers. Wullenweber (1968) and Palleske & Herrmann (1968) have studied the effect of blood gases on the S.C.B.F. using heat clearance techniques. Smith et al (1969) and Flohr et al (1969) have also investigated the effects of CO_2 on the spinal circulation.

The arterial blood pressure is another factor which could potentially determine S.C.B.F., although it has been demonstrated that within a wide range blood pressure has little effect on C.B.F. (Harper 1965, Rappela & Green 1964). Field et al (1951), Otomo et al (1960) and Kindt (1971) have all investigated the effects/

effects of blood pressure on S.C.B.F., although all their results are not in agreement.

The study presented in Part II is divided into 3 sections.
Section 1 presents the measurement of S.C.B.F. at normocarbia, normoxia and normotension. A comparison of flow at different segments is made and the effect of different anaesthetics discussed.
Section 2 evaluates the effect of the blood gases, carbon dioxide and oxygen on the blood flow.
Section 3 is concerned with the role of blood pressure in controlling the S.C.B.F.

SECTION I

The spinal cord blood flow in the anaesthetised dog under conditions of normocarbia, normoxia & normotension.

METHODS:

Unselected dogs were used. In the majority, anaesthesia was induced with thiopentone (25 mg/Kg) and maintained with a 70% nitrous oxide/oxygen mixture and 0.5 - 1% trichlorethylene or 0.5% Halothane. In addition to these animals maintained on anaesthetic-gas mixtures, several dogs were also anaesthetised with pentobarbitone (25 mg/Kg) and maintained on 70% N_2O/O_2. The anaesthetic-gas mixture was delivered through a Palmer pump with ventilation adjusted to maintain normocarbia during surgical preparation and measurements. End tidal carbon dioxide concentration was monitored continuously with an infra-red analyser.*

A femoral artery was cannulated and mean arterial blood pressure measured with a damped mercury manometer. This cannula also allowed collection of arterial samples for blood gas analysis. During each blood flow estimation, blood pH, pCO_2, pO_2 were measured using standard electrodes**. Any base deficit was corrected with 8.4% sodium bicarbonate. The P.C.V., was estimated by the micro-haematocrit method (Fisher 1962).

Pharyngeal temperature was measured with a mercury thermometer and heating lamps were used to maintain the temperature between 37 - 38°C.

Dorsal laminectomies were performed to expose the required cord segments, with the dura intact.

Approximately 1 - 2 µL of Xe^{133} dissolved in saline (activity 1 mC/ml) was drawn into a Hamilton syringe, care being taken not to include air bubbles. (The actual amount injected was arranged to give a maximum count rate of 300 c.p.s.)

The recording apparatus consisted of an uncollimated scintillation counter with a one inch sodium iodide crystal coupled through a ratemeter to a linear recorder. The count range was 0 - 300 c.p.s., with a one second time constant. The paper speed was 2 cm. per minute.

The/

* Capnograph Godart

** Radiometer. Copenhagen.

The scintillation counter was positioned one to two cms., above the cord and the background count measured. The injection of Xe^{133} was made obliquely into the mid-line through the intact dura. The clearance curve was recorded for twenty minutes or until the background count was reached. In certain measurements 0.2 µL of congo red was included in the syringe to identify the site of injection.

Approximately twenty minutes elapsed between measurements, during which time the dura was covered with a swab soaked in saline at 37°C.

Analysis of the clearance curves

After subtraction of background, the clearance curves were transposed onto semi-logarithmic paper. Those curves showing more than one component were analysed by compartmental analysis (Lassen et al 1963) dividing them into fast and slow components. The blood flow was calculated from the formula -

$$\text{S.C.B.F.} = \frac{\lambda \times \log_e 2 \times 60}{T_{\frac{1}{2}}} \times 100$$

S.C.B.F. = spinal cord blood flow (ml/100g/min)

λ = partition coefficient: tissue/blood. (This varies with the haematocrit (Veal & Mallett 1965). The values for λ were considered to be the same as those obtained for grey and white matter in the brain.

$T_{\frac{1}{2}}$ = time in seconds for the activity to decrease to one half of the initial value and is calculated from the semilog. plot.

RESULTS:

Approximately 60% of clearances were monoexponential. Fig. 27 illustrates the semi-logarithmic plot of a monoexponential clearance and the site of the cord injection for this clearance is illustrated in Fig. 28a. The remainder of the curves were biexponential (Fig. 29) and from these latter, the fast component, or flow in the grey matter (G.M.) and the slow component, or white matter (W.M.) flow, were extracted (Fig. 30). The site of injection for the curve obtained in Fig. 29 is also illustrated in Fig. 28b. (see discussion for the validity of these assumptions).

Table 3 demonstrates the reproducibility of the flows in the W.M., over a period of six hours in three dogs. (In each dog the runs not mentioned were used to investigate the effects of pCO_2 on flow). The flows in both Tables 3 & 4 have been corrected to a $paCO_2$ of 40 mm.Hg. (see discussion)

The results for a larger series are presented in Table 4. The mean blood flow in the white matter in 8 dogs (25 observations) was 15.7 ± 6.6 ml/100g/min.

The mean deviation of each flow from the average at its site was 7.3% and 80% of measurements had a variation of less than 10% from the mean flow for the cord segment.

The variation in flow rates in the W.M., between different thoraco-lumbar segments in the same dog, was studied by injecting two segments and recording the clearance from each simultaneously. The segments were shielded from each other by lead. The results are presented in Table 5.

A comparison of the effects of trichlorethylene, Halothane and pentobarbitone anaesthesia on the flow in the W.M., was studied using segments T12 and T13. (Table 6) There was no significant difference in S.C.B.F., between dogs anaesthetised with any of the three methods. There was, however, a significant difference in mean arterial blood pressure between dogs anaesthetised with trichlorethylene or pentobarbitone and those anaesthetised with Halothane. ($P < 0.01$)

A much smaller number of estimations of the flows in fast component were made and the results presented in Table 7. The mean/

mean blood flow, calculated from the fast component, for all the observations was 48.4 ± 23.7 ml/100g/min., and this is significantly greater than the flow in the W.M. ($P < 0.001$)

The mean deviation of each flow from the average at its site was 16% and 50% of clearances had a variation of greater than 10% from the mean flow at the segment.

Fig. 31 illustrates the failure of Xe^{133} clearance after cardiac arrest, thus showing that the major part of the isotope clearance is by the bloodstream and not diffusion into adjacent structures.

DISCUSSION:

The anatomical identification of the fast and slow components of the clearance curve has been studied in relation to cerebral blood flow. There is good evidence that the slow component represents the flow in the W.M., Espagno & Lazorthes (1966) obtained a monoexponential slow clearance after injection of Xe^{133} into the cerebral W.M. It has also been demonstrated by autoradiographic techniques that the slow component represents the flow in the W.M. (Lassen 1968) The flows obtained from mono-exponential clearances in the present experiments were very similar to those obtained from the slow component in the same dog and the congo-red marking suggested that these monoexponential clearances resulted from an injection into the W.M. (Figs. 27 & 28). It has, therefore, been assumed, on reasonable evidence, that the monoexponential clearances and the slow component of biexponential clearances, represent the flow in the W.M. Espagno & Lazorthes found that the slow component of the biexponential curves, after cortical injection, is faster than the monoexponential clearance after direct injection of deep W.M. They suggest this faster flow arises from the sub-cortical W.M. In the present study there was no significant difference between the flows calculated from the slow component and those from monoexponential clearances, recorded from the same dog.

It is known that alterations in $paCO_2$ affect the S.C.B.F., (Flohr et al 1969, Smith et al 1969) and for this reason a correction must be applied when comparing flows at slightly varying $paCO_2$. The change in blood flow in response to a change in $paCO_2$ was measured (Fig. 32) and from this graph, the flows at normocarbia/

normocarbia were corrected to a standard $paCO_2$ of 40 mm.Hg., as suggested by Harper et al (1961). These corrections are illustrated in Table 3, which demonstrates how the flows may be under or over estimated, if allowance is not made for variations in $paCO_2$. This correction also allows valid comparison between the flows in different dogs (Table 4).

The results demonstrate that under apparently identical situations there is a marked variation in flows between different dogs varying from approximately 10 ml/100g/min., to 30 ml/100g/min. In spite of the wide range of flows between different dogs, the flows at one segment in the same dog were reasonably reproducible over a period of six hours under constant experimental conditions (Tables 3 & 4). Smith et al (1969), in the goat, also found a marked variation in flows at the same segment, between different animals and in distinction to the present study, found variations between lumbar and thoracic segments in the same animal. This discrepancy is probably due to the fact that the present author was measuring flow in the W.M., whereas Smith et al were estimating the average cord blood flow,which takes into account flow in the G.M.

Only one of four dogs in the present experiments showed a significant variation in the W.M., flow between different segments of the cord. (Table 5) Fieschi et al (1968) have shown that the blood flow is approximately the same in numerous areas of sub-cortical W.M., and that it is homogeneously perfused, unlike the G.M. It is, therefore, reasonable to suppose that there is constancy of flow through the W.M., of all the thoracolumbar cord segments in the anaesthetised dog, as suggested in the present experiments.

It is known that in the anaesthetised animal the cerebral cortex is heterogeneously perfused in common with most areas of G.M., so far examined. This has been shown by beta clearance curves using Krypton 85 (Harper et al 1961) and autoradiography (Fieschi et al 1968). However, Harper & Jennett (1968) have shown a good correlation between the fast component of the gamma clearance curves and the average cortical blood flow measured by beta clearance. The fast component has been assumed to represent the flow in the G.M., at the site of injection.

The/

The flows in the G.M., are, as expected, significantly greater than those in the W.M. There has, however, been difficulty in obtaining reproducible results in the same dog under constant conditions. There are several possible reasons for this:-

(1) The initial portion of the clearance curve, which contains the fast component, could not be accurately recorded due to removal of the needle from the cord and the Xe^{133} remaining in the syringe affected the count rate.

(2) There is the possibility of intercompartmental diffusion of Xe^{133}, especially from W.M. to G.M., as discussed by Gillespie (1968).

(3) As stated previously the G.M., is heterogeneously perfused and the actual flow measured in these experiments would depend on the siting of the injection in the cord. It is, therefore, possible that if consecutive injections were placed so that clearances were obtained from different areas of G.M., the flows would not be the same.

Smith et al (1969) surmounted this problem by calculating the average cord blood flow. They used a micromanipulator to ensure subsequent injections were made into the same area. The present author could not achieve consistent results by calculating the average blood flow and this is probably due to the fact that the injections were made freehand. Approximately 60% of all clearances were monoexponential and it would obviously not be possible to calculate the average blood flow in these cases. For these reasons it has been decided to study S.C.B.F., in relation to the slow component and it has been found that this shows similar responses to changes in pCO_2, pO_2 and blood pressure, as are found in the brain (see Sections 2 & 3).

Perhaps one major criticism of the method is the necessity to inject the indicator into the spinal cord, thus causing at least some injury to the tissue.

The reasons for using a method utilising intramedullary injection have been given by Smith et al (1969). It is suggested that/

that the degree of trauma is insufficient to invalidate the results for a number of reasons:-

(1) There is the precedent of the direct injection technique to measure blood flow in muscle (Lassen et al 1964) and brain (Espagno & Lazorthes 1966) and in both situations the method has proved satisfactory.

(2) Histological sections of the cords taken after six to eight injections into one segment revealed only small focal haemorrhages. The trauma at one area of the cord was minimised by moving the needle to different locations in the same segment for subsequent injections.

(3) The results obtained in these experiments compare favourably with those obtained by other workers (Table 8).

(4) It has been shown by this method that autoregulation is present in the spinal cord (see Section 3) and as demonstrated by Reivich et al (1969) and Fog (1968) autoregulation in the brain may be lost following trauma.

In order to ascertain whether any leakage of isotope along the injection tract occurred, any blood or C.S.F., that accummulated on the dura in initial experiments, was removed but showed no radioactivity. Its removal did not result in any drop in count rate.

The choice of anaesthetic has been shown to affect cerebral blood flow. (McDowall 1965: McDowall & Harper 1965: Landau et al 1955) McDowall, Harper & Jacobson (1964), have shown that 0.4 - 0.9% trichlorethylene did not cause a significant alteration in cerebral blood flow compared with control values using light nitrous oxide anaesthesia. In a later study McDowall (1967) showed that during the first twenty minutes of anaesthesia with 0.5% Halothane, a flow increase of 16% occurred but after twenty minutes flows returned to control values. As no measurements were made in/

in this present study until two hours after administration of 0.5% Halothane, it is likely that the latter conditions apply. Landau et al (1955), using a short acting barbiturate anaesthetic, thiopentone, noted no difference in S.C.B.F., in the white matter, from values obtained in unanaesthetised cats. In this present study, using pentobarbitone, no significant difference was noted when compared with the two volatile anaesthetics. The difference in blood pressure in dogs anaesthetised with either trichlorethylene or pentobarbitone and those anaesthetised with Halothane, should not have influenced flows. It has been shown by Kindt (1971) and Griffiths (Section 3) that changes in pressure over the range encountered in this study, do not alter S.C.B.F. To date no detailed studies have been made on the effect of anaesthetics on S.C.B.F.

SECTION 2

The effect of blood gases on the spinal cord blood flow.

METHODS:

Eighteen unselected dogs were used in the experiments, nine being used to study the effects of $paCO_2$ on S.C.B.F., and nine to study the effects of paO_2. For the studies with CO_2, anaesthesia was induced with thiopentone (25 mg/Kg) and maintained on 70% nitrous oxide/oxygen mixture and either 0.5 - 1% trichlorethylene or 0.5% Halothane. For the studies with hypoxia, anaesthesia was induced with pentobarbitone (25 mg/Kg) and maintained with 70% N_2O/O_2 mixture. The anaesthetic-gas mixture was delivered through a Palmer pump with ventilation adjusted to maintain normocarbia during surgical preparation and measurements. End tidal CO_2 concentration was monitored with an infra-red analyser.* The inspired oxygen concentration was measured with an oxygen analyser**. A femoral artery was cannulated and mean arterial blood pressure (B.P.) measured with a damped mercury manometer. This cannula also allowed collection of arterial samples for blood gas analysis. During each blood flow estimation, blood pH, pCO_2, and pO_2 were measured using standard electrodes***. Any base deficit was corrected with 8.4% sodium bicarbonate. The P.C.V., was measured using the microhaematocrit method and the result used in the selection of λ (tissue/blood partition coefficient).

Pharyngeal temperature was measured with a mercury thermometer and heating lamps were used to maintain the temperature between 37 - 38°C.

Dorsal laminectomies were performed to expose the required cord segments (T12 and T13) with the dura intact. Hypercarbia was produced by adding CO_2 to the inspired gases until the capnograph showed a constant inspired concentration of 7 - 9%. Hypocarbia was produced by hyperventilation (increase in pump volume/same rate) until the end tidal CO_2 concentration was reduced to 3 - 4%.

Graded hypoxia was achieved by reducing the inspired oxygen concentration and increasing the N_2O to maintain a fixed total volume.

After/

* Capnograph Godart.

** Servomex Controls Ltd.

*** Radiometer Copenhagen.

After any alteration in any blood gas tension, at least ten minutes elapsed before a blood flow estimation. The clearance of Xe^{133} after direct injection into the spinal cord was monitored with an uncollimated scintillation counter, coupled through a ratemeter to a linear recorder. The recording was transposed onto semilogarithmic paper for calculation of $T\frac{1}{2}$.

The blood flow was calculated from the formula:-

$$\text{S.C.B.F. (ml/100g/min)} = \frac{\lambda \times \log_e 2 \times 60}{T\frac{1}{2}} \times 100$$

RESULTS:

(1) $paCO_2$ & S.C.B.F.

Segments T12 and T13 in nine dogs were used to study the effects of pCO_2 on S.C.B.F., when the $paCO_2$ was varied between 20 mm.Hg., and 140 mm.Hg. The influence of hypercarbia is presented in Table 9. Hypercarbia caused a significant increase in flow with both trichlorethylene and Halothane anaesthesia, the significance being slightly greater with Halothane. There was no significant difference between the hypercarbic flows using Halothane and trichlorethylene. There was no significant change in blood pressure as a result of hypercarbia. The correlation between the percentage change in flow produced by alteration of the arterial pCO_2 is shown (Fig. 32). The percentage change in flow is used as there are wide variations in the S.C.B.F., between individuals, even at the same segment (Section 1 & Smith et al 1969). There is a high linear correlation between the change in flow and the $paCO_2$ ($r = 0.87$ $P < 0.001$) and raising the $paCO_2$ from 40 mm.Hg., to approximately 85 mm.Hg., doubles the blood flow in the white matter.

If the absolute blood flows are plotted against $paCO_2$ then the correlation coefficient is 0.71. Table 10 shows the flow variation produced by alteration of $paCO_2$ in a typical case.

The absolute sensitivity (defined as the linear gradient of the CO_2 response curve i.e., the ml/100g/min., change in S.C.B.F., per mm.Hg., change in $paCO_2$) to $paCO_2$ was studied by comparing the flow change which occurred when the $paCO_2$ was raised from 40 mm.Hg., to approximately 60 mm.Hg., or above, or lowered from 40 mm.Hg., to below 30 mm.Hg., in each dog. The results are presented in Table 11. The mean sensitivity for the flows at hypocarbia is 0.27 ± 0.14 ml/100g/min./mm./Hg., and at hypercarbia 0.39 ± 0.21 ml/100g/min./mm.Hg. There is no significant difference between these values ($p > 0.2$). The mean sensitivity for all flows is 0.36 ± 0.2 ml/100g/min./mm.Hg. In some dogs there was a variation in sensitivity between either the hypocarbic and hypercarbic flows or separate hypercarbic flows.

(2) paO_2 & S.C.B.F.

Fig. 33/

Fig. 33 illustrates the percentage change in S.C.B.F., which occurred in nine dogs with decreasing paO_2. It is evident that no change in flow occurs until the paO_2 has reached approximately 60 mm.Hg., when a sharp increase in flow occurs reaching maximal levels at paO_2 of 30 - 40 mm.Hg. The change in absolute blood flow, as a result of decreasing paO_2 is shown in six dogs (Fig. 34). When the percentage change in S.C.B.F., was plotted against blood oxygen saturation the maximal flows occurred at a saturation of approximately 60% and the change in S.C.B.F., between 100% and 60% saturation was logarithmically correlated ($r = -0.811$. $p < 0.001$). Below 60% saturation, there was a decrease in the S.C.B.F., response. In one dog the paO_2 was lowered to 20 mm.Hg., from normoxia (paO_2 165 mm.Hg.) resulting in an 8% increase in flow. the paO_2 was then raised to 31.5 mm.Hg., resulting in a 130% increase in flow from normoxia.

In four dogs the effect of hypocarbia co-existant with hypoxia was studied. (Table 12) It is evident that the usual vaso-constrictory action of hypocarbia was present in hypoxia. In all investigations, bar one (Dog 44 run 4), the hypoxic, hypocarbic flow was greater than the flow at normoxia and normocarbia. The effect of hypocarbia varied with the degree of hypoxia, having a greater vasoconstrictory effect with higher paO_2 levels.

DISCUSSION:

It is apparent that CO_2 has a similar action on the S.C.B.F., as on the C.B.F. This similarity has been noted by previous workers. Wullenweber (1968), using a heat clearance technique, demonstrated an increase in S.C.B.F., to hypercarbia and Palleske and Herrmann (1968) using the same method confirmed these observations in pigs. The heat clearance technique allows only qualitative results but nevertheless demonstrates clearly the vasodilatory effect of CO_2.

Smith et al (1969) presented quantitative results to demonstrate the increase in S.C.B.F., during hypercarbia and the decrease/

decrease in hypocarbia. The present results confirm the previous publications and suggest that the flow response in the white matter of the cord is similar to that found in the cerebral cortex. Harper et al (1961) showed that raising the $paCO_2$ from 30 - 70 mm.Hg., doubled the cortical flow and in the present experiments a comparable response was obtained. The overall results (Fig. 32) suggest a continuous change in S.C.B.F., between pCO_2 20 and 80 mm.Hg., and compare with Harper & Glass's (1965) results for C.B.F. These authors suggest an upper limit of $paCO_2$ above which no further increase in flow occurs. This is stated to be 80 - 90 mm.Hg. Increases in S.C.B.F., occurred for $paCO_2$ levels above these figures but the number of observations at extreme hypercarbia are too few to draw definite conclusions. The sensitivity of the cord vessels to $paCO_2$ has been investigated by Flohr et al (1969) in cats, using a particle distribution method. They found a linear correlation between thoracic cord blood flow and $paCO_2$ ($r = 0.5$) and an absolute sensitivity of 0.54 ml/100g/min. mm.Hg. Smith et al (1969) found areas of high and low sensitivity (0.617 & 0.154 ml/100g/min/mm.Hg.). The present results show a mean sensitivity of 0.36 ml/100g/min./mm.Hg. The variations in results probably depend to some extent on variations in experimental technique. It was apparent, however, in the present experiments that the sensitivity to $paCO_2$ could vary in the same dog under apparently constant conditions. There was no obvious evidence of the dichotomy observed by Smith et al (1969). It would appear both from the present observations and from those of Smith et al that on occasions only very small increases in flow occur which may not even exceed the coefficient of variation for the method. It has also been observed in the present experiments, that these small increases may be followed by a much larger increment in a subsequent observation, even when the experimental conditions remain constant. It is possible that some of these very low sensitivities could be attributed to experimental errors.

Flohr et al (1969), comparing the absolute sensitivity to $paCO_2$ in various areas of the C.N.S., suggest that it is related to the blood flow, being greater in areas with a high initial blood/

blood flow. In the present experiments an attempt was made to determine if the sensitivity of the thoracic cord to CO_2 was related to the flow at normocarbia. The greatest sensitivity to CO_2 was noted in the dog with the highest S.C.B.F., at normocarbia (Table 3, Dog 4) but this tendency was not seen in other dogs. A similar lack of correlation between flow and sensitivity in the thoracolumbar cord was demonstrated by Smith et al (1969).

It is well known that hypoxia induces vasodilation of the cerebral circulation resulting in an increased blood flow. It is important, however, to control ventilation to ensure no concurrent hypocarbia occurs. In the hypoxic normocarbic situation, it has been shown by McDowall (1966) that below a paO_2 of 50 mm.Hg., there is a sharp increase in C.B.F., and at 30 mm.Hg., the flow is about 120% greater than at normoxia. Haggendal & Johansson (1966) showed that C.B.F., increased by about 100% when the arterial oxygen saturation was reduced from 90 to 20 or 30%. They suggested hypoxia has a weaker dilator action on cerebral vessels than hypercarbia.

In the spinal cord Palleske & Herrmann (1968) have shown, qualitatively, the increase in S.C.B.F., accompanying hypoxia. This increase occurred even in the presence of decreasing cardiac output and blood pressure. Flohr et al (1970) found no change in S.C.B.F., when the paO_2 was varied between 55 and 160 mm.Hg., at normocarbia and normotension.

These results suggest that the effect of hypoxia on the spinal cord is very similar to that on the brain. The present experiments support this suggestion. The blood flow remains constant above a paO_2 of approximately 60 mm.Hg., below which, there is a sharp increase in flow. It is suggested that hypoxia of paO_2, 30 - 40 mm.Hg., is equally effective as $paCO_2$, 80 - 90 mm.Hg., in causing spinal vasodilation.

A feature shown in the present experiments, which has not been commented upon by other workers, is the decrease in S.C.B.F., below a paO_2 of approximately 30 mm.Hg. (saturation of approximately 60%). The reason for this is not obvious at present. In a minority of cases it was possibly due to hypotension developing. Although/

Although the blood pressure did not fall below the normal autoregulatory range, it has been shown that effective autoregulation is eliminated in hypoxia, both in the brain (Freeman & Ingvar 1968, Haggendal & Johansson 1966) and in the spinal cord (Section 3). In the other dogs, however, there was no significant decrease in blood pressure. It is probable that this decline in S.C.B.F., below paO_2, 30 mm.Hg., is quite genuine, as illustrated in the dog, where the paO_2 was initially reduced to 20 mm.Hg., and then gradually raised.

It has also been clearly demonstrated in the present experiments that hypoxic vasodilation takes precedence over hypocarbic vasoconstriction. The effect is graded, the vasodilation being greater at lower oxygen tensions. A similar situation was found in goats, (Alexander et al 1968), where the C.B.F., increased with combined hypoxia and hypocarbia.

Flohr et al (1970) have studied the effects of increasing hypoxia at hypercarbia. They found that the S.C.B.F., showed an increase at a higher paO_2 than at normocarbia. The threshold at hypercarbia was a paO_2 of about 70 mm.Hg.

It is interesting to contrast the response to $paCO_2$ and paO_2. Whereas there is a continuous response to changes of $paCO_2$, there is a definite threshold for paO_2 (approximately 60 mm.Hg.) above which, large alterations in oxygen tension have no effect on flow.

The mechanism by which the blood gases alter the C.B.F., has been investigated in some detail, particularly with respect to CO_2. Evidence has been presented to suggest that $paCO_2$ acts on a brain stem centre (Shalit et al 1968). However, this is not widely accepted and most workers suggest that CO_2 acts directly on the cerebral vessels. Gotoh et al (1961) have demonstrated an increase in C.B.F., when 35% CO_2 in air was applied locally to the cortex. It would appear that CO_2 also acts locally on the cord vessels as Kindt et al (1970) demonstrated the usual vasodilatory response to CO_2 in cords subject to high cervical transection. Gotoh et al also demonstrated a fall in C.B.F., when 100% oxygen was applied locally to the cortex.

It is thought that one main factor affecting C.B.F., is the extra-cellular pH of the brain around the arterioles (Lassen 1968). CO_2 can diffuse rapidly from the blood through the vascular endothelium which acts as an effective barrier to hydrogen and bicarbonate ions. The tissue pH is, therefore, a function of the $paCO_2$ and tissue bicarbonate concentration. This hypothesis was outlined by Gotoh et al (1961) and has been supported by other workers. Lassen et al (1970) have demonstrated the changes in vessel diameter, as a result of periarteriolor injection of mock C.S.F. at varying pH. Bicarbonate free fluid caused dilation, whereas higher concentration of bicarbonate caused constriction.

It is known that in hypoxia there is an increase in tissue and C.S.F. lactate and the lactate/pyruvate ratio. (Kaasik et al 1968, Mines & Sonensen 1969, Leusen et al 1968). This tissue lactate is thought to be the origin of the hydrogen ions causing vasodilation.

It has also been demonstrated (Harper & Bell 1963) that neither acute metabolic acidosis nor alkalosis produced by intravenous infusion of lactate or bicarbonate, at a constant $paCO_2$, alter the C.B.F. Alteration of C.S.F. pH., has been reported to have varying correlations with C.B.F. Skinkoj (1968) and Angoli (1968) claimed a convincing correlation, whereas this was not found by McDowall & Harper (1968) and Plum et al (1968). The reason for these discrepancies is not clear but several factors may have influenced results, such as the degree of acuteness of the C.S.F., pH., change or tissue damage etc. These relationships have been discussed by Severinghaus (1968). It would appear that the effect of the blood gases on S.C.B.F. is similar to the effect on C.B.F., in both magnitude and direction and in view of this and the other available information, it would be surprising if there were any major differences between the control of blood flow in either organ.

SECTION III

The Effect of Blood Pressure on Spinal Cord Blood Flow

Methods:

Twenty-five unselected dogs were used, eleven for the effects of hypotension at normocarbia and normoxia (Group A), eight at normocarbia and hypoxia (Group B) and six at normoxia and hypercarbia (Group C). Seven of the normoxic, normocarbic group were induced with thiopentone (25 mg/kg) and maintained on 0.5% Halothane in a 70% nitrous oxide, oxygen mixture, whilst the others were anaesthetised with pentobarbitone (25 mg/kg) and maintained on the N_2O/O_2 mixture. The dogs in the other two groups were all anaesthetised with pentobarbitone. The gas mixture was delivered through a Palmer pump with ventilation adjusted to maintain normocarbia during surgical preparation. A femoral artery was cannulated and the mean arterial blood pressure measured with a damped mercury manometer. This cannula also allowed collection of arterial samples for blood gas analysis. During each estimation, blood pH, $paCO_2$ and paO_2 were measured using standard electrodes*. Any base deficit was corrected with 8.4% sodium bicarbonate. The P.C.V., was measured using the microhaematocrit method and the result used in the selection of (tissue/blood partition coefficient), as described on page 39. The pharyngeal temperature was measured with a mercury thermometer and heating lamps were used to maintain the temperature between 37 - 38°C.

Dorsal laminectomies were performed to expose the required cord segments (T12/T13) with the dura intact. A control measurement was made under conditions of normoxia, normocarbia and normotension. In the dogs of Group A, the blood pressure was then decreased as described below. In dogs of Group B, hypoxia was induced by increasing the percentage of N_2O in the inspired gases until the paO_2 was 30 - 45 mm.Hg. A second measurement was made at normotension to ensure that the S.C.B.F. had increased by the expected amount (Section II) and the blood pressure was then reduced as described overleaf. In dogs of Group/

Group C, hypercarbia was produced by adding CO_2 to the inspired mixture until the $paCO_2$ was 85 - 100 mm.Hg. A second measurement was made at normotension to ensure that the expected vasodilation had occurred (Section II). The blood pressure was then reduced.

Graded hypotension was produced by bleeding the dog, via the femoral cannula, into a reservoir. The S.C.B.F. was determined at least ten minutes after the pressure had stabilised. In three dogs of Group A, a large diameter cannula was inserted directly into the caudal aorta through a laparotomy incision. During a clearance to measure S.C.B.F. the blood pressure was reduced rapidly by bleeding via this cannula.

The clearance of Xe^{133} after direct injection into the spinal cord was monitored with an uncollimated scintillation counter coupled through a ratemeter to a linear recorder. The clearance curve was transposed onto semi-logarithmic paper for the calculation of $T\frac{1}{2}$.

The blood flow was calculated from the formula -

$$\text{S.C.B.F. (ml/100g/min)} = \frac{\lambda \times \log_e 2 \times 60}{T\frac{1}{2}} \times 100$$

Results:

Group A Normoxia and Normocarbia

The percentage change in flow with progressive hypotension is presented in Fig. 35 and the absolute changes in flow are shown in Fig. 36. Variations in blood pressure between 150 and approximately 60 mm.Hg. did not significantly alter the flow. Below 60 mm.Hg. the flow decreased with reduction of pressure.

In the three dogs where pressure was decreased rapidly during a clearance, no change in the slope of the curve was evident between 180 and approximately 100 mm.Hg. Below 100 mm.Hg. a decrease in the clearance rate was noted following the rapid exsanguination. Fig. 37 demonstrates two clearances in the same dog at different initial arterial pressures.

Group B/

Group B Hypoxia and Normocarbia

Fig. 38 shows the effect of hypotension on blood flow in a situation where hypoxia caused a marked vasodilation. The percentage change in S.C.B.F., for 8 dogs is shown. There is a wide scatter in points, especially at higher pressures but a linear correlation between the flow change and pressure was present ($r = 0.667$ $p < 0.001$). The changes in absolute blood flow during hypotension are shown in Fig.39. These results show that in general the S.C.B.F. falls progressively with reductions in blood pressure, although in two dogs autoregulation was present above a blood pressure of 110 mm.Hg.

Group C Hypercarbia and Normoxia

Fig. 40 shows the percentage change in S.C.B.F. in hypotension where the vessels are dilated due to hypercarbia. There is a linear correlation ($r = 0.749$ $p < 0.001$). The changes in absolute blood flows are shown in Fig. 41. Again the blood flow decreases with the blood pressure, although in some dogs a limited form of autoregulation is shown at higher pressures.

Discussion:

It is evident from Figs. 35 and 36 that at normoxia and normocarbia the blood pressure may be altered between 150 and approximately 60 mm.Hg. without causing a significant change in blood flow. This is the phenomenon known as autoregulation. It is apparent from Fig. 36 that autoregulation can occur to arterial pressures of about 40 mm.Hg. in some dogs. Autoregulation has been repeatedly demonstrated in the canine cerebral circulation (Harper 1965: Rapela & Green 1964: Haggendal & Johansson 1966). Previous to these quantitative studies, direct observation of the pial vessels had shown dilation in response to hypotension and constriction to hypertension (Fog 1968). Kindt (1971) demonstrated autoregulation to increasing blood pressure, induced by noradrenaline, in the/

the cervical cord of monkeys. He further showed that this feature was retained after high cervical cord transection. Otomo et al (1960) noted no change in cord pial vessel diameter until the blood pressure had fallen by about 20%. They suggest that blood pressure is the chief factor controlling blood flow and oxygen tension in the cord. The present experiments (hypotension) and those of Kindt (1971) (hypertension) do not support these findings.

Autoregulation allows normal functioning of brain energy metabolism to markedly reduced arterial pressures. Siesjo et al (1971) measured brain concentrations of A.T.P., A.D.P., A.M.P. and creatine phosphate, in rats made progressively hypotensive. No significant change in any of these metabolites was found until the arterial pressure dropped to 35 mm.Hg. These experiments also suggest that autoregulation is not a result of gross impairment of brain energy metabolism.

The failure of rapid exsanguination, above a pressure of 100 mm.Hg. to alter the clearance curves also supports the concept of autoregulation. It is likely that some temporary decrease in flow does occur but the technique employed in this study is not designed to measure transitory changes in flow and provided the flow rapidly returns to its former value, no decrease in the slope will be seen. Rapela and Green (1964) found that the C.B.F. returned to normal approximately 30 seconds after clamping of the common carotid arteries.

The situation is changed somewhat in hypercarbia or hypoxia. The present experiments suggest that in both cases autoregulation tends to be abolished, although in both hypercarbia and hypoxia some degree of autoregulation was found in occasional dogs. Partial autoregulation only occurred at higher pressures and was never seen below about 90 - 100 mm.Hg. This autoregulatory tendency at higher pressures probably accounts for the scatter in Fig. 38.

Harper (1965) found a linear relationship between C.B.F. and arterial pressure at hypercarbia. He suggests that with the vasodilation due to hypercarbia, the vessels are unable to dilate further with a falling blood pressure. He supports this theory/

theory by presenting the effects of CO_2 on C.B.F. at hypotension where, at a pressure of 50 mm.Hg. hypercarbia and hypocarbia had little or no effect on C.B.F.

There is not universal agreement on these topics. Haggendal & Johansson (1966) found a significant but reduced increase in C.B.F. in hypercarbic hypotensive (B.P. 60 mm.Hg.) dogs and showed autoregulation persisting at higher blood pressures. Ekstrom-Jodal, Haggendal & Nilsson (1970), in further studies, confirmed their findings that autoregulation did occur with vasodilation due to CO_2 and papavarine. The results from the present experiments when examined in total (Fig. 40) tend to support the linear correlation, although individual dogs did show autoregulation at higher pressures.

Raichle & Stone (1972) investigated the effect of hypercarbia on C.B.F. in rhesus monkeys which were exposed to 6, 9 and 12% CO_2. With increasing CO_2 levels, autoregulation was only present at higher blood pressures until at 12% CO_2 it could not be demonstrated. The animals were then placed in a sealed environment chamber at 6% CO_2 for five days. The C.S.F. pH was normal after this time, due to a rise in the bicarbonate ion. When autoregulation was retested at 6% CO_2, it was found to be identical to that at normocarbia and a degree of autoregulation was shown at 12% CO_2. This latter finding suggests that the loss of autoregulation in acutely hypercarbic animals is due to a decrease in perivascular pH.

Hypoxia is known to abolish or impair cerebral autoregulation. (Freeman & Ingvar 1968) Haggendal & Johansson (1966) found that when the arterial oxygen saturation was reduced to less than 60%, a passive pressure-flow relationship developed. In a later study, Ekstrom-Jodal, Haggendal & Nilsson found a functioning autoregulation at marked arterial hypoxia (oxygen saturation 40%) in some dogs.

In the present studies, autoregulation tended to be abolished at arterial oxygen tensions of between 30 and 45 mm. Hg. However, in two dogs autoregulation was present at higher arterial pressures (above approximately 110 mm.Hg.).

It/

It is evident that at normoxia and normocarbia the spinal cord of the anaesthetised dog demonstrates a well functioning autoregulation. At both hypercarbia and hypoxia this tendency is impaired. Why certain dogs show partial retention of autoregulation at higher pressures is, at present, unknown. The mechanism promoting cerebral autoregulation is also unknown. At present the two main hypotheses are concerned with metabolic and myogenic factors. The myogenic theory implies that changes in transmural pressure lead to alterations in vasomotor tone, whilst the metabolic theory suggests that alterations in tissue pH, following the reduction in perfusion pressure, are responsible for the changes in vascular calibre.

Ekstrom-Jodal et al (1969) presented evidence in favour of the myogenic theory. This was based on the presence of autoregulation at hypocarbia and hypercarbia (this is not universally accepted) and the failure of autoregulation when the perfusion pressure was reduced by increasing the central venous pressure. Symon, Held & Dorsch (1971) also support the myogenic nature of autoregulation. They increased the pressure in branches of the middle cerebral artery by direct injection of fluid and measured the venous outflow from the brain with flowmeters. Using this system they found a functioning autoregulation at arterial pCO_2 of 60 - 70 mm.Hg. and a short latency of response to the pressure increments ($<$ 2 seconds). Autoregulation was, however, abolished by hypoxia.

The work of Raichle and Stone (1971) and Harper (1965), which has been previously described, suggest that metabolic factors are of importance and this view is also taken by Rapela and Green (1964). The problem, however, is far from settled.

Autoregulation may also be abolished by disease or trauma. Reivich et al (1969) demonstrated loss of autoregulation in cats brains, which had been traumatised by a jet of compressed nitrogen. This point illustrates the necessity for atraumatic methods in blood flow measurement. In the direct injection/

injection technique (as in the present study) the trauma caused by the needle is obviously minimal as autoregulation is not abolished. Palleske (1969) produced cord oedema with a cold injury and demonstrated loss of S.C.B.F. autoregulation. The flow passively followed changes in blood pressure.

Detailed studies of S.C.B.F. in disease have yet to be made but is is quite probable than in acute trauma auto-regulation will be impaired as in the hypercarbic or hypoxic dogs.

GENERAL CONCLUSIONS

The material presented has been concerned with two differing aspects of the spinal cord, namely the pathology of the myelopathy caused by disc protrusions and the control of S.C.B.F. Although at first glance these subjects may appear unrelated, it is suggested that they are complementary. The pathology, both of the localised and of the extensive myelopathy, has suggested that disturbances of blood flow are important in the pathogenesis. It is not proposed that ischaemia is the only factor involved. Indeed, in the compressive lesion it may only be of secondary importance. However, in the malacic and diffusely demyelinated cords and in the extensive myelopathy, vascular factors are probably of major importance. This statement requires direct proof, for instance, the demonstration of decreased S.C.B.F. or impaired perfusion. Such evidence is not easily gained without some form of measurement of S.C.B.F. When this study was started no satisfactory clinical methods were available to measure flow and indeed the actual control of the spinal circulation was not absolutely understood. For these reasons it was deemed important to study the normal cord circulation and physiological factors which control it. The results of these studies have been presented in Part II and it appears that the control of S.C.B.F. is almost identical to the control of the cerebral circulation. No studies of S.C.B.F. in disease has been presented, although the absence of autoregulation in hypoxia and hypercarbia may be relevant to the traumatised cord. Present and future studies are directed at examining S.C.B.F. in disease and experimental injury in the hope of obtaining evidence of vascular derangement in the pathogenesis of the myelopathy of disc protrusion.

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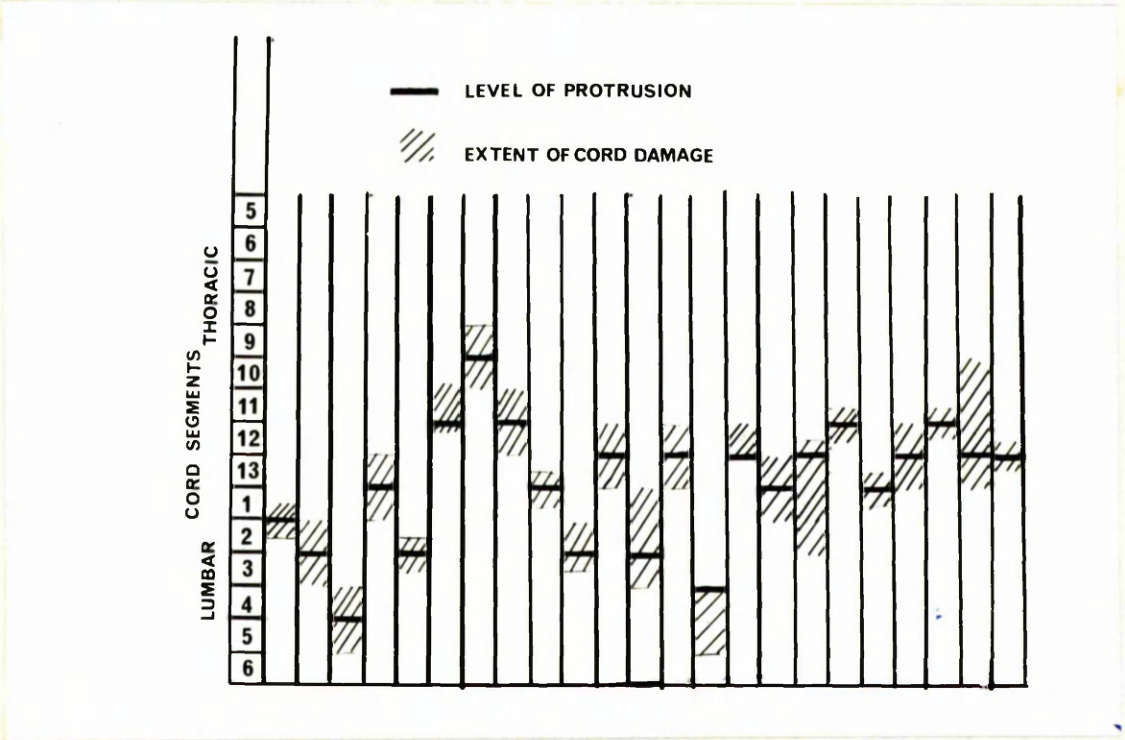


Fig. 1 This demonstrates the level of the disc protrusion and extent of the cord damage in the 23 cases.

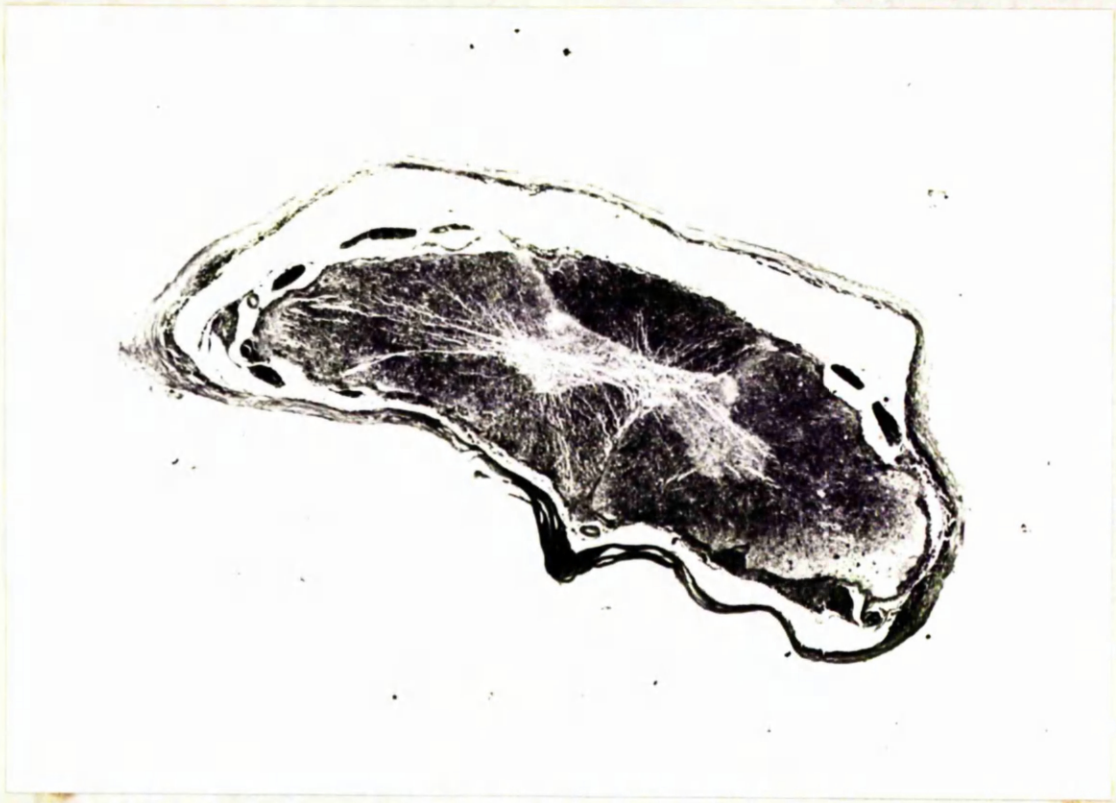


Fig. 2 Compressed cord at junction of T9/10 segments showing the radial fissures in the W.M., and anchoring effect of the denticulate ligament on the left. Survival time - 3 weeks H. & E. x 15.

Fig. 3a L5 segment showing distribution of malacia and lack of cord compression. Survival time - 7 weeks H. & E. x 15.

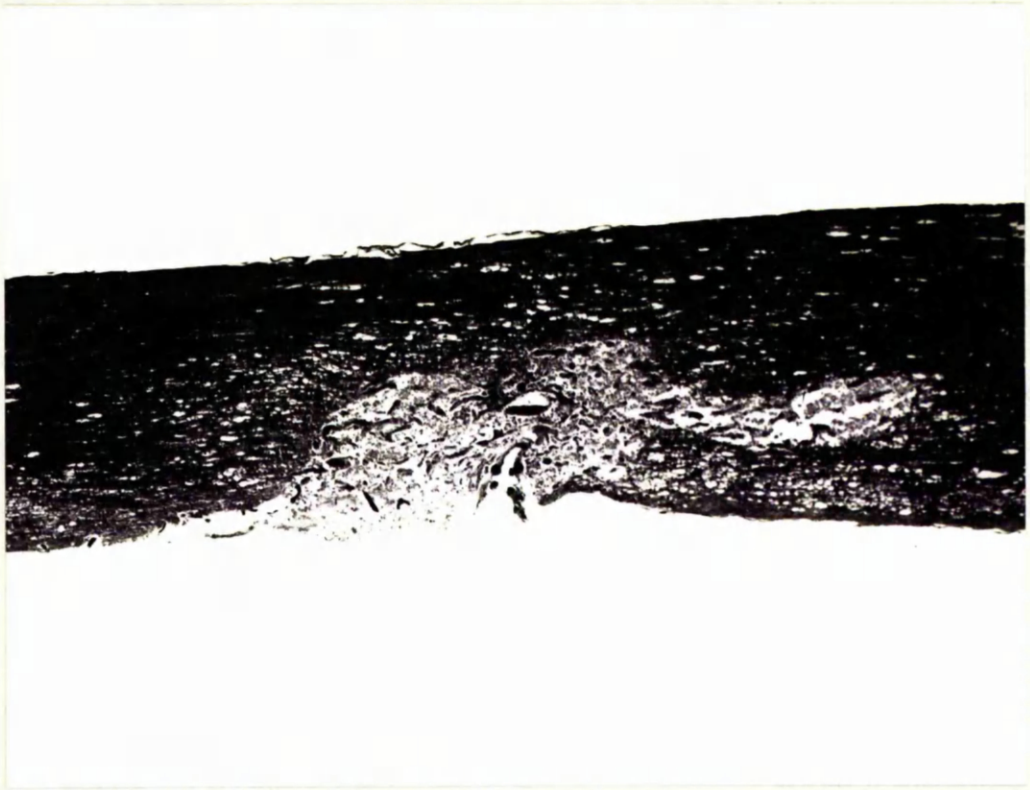


Fig. 3b Longitudinal section of cord to show malacic area from L2 - L3. Survival time - 7 weeks. H. & E. x 9.

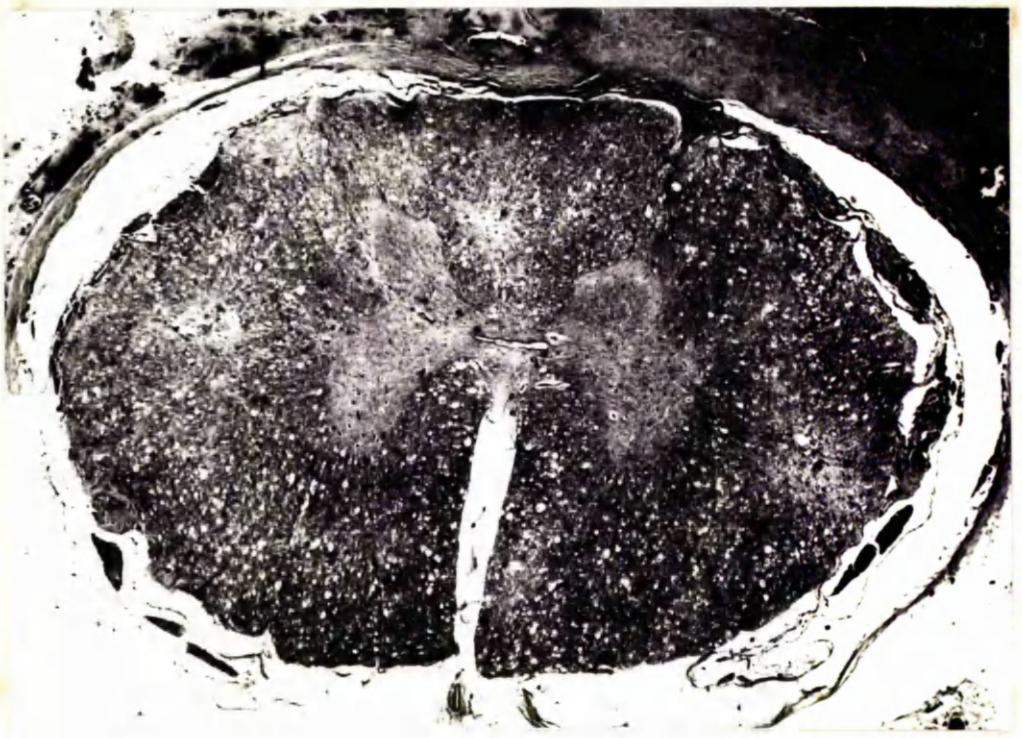


Fig. 4a T13 segment, showing diffuse demyelination. There are small irregular malacic areas in both lateral columns and the base of the dorsal columns. Survival time - 6 weeks H. & E. x 15.

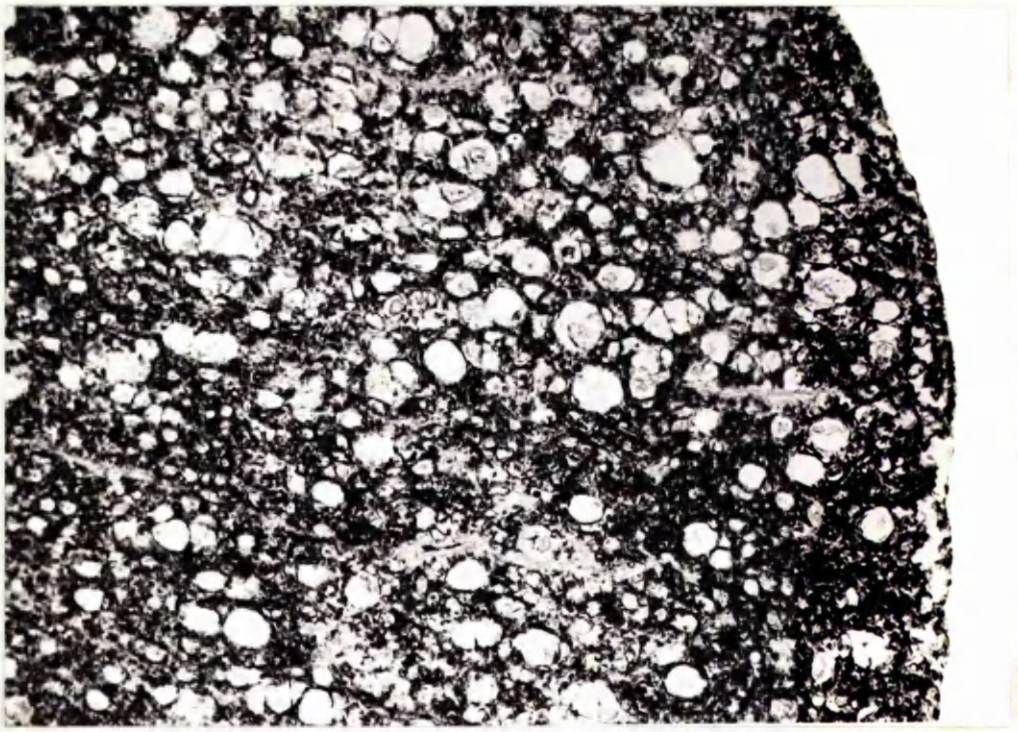


Fig. 4b W.M. from cord with diffuse demyelination, showing swelling of myelin sheaths and myelin breakdown debris. Weigart Pal x 150.

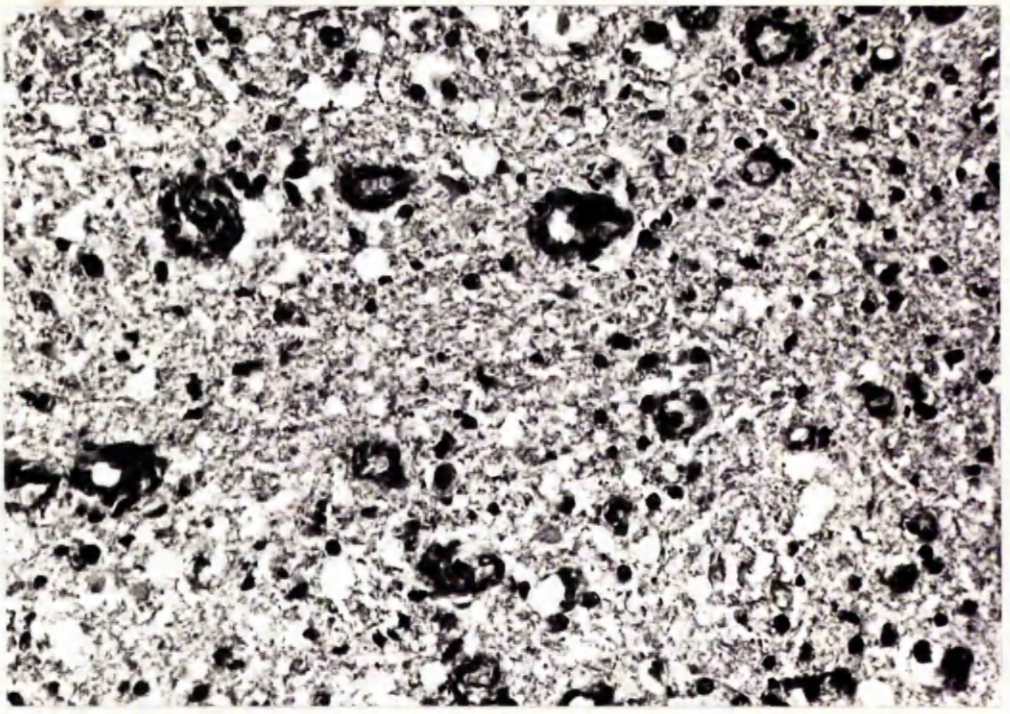


Fig. 5a Area of W.M. from compressed cord showing adventitial thickening of blood vessels. Survival time - 12 weeks M.S.B. x 300.

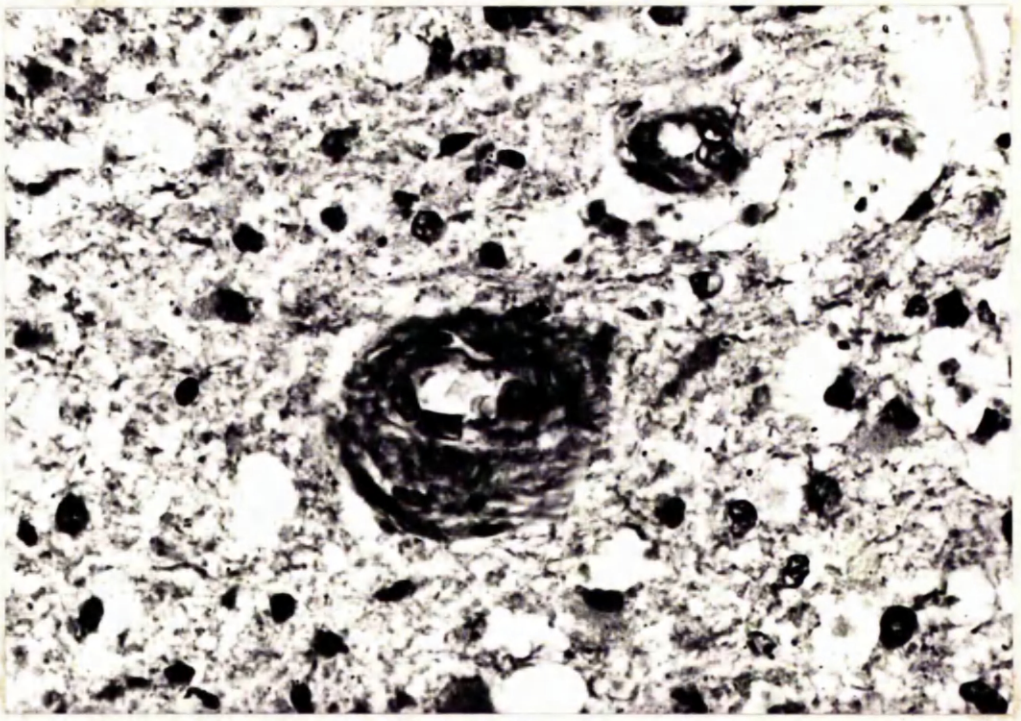


Fig. 5b 2 blood vessels from the above cord to show adventitial connective tissue. M.S.B. x 800.

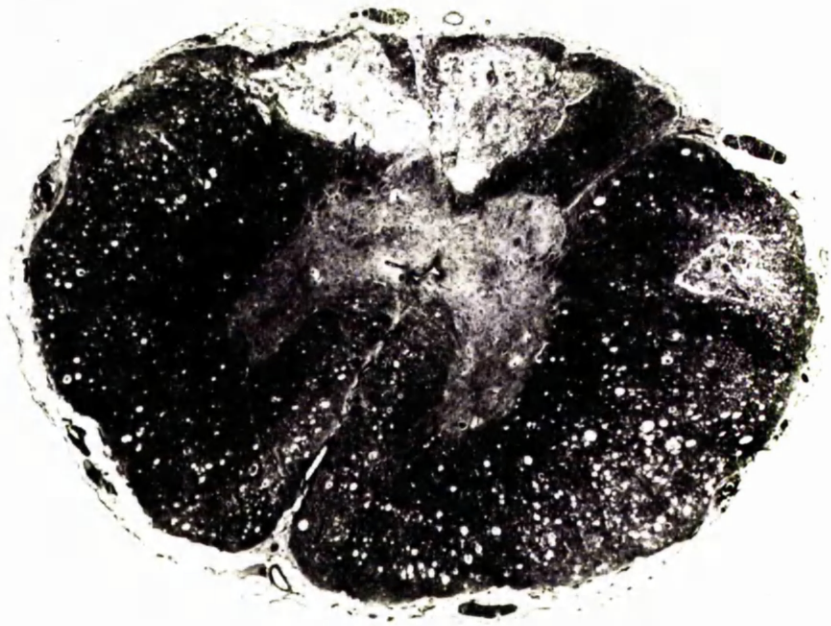


Fig. 6a Section from caudal part of T10 segment. Survival time - 4 weeks. H. & E. x 15.

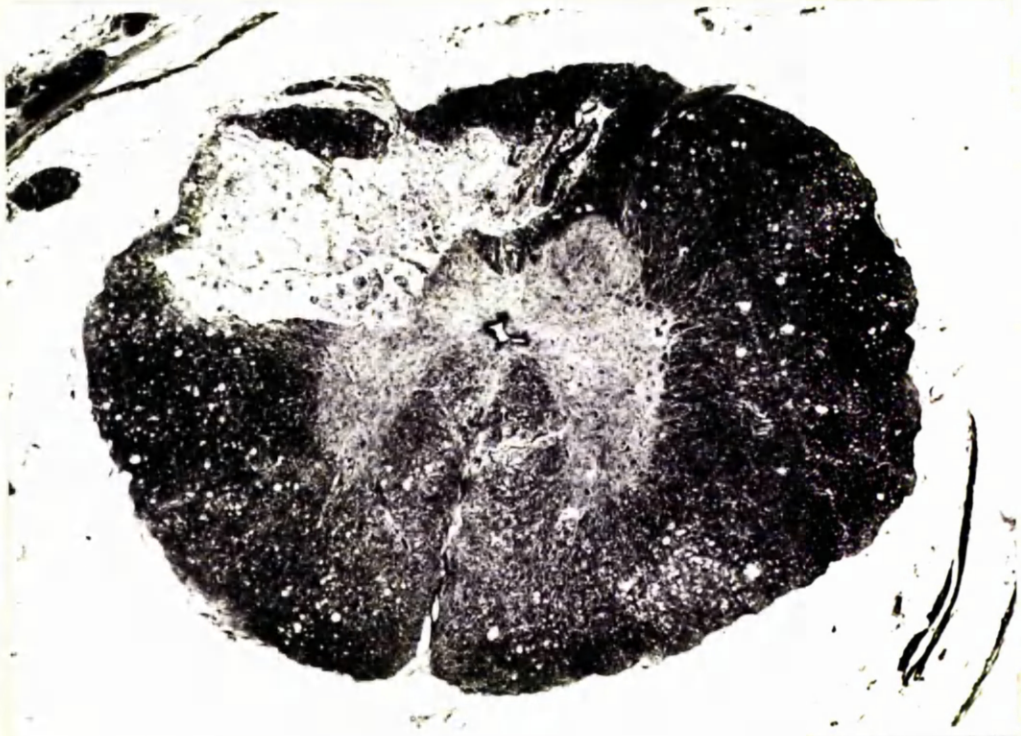


Fig. 6b Section from the middle of T11 segment of the above cord. H. & E. x 15.

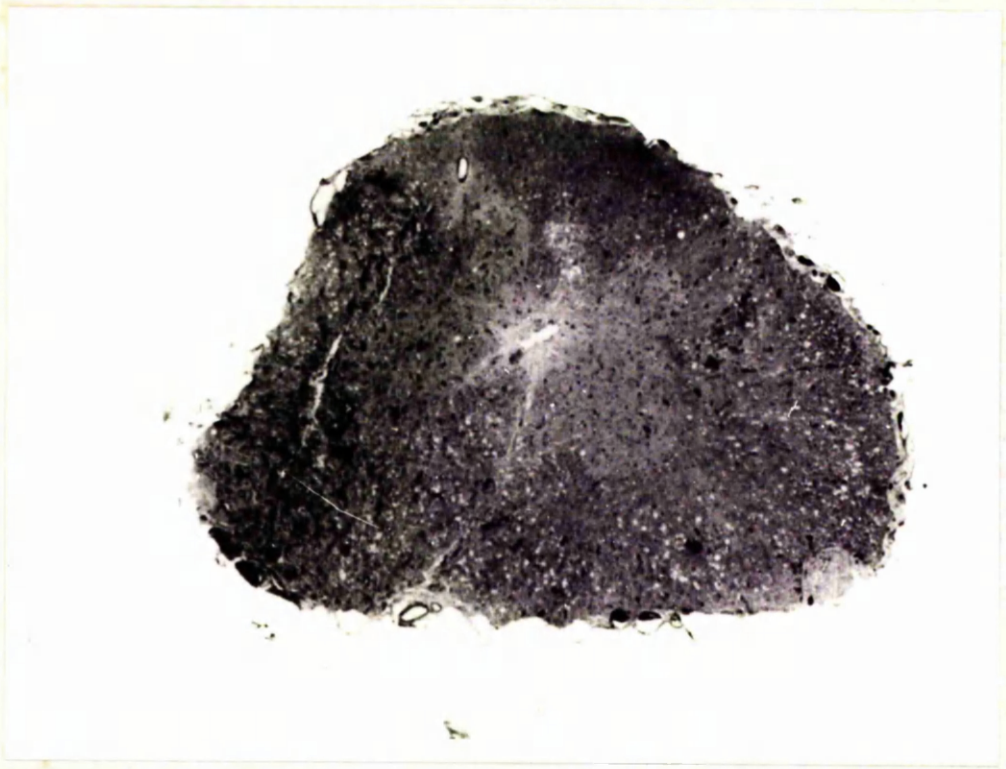


Fig. 7 T13 segment from cord showing both compression and malacia. There is lateral compression of the left lateral funiculus and a crescentic infarct of the same funiculus. Survival time - 12 weeks. H. & E. x 15.

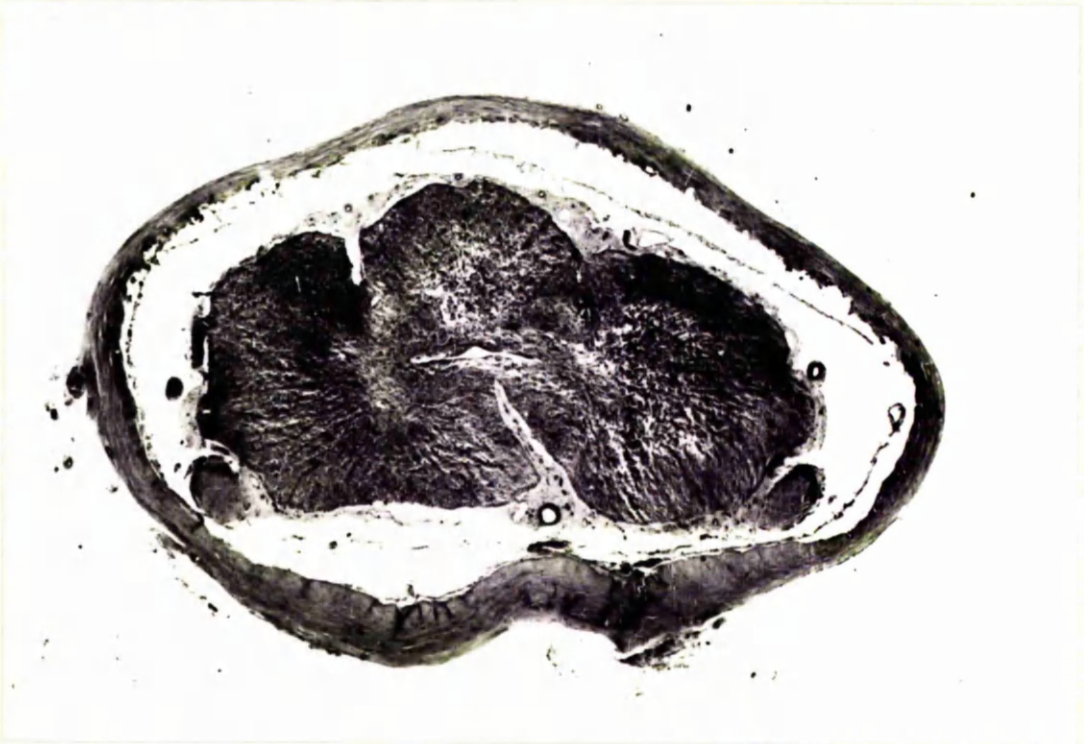


Fig. 8 T13 segment showing malacia in base of dorsal funiculus, right lateral and ventral funiculi and G.M. The peripheral W.M., is spared. Survival time - 1 year. H. & E. x 15.

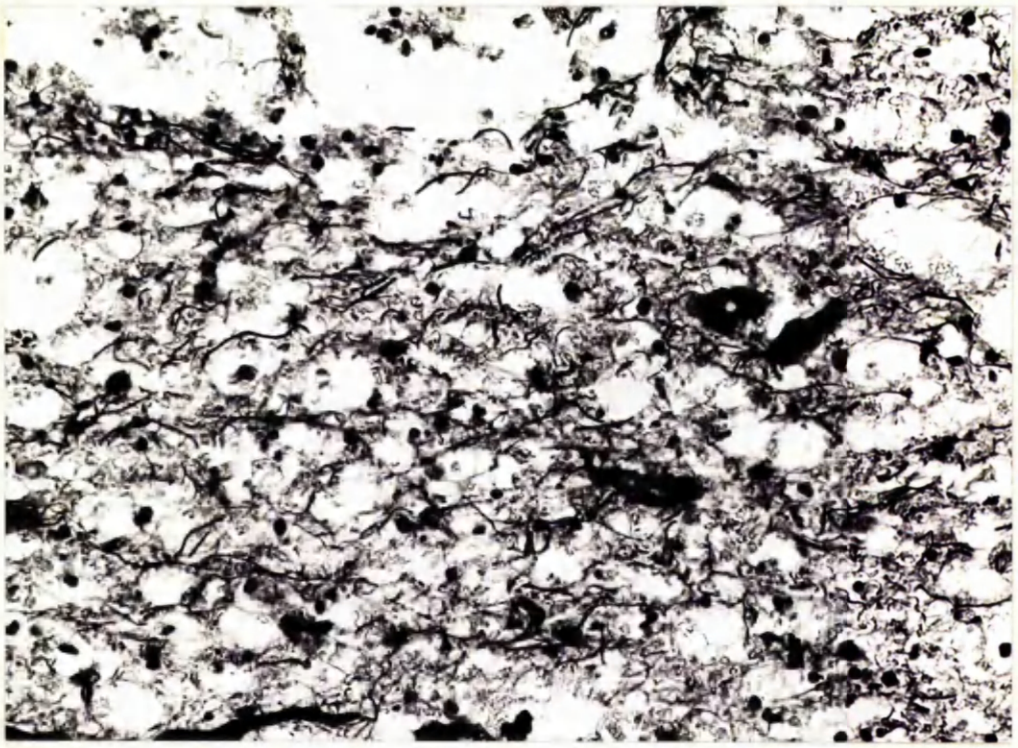


Fig. 9 L2 segment showing demyelinated area with degenerating fibres and a fine neuroglial sclerosis. Survival time - 6 weeks. Holzer x 300.

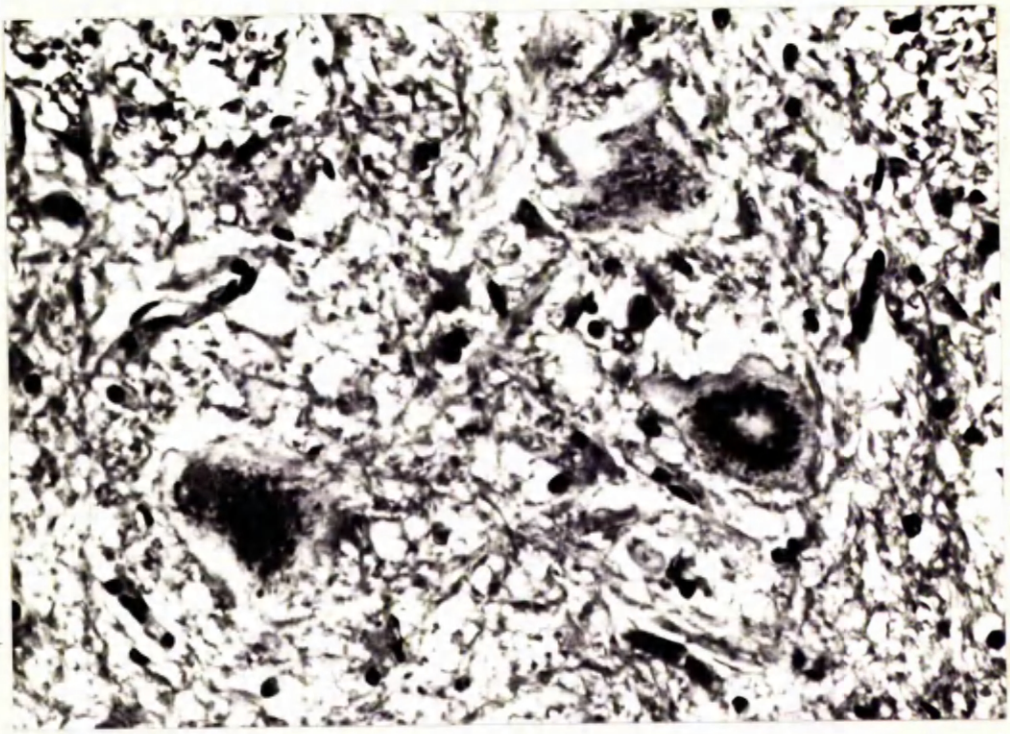


Fig. 10a Neurones from L5 segment showing peripheral chromatolysis and diffuse loss of Nissel granules. Survival time - 7 weeks. H. & E. x 500.

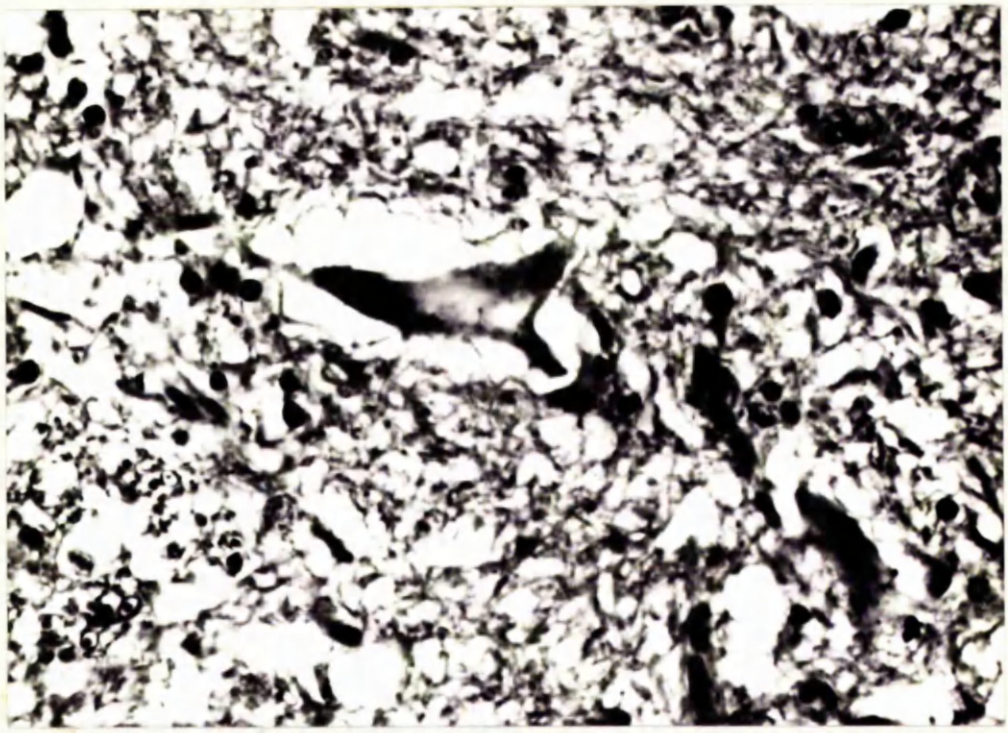


Fig.10b Two shrunken, sclerotic neurones from L5 segment of above cord. H. & E. x 500.

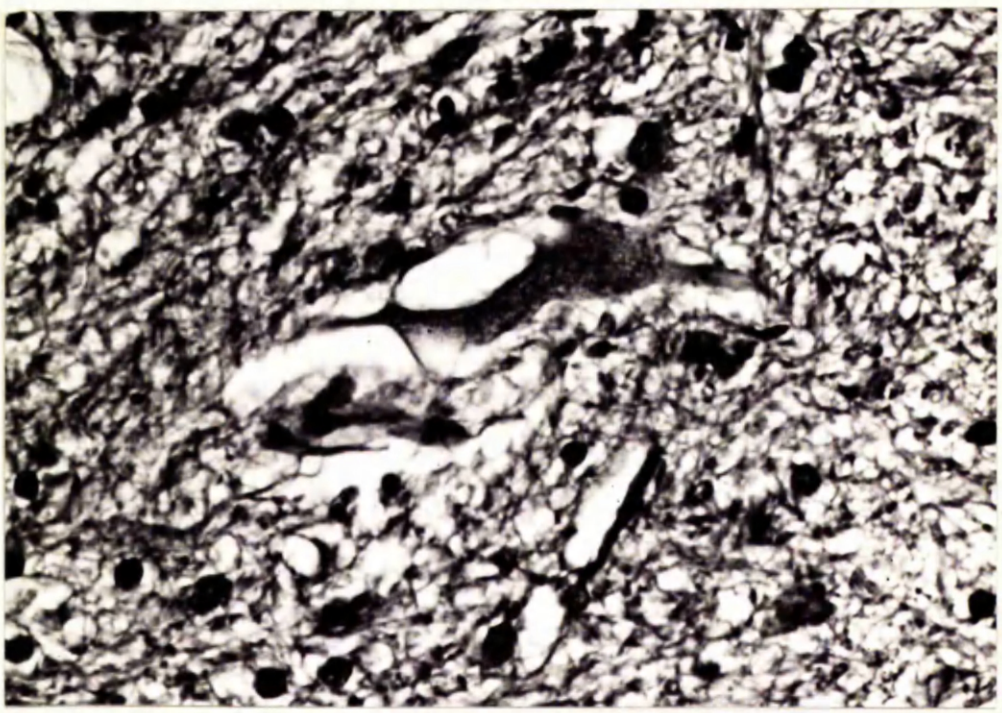


Fig. 10c Shrunken, distorted neurone with possible vacuolation at T10 segment. Survival time - 5 weeks. H. & E. x 600.

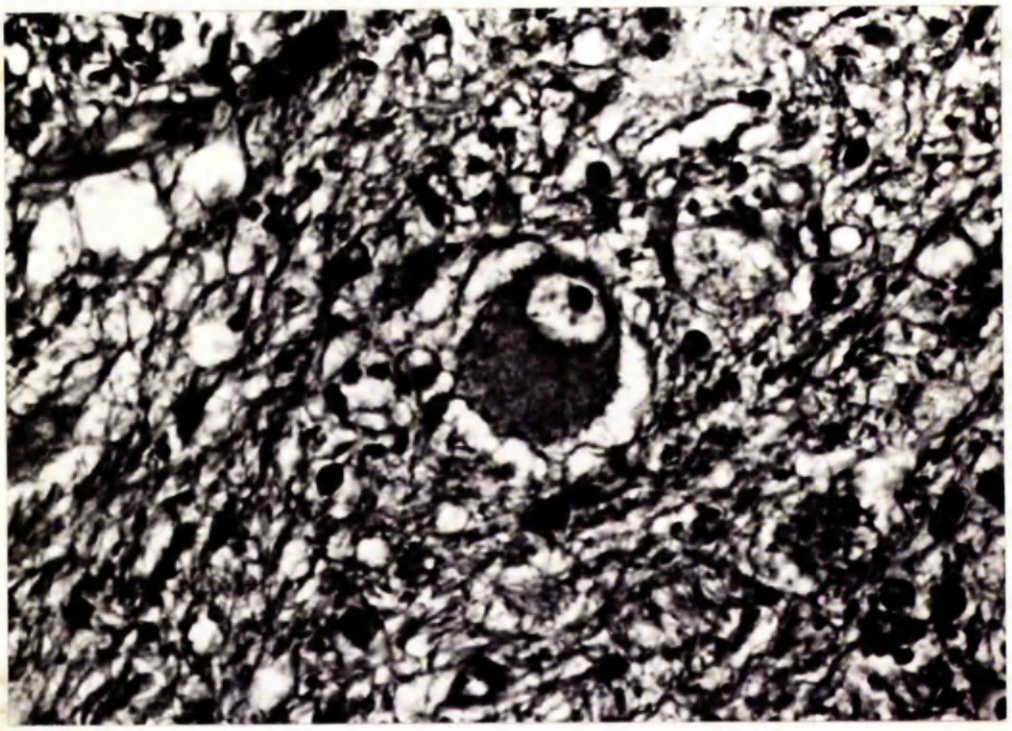


Fig. 10d Neurone showing chromatolysis, eccentric nucleus and rounding of cell outline. T10 segment. Survival time - 5 weeks. H. & E. x 600.

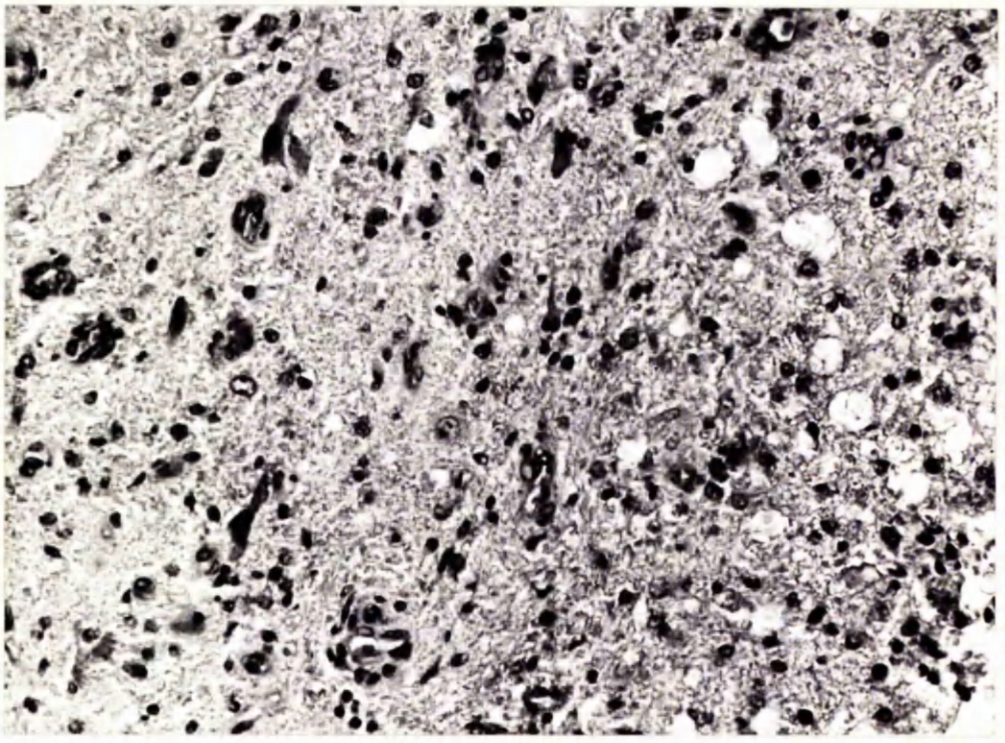


Fig. 11a Part of G.M., bordering an area of malacic W.M. There is gliosis with increase in microglia and astrocytes. The astrocytes show moderate swelling of the cell body. Survival time - 12 weeks. H. & E. x 300.

Fig. 11b Area of G.M. showing increase in astrocytes. Survival time - 8 weeks. Cajal x 300.

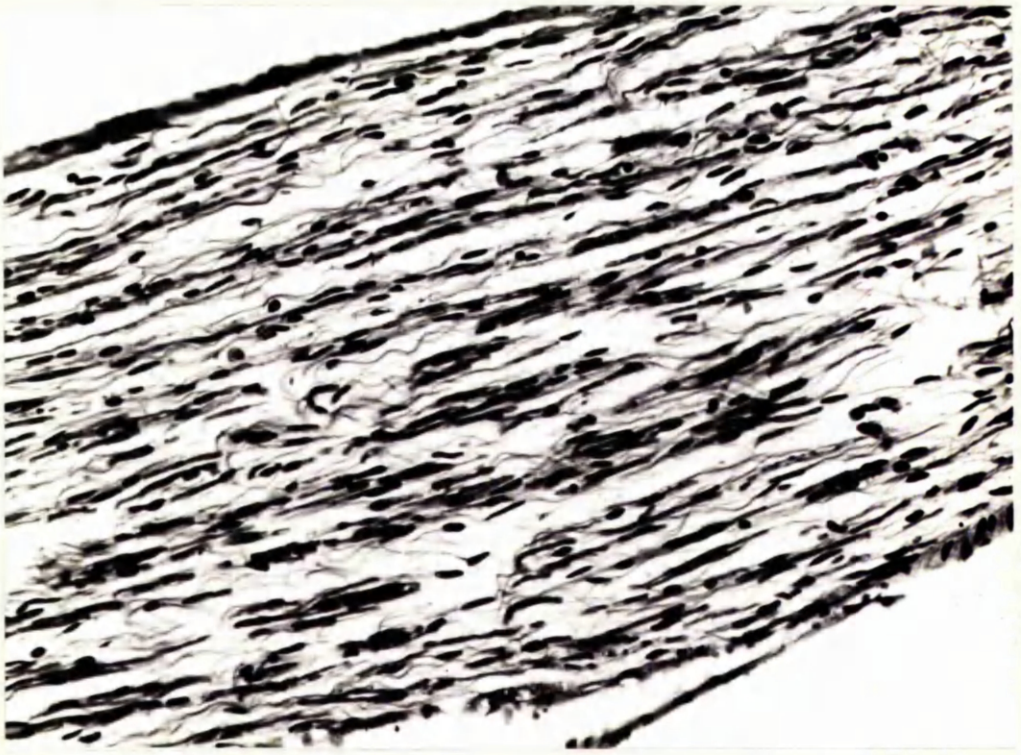


Fig. 12 Dorsal nerve root showing marked loss of nerve fibres and moderate increase in fibrous tissue. Survival time - 1 year. van Gieson x 300.

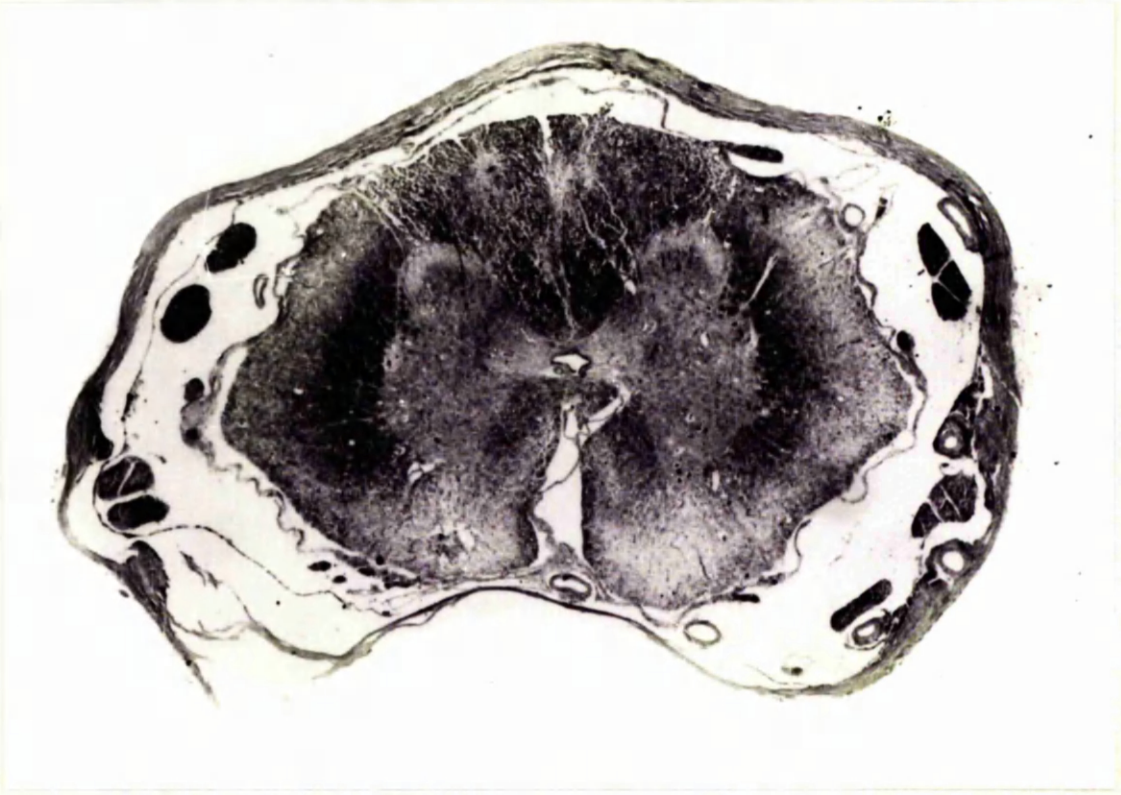


Fig. 13 L2 segment from cord with protrusion compressing junction of T12/13 segments, showing degeneration of lateral and ventral funiculi and centre of dorsal funiculus. There is a malacic area in the left ventral funiculus. Survival time - 1 year. van Gieson x 15.

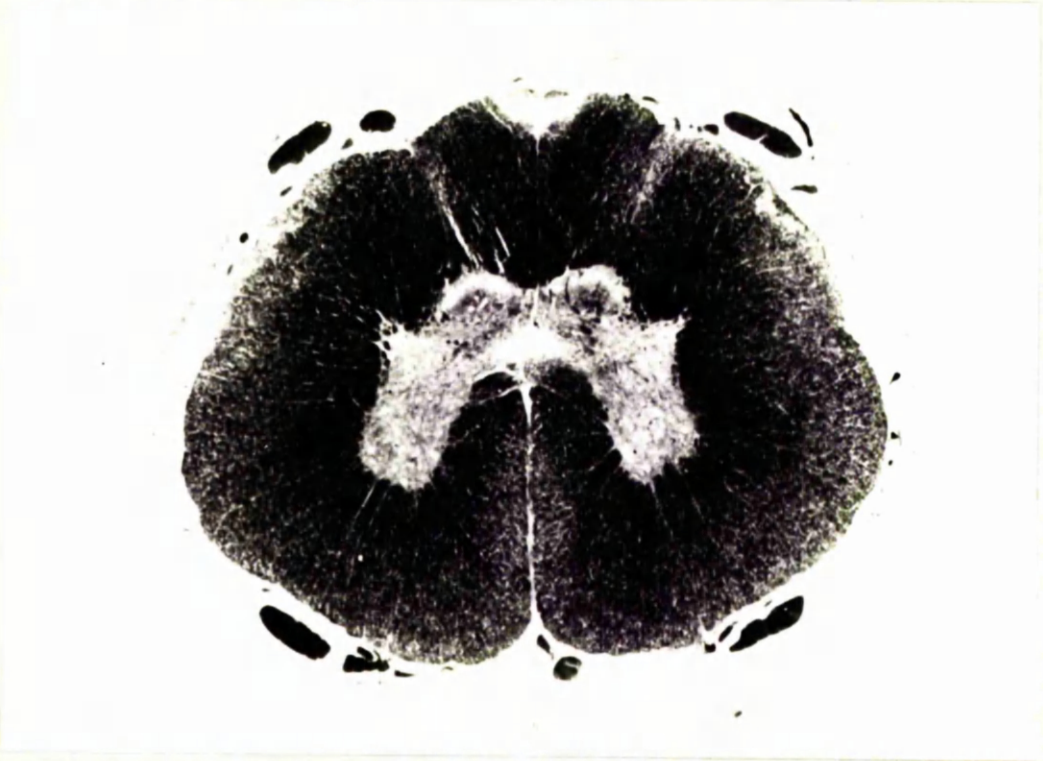


Fig. 14 T5 segment from a cord with the main lesion at T12 showing ascending Wallerian degeneration. Survival time - 1 year. Weigart Pal x 15.

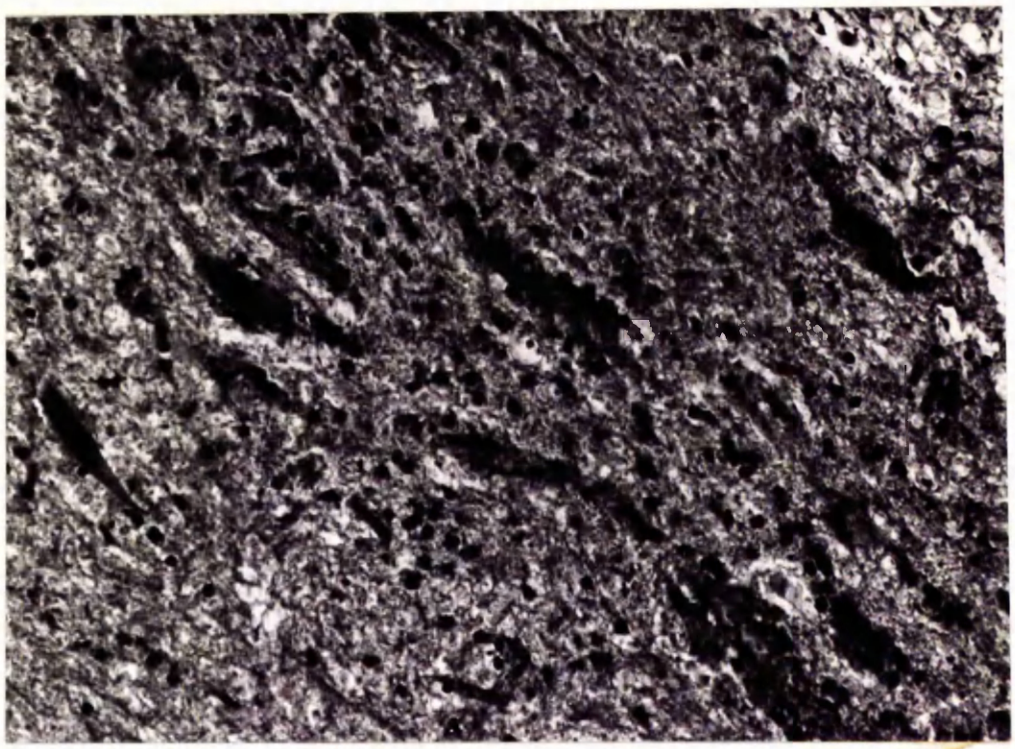


Fig. 15 Area of ventral G.M. showing neutrophil infiltration and ischaemic neurones. Survival time 8 days. H. & E. x 300.

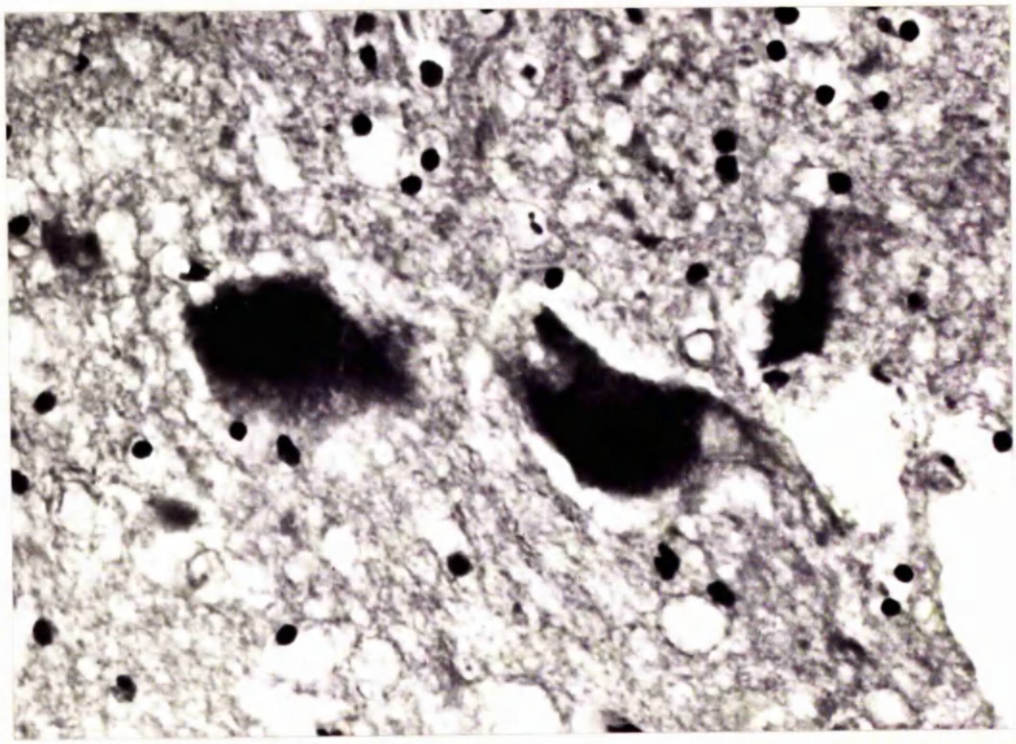


Fig. 16a Two neurones from a necrotic segment showing shrinkage of both cytoplasm and nucleus and a prominent nucleolus. This was regarded as an early ischaemic change. H. & E. x 750.

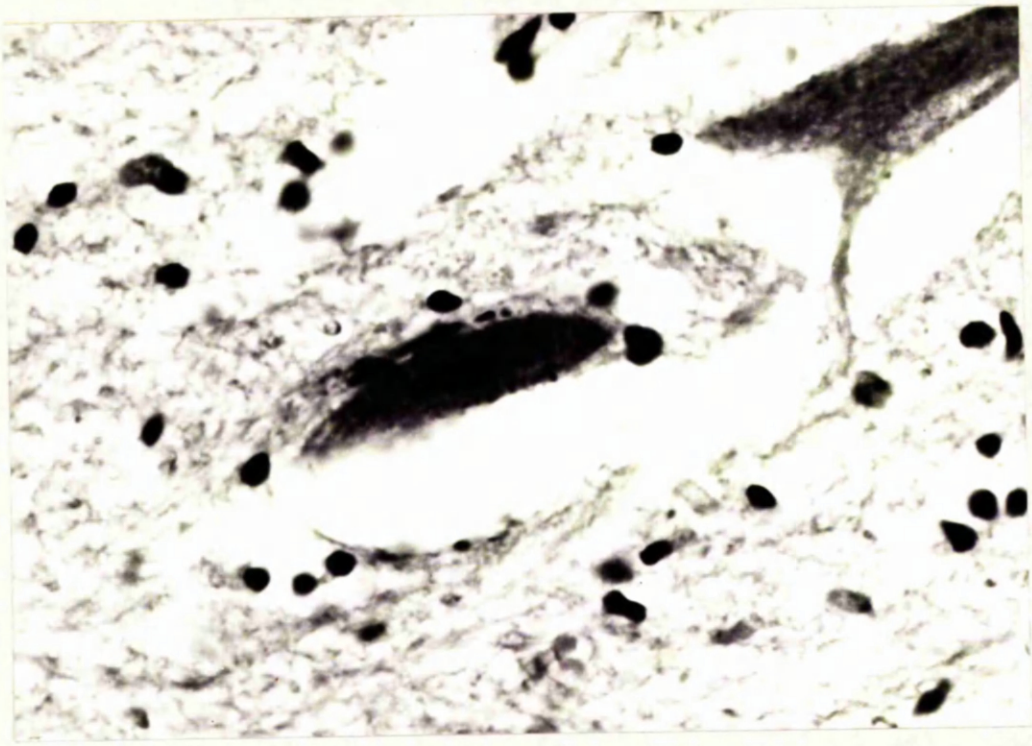


Fig. 16b An ischaemic neurone with shrunken cytoplasm and pyknotic nucleus showing the degenerate boutons terminoux around the periphery. H & E x 900.

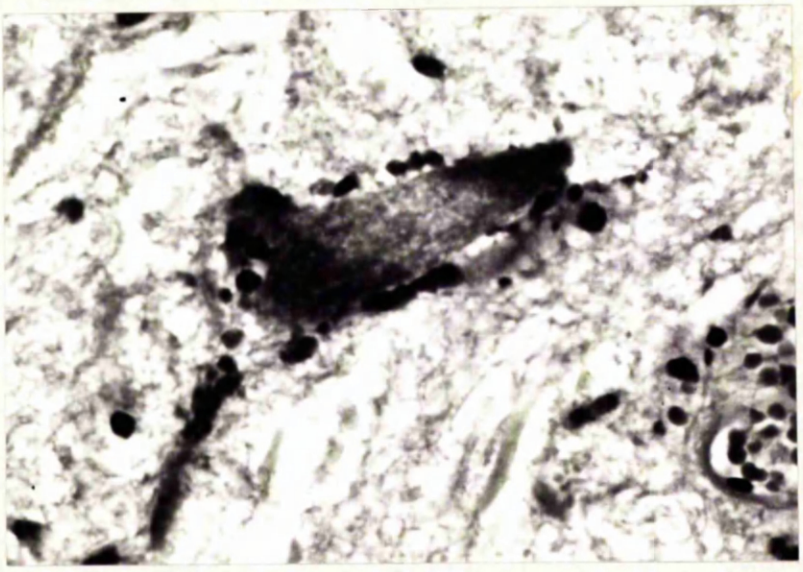


Fig. 16c A neurone showing similar changes to those in Fig. 16b. H & E x 800.

Fig. 16d Two neurones showing ischaemic necrosis. Degenerate boutons are present on the lower border of the larger cell. H & E x 900.

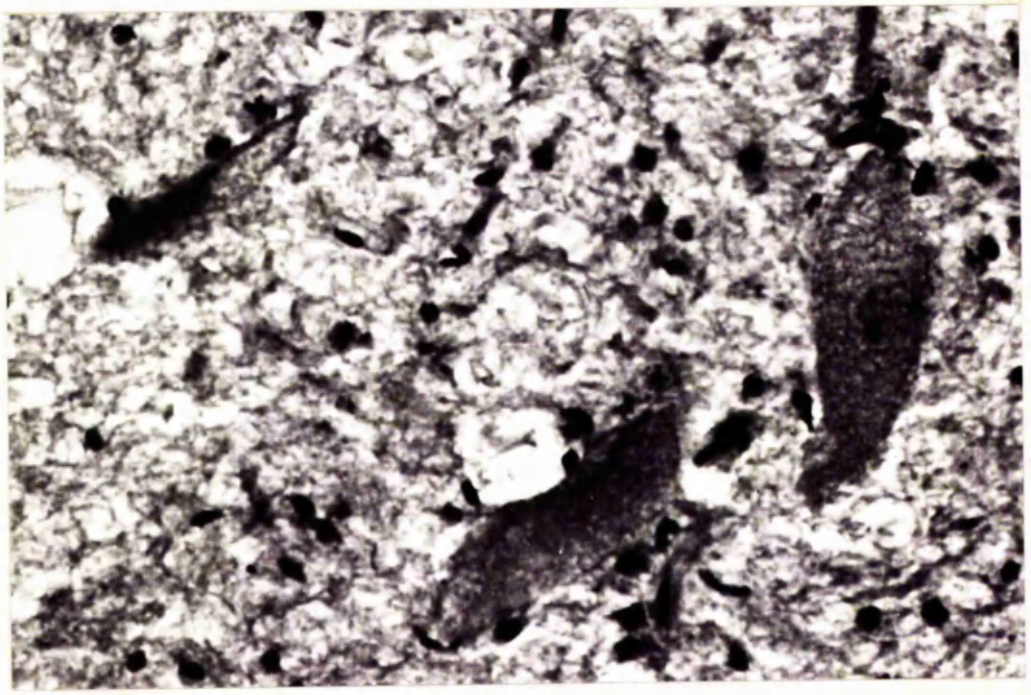


Fig. 16e Neurones in later stages of ischaemia showing marked eosinophilia of the cytoplasm. A faint nuclear outline is present in one cell. H & E x 750.

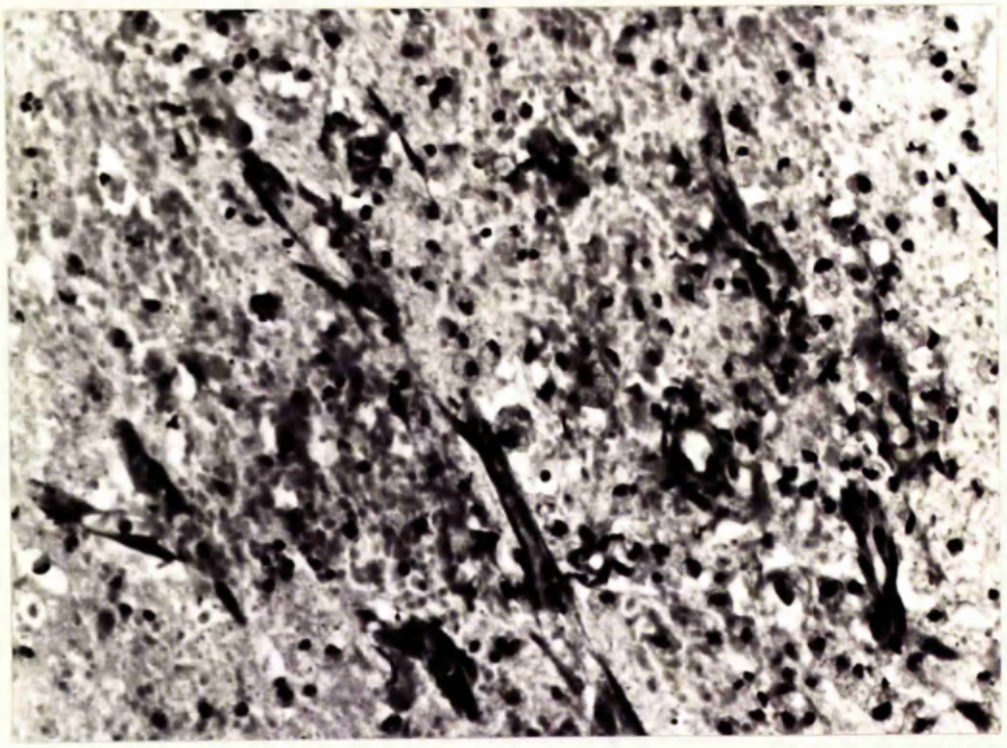


Fig. 17 Area of G.M. showing marked capillary endothelial hyperplasia. There is marked haemorrhage into the tissue and some neutrophil infiltration. Lipid phagocytes are also evident around vessels. H & E x 300.

Fig. 18 Sub-totally necrotic cord showing preservation and proliferation of blood vessels and a marked accummulation of lipid phagocytes. There is a thin strip of surviving W.M. around the ventro-median sulcus. van Gieson x 26.

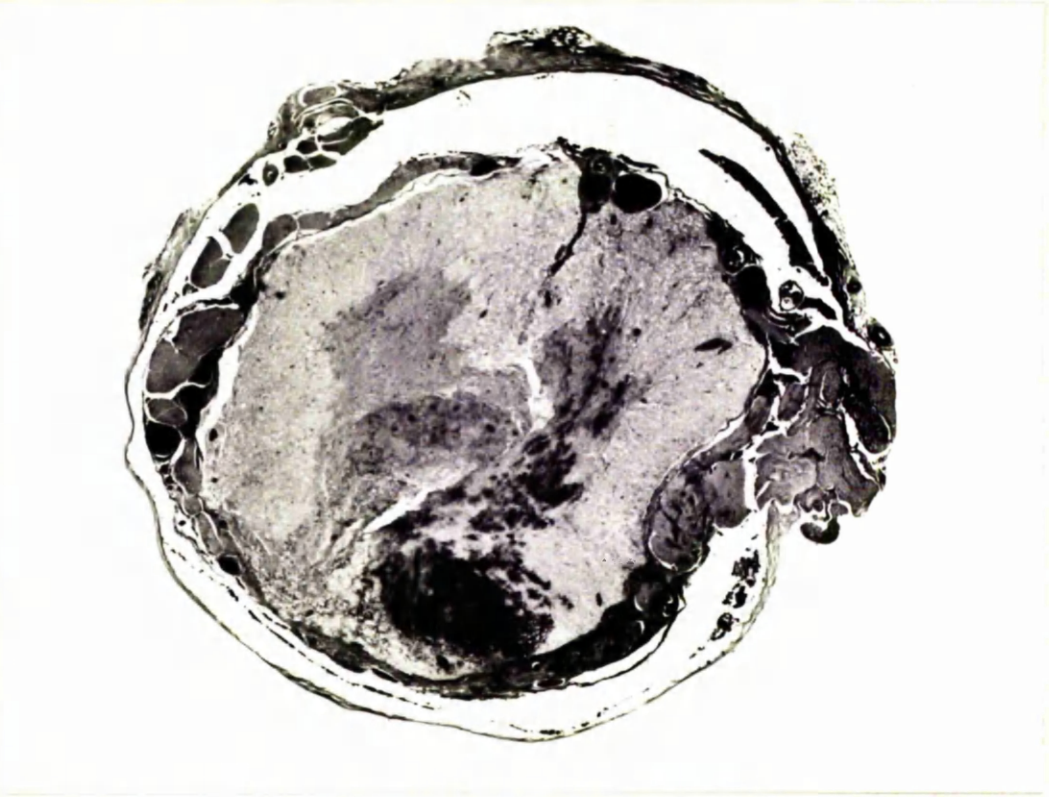


Fig. 19 Segment showing sub-total necrosis with marked haemorrhage in the G.M. on the left and the dorsal columns. The spinal veins are severely congested. H & E x 12.

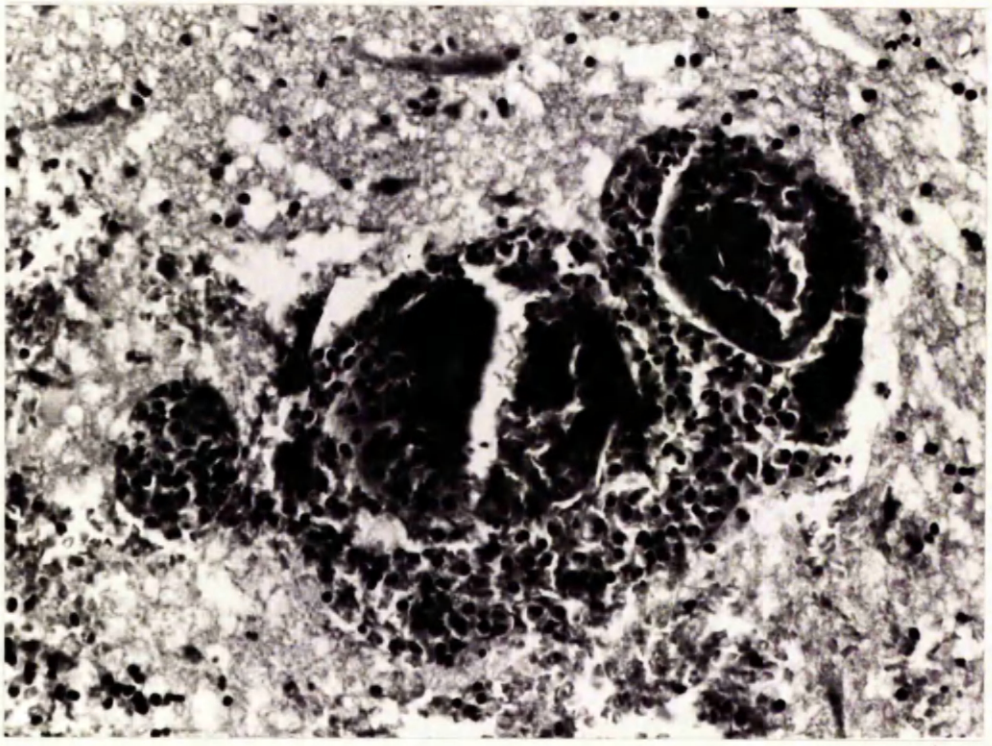


Fig. 20 Necrotic intramedullary vessels showing vascular stasis, perivascular haemorrhage and marked migration of neutrophils into surrounding tissues. H & E x 300.

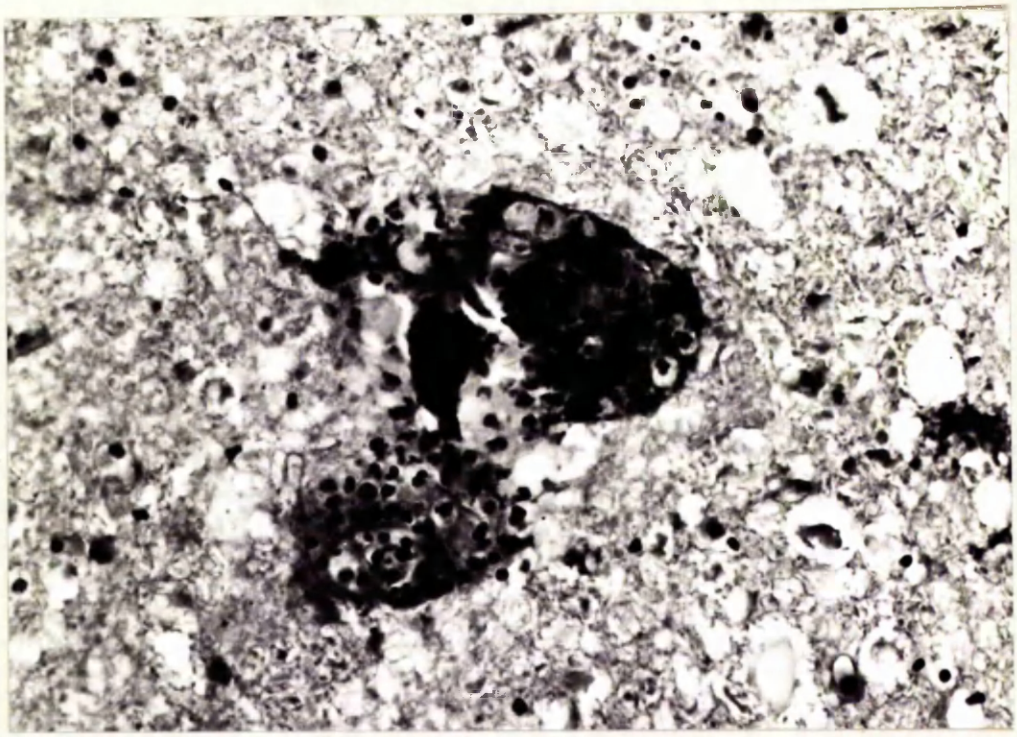


Fig. 21 Two intramedullary arteries with necrotic walls and perivascular deposits of fibrin. M.S.B. x 400.

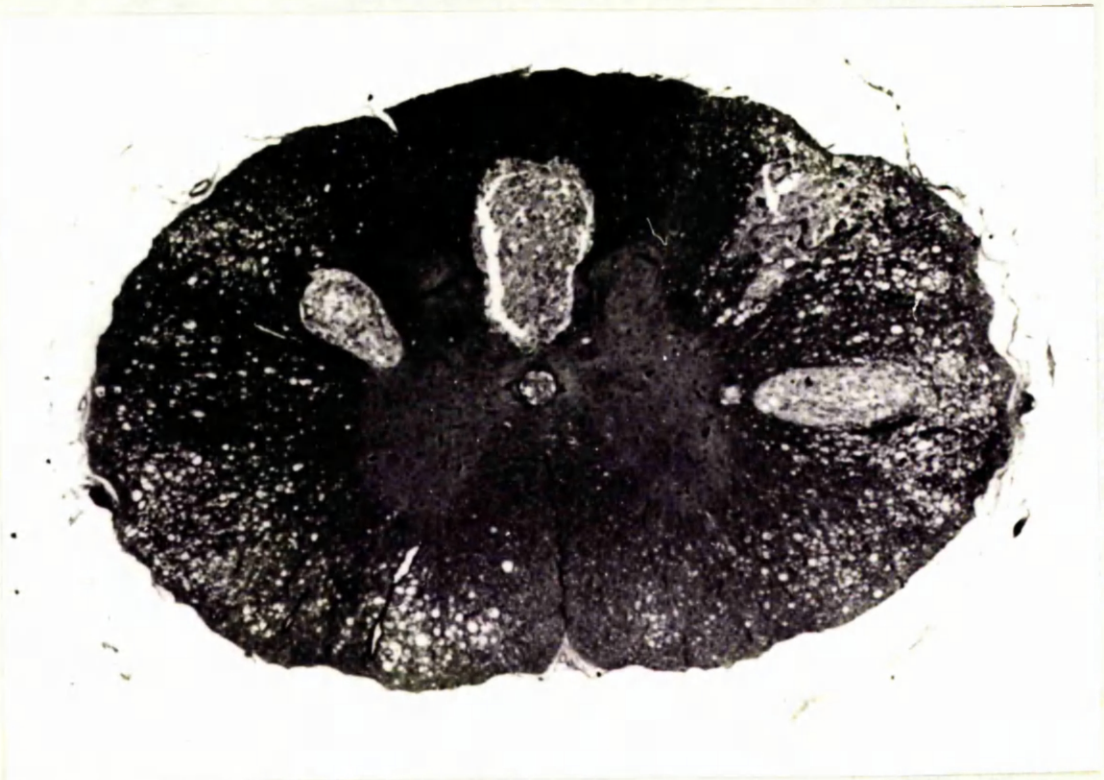


Fig. 22 Segment with "lesser damage" showing localised infarcts of W.M. and diffuse patchy demyelination. H & E x 15.

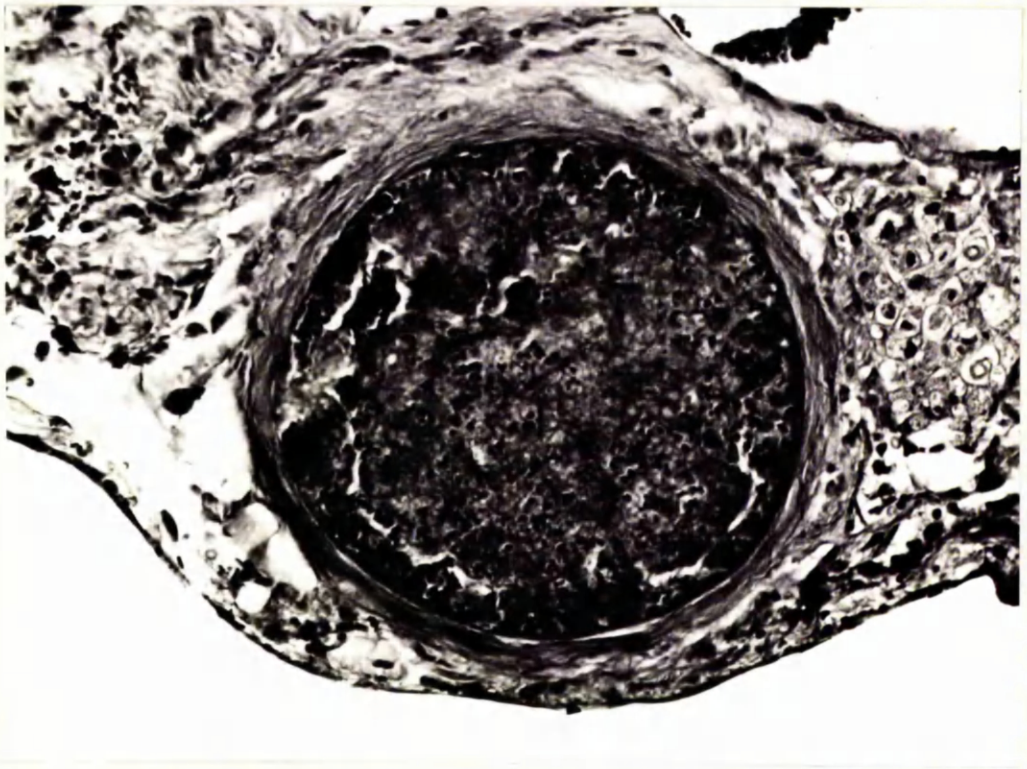


Fig. 23 Lateral pial artery showing thrombosis. H & E x 300.

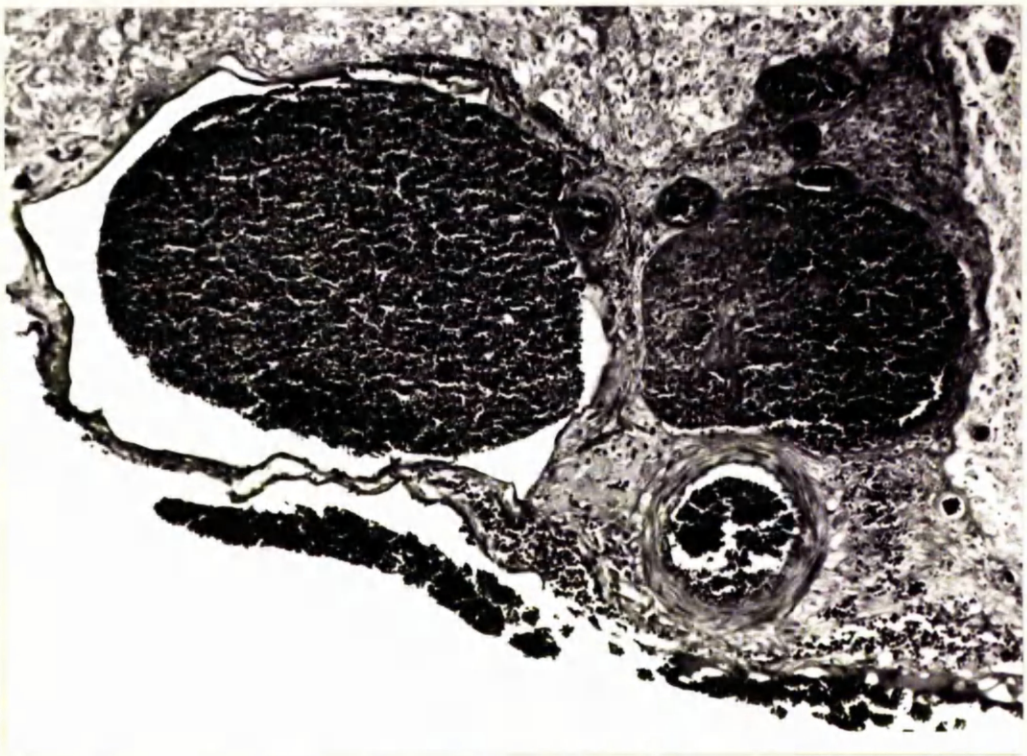


Fig. 24 Ventral spinal artery and veins of a sacral segment showing marked venous congestion and some meningeal haemorrhage. The vein on the right has a necrotic wall and there are fibrin strands in the lumen. H & E x 150.

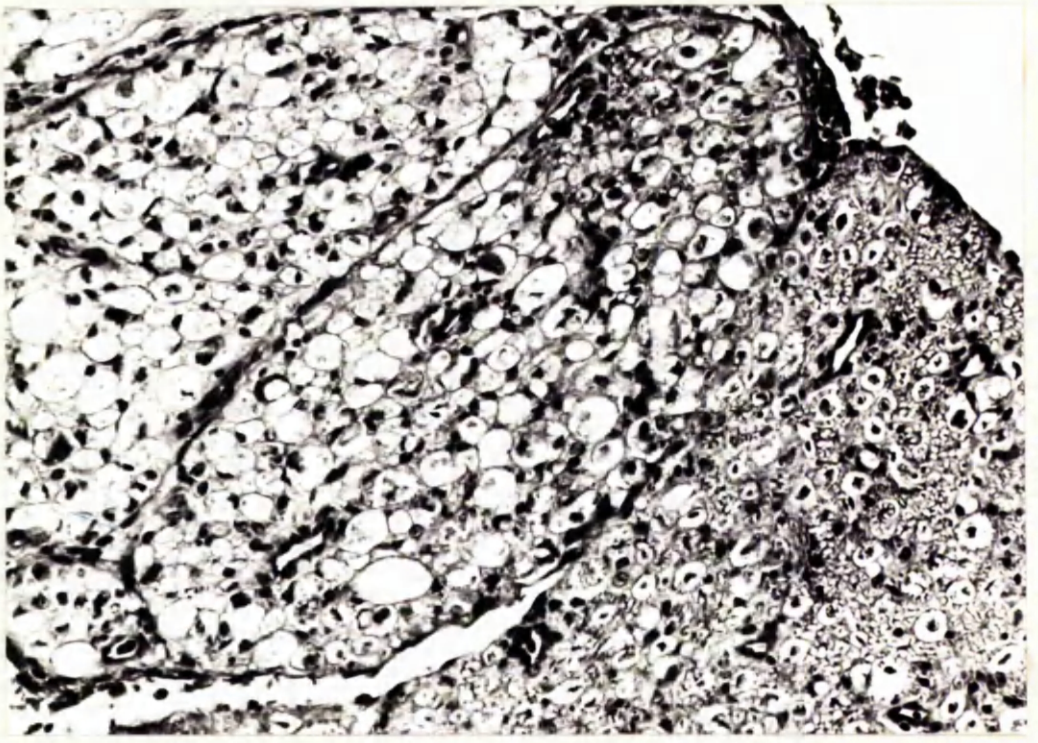


Fig. 25 Ventral nerve root showing Wallerian type degeneration to upper left with swelling of myelin sheaths and presence of macrophages. The area to the lower right is normal. H. & E.x300.

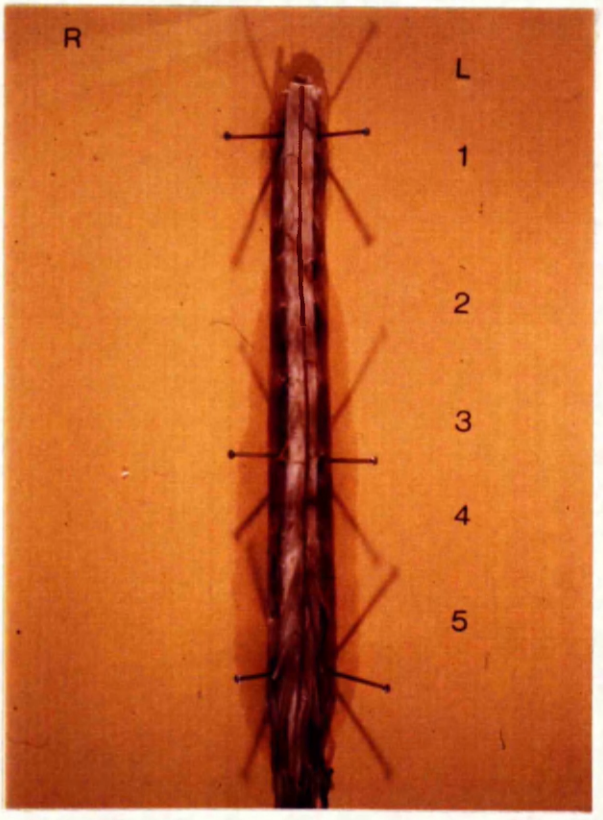


Fig. 26 The ventral aspect of the lumbar cord of a dog with the arterial system injected with Tensil. In this case the major medullary artery accompanies the 5th lumbar ventral nerve root on the left. The ventral spinal artery and smaller medullary arteries are also evident.

Fig. 27 The semilogarithmic plot of the clearance curve obtained by injection of Xe^{133} at the site shown in Fig. 28a. This is a monoexponential curve which when transposed onto semilogarithmic paper gives a straight line. This shows that the injected tissue is homogeneously perfused.

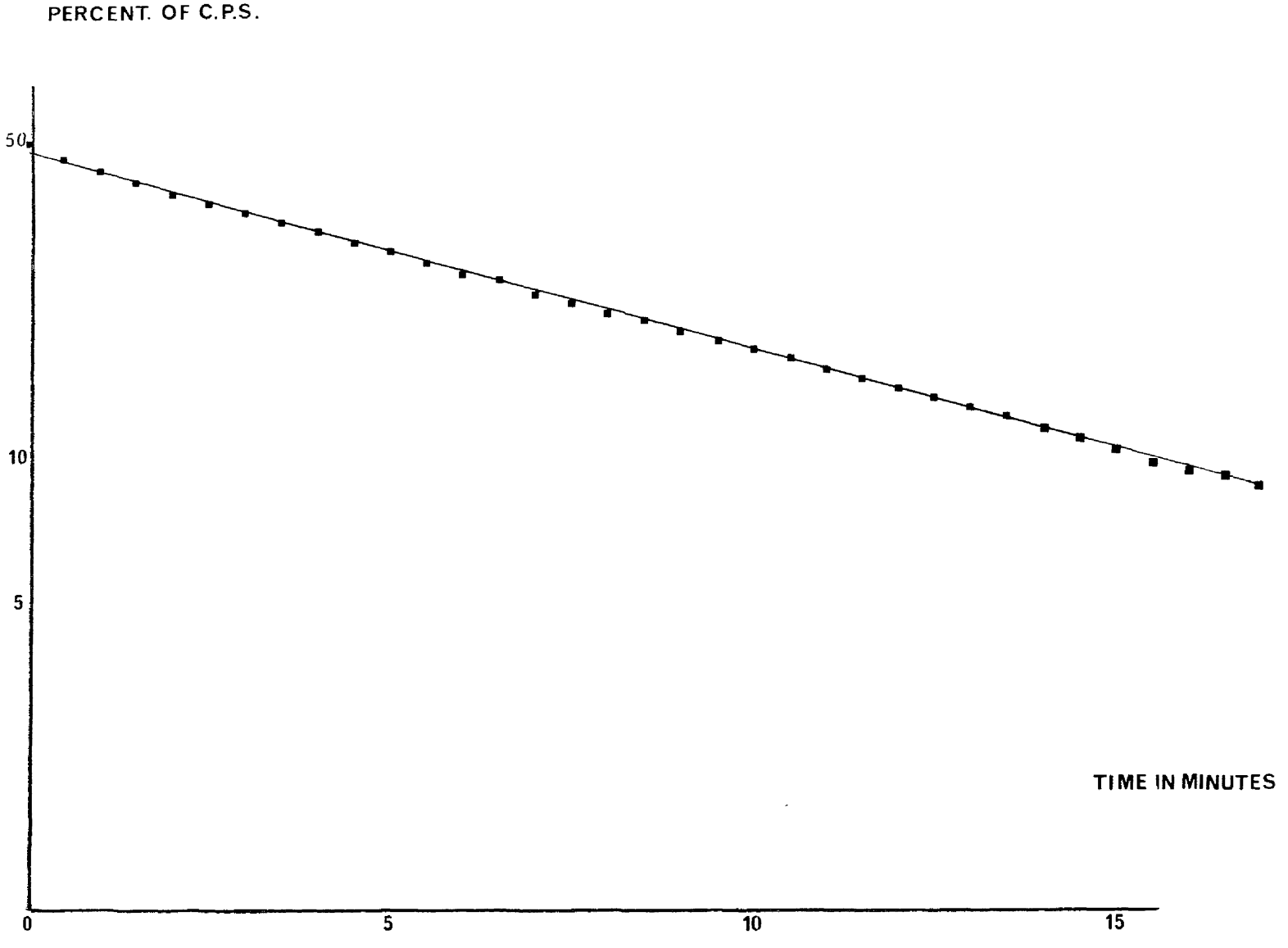
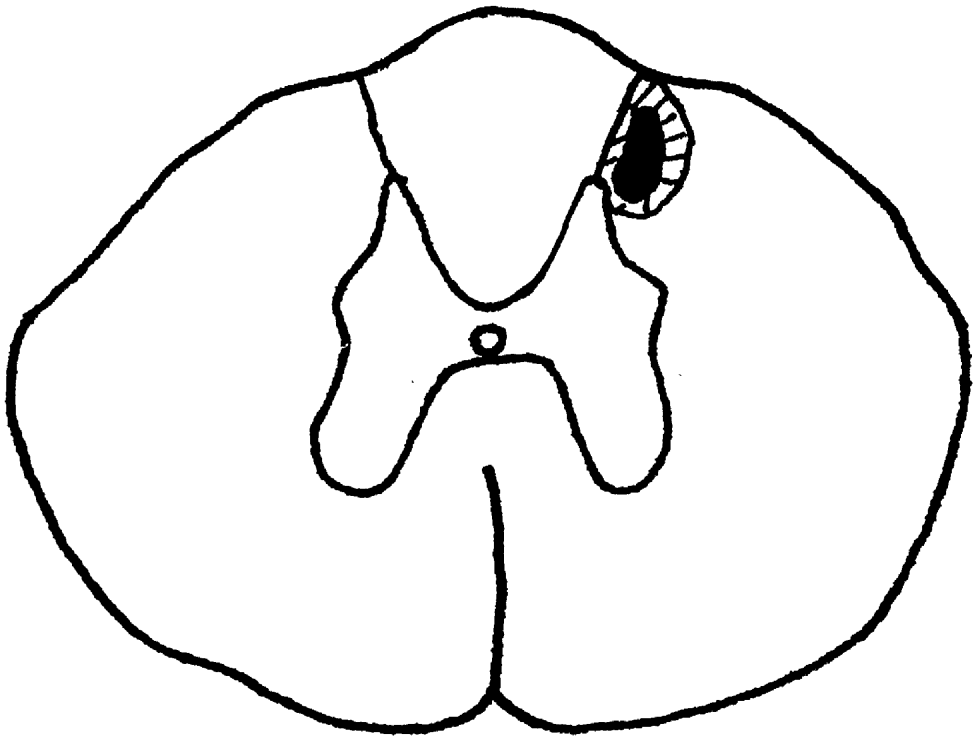

PERCENT. OF C.P.S.
50
10
5
0
5
10
15
TIME IN MINUTES

Fig. 28a (upper) A drawing of the cord from which the clearance curve in Fig. 27 was obtained.

Fig. 28b (lower) The cord from which the curve in Fig. 29 was obtained.

In both cases the site of injection of the congo red dye is illustrated. The black area is the site of maximal dye concentration and the hatched area shows the limit of diffusion of congo red.



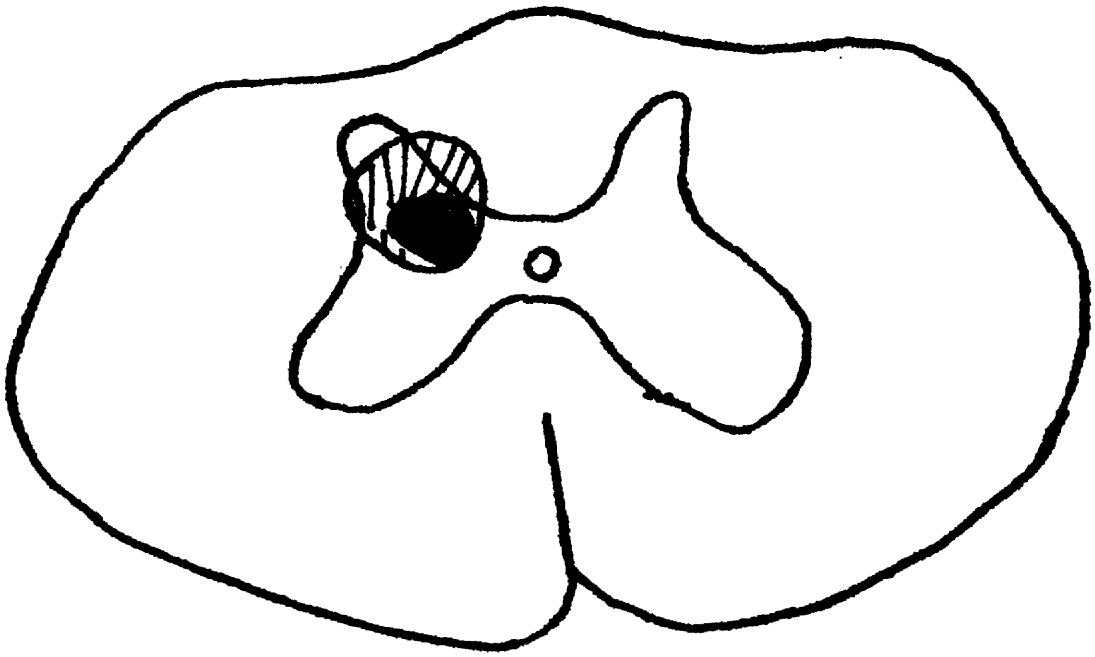


Fig. 29 An example of a biexponential clearance curve as obtained on the potentiometric recorder.

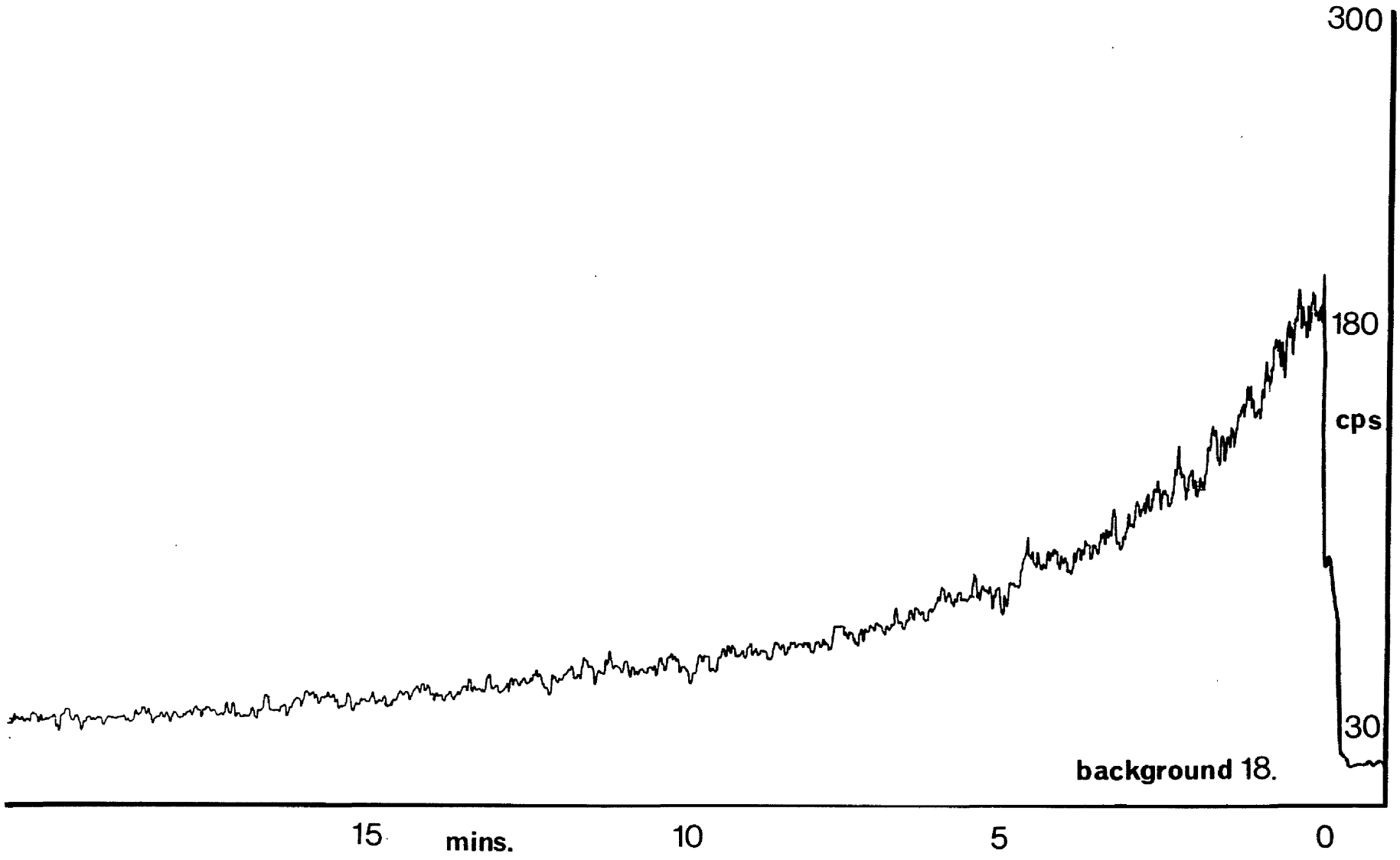

300
180
cps
30
background 18.
15
mins.
10
5
0

Fig. 30 The semilogarithmic plot of the biexponential clearance curve shown in Fig. 29. The fast component (dotted line) and slow component (solid line) are illustrated and the $T_{\frac{1}{2}}$ and blood flow for each is given. The fast component is obtained by subtracting the slow component from the initial slope.

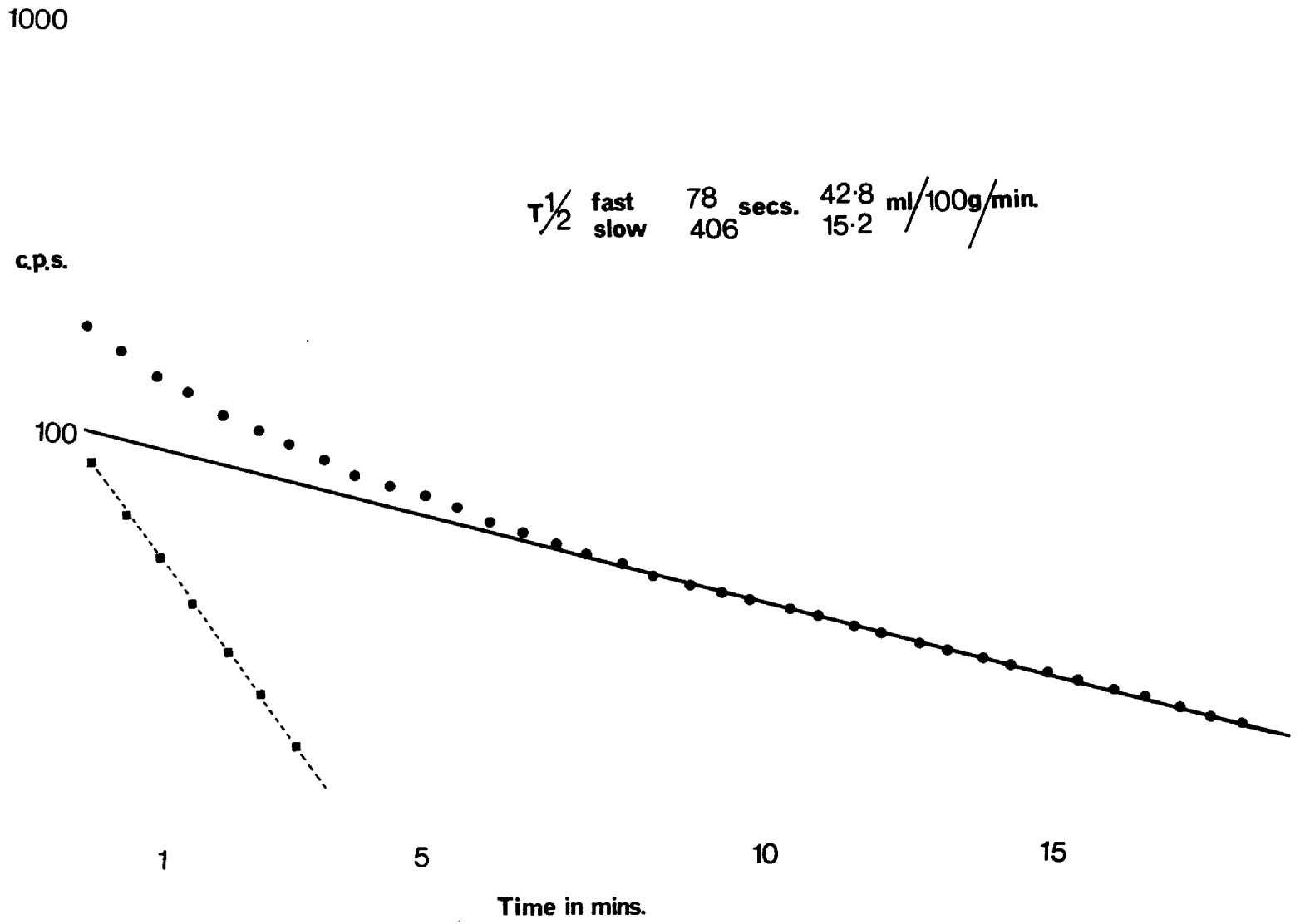

1000
T½ fast 78 secs. 42·8 ml/100g/min.
slow 406 15·2
c.p.s.
100
1
5
10
15
Time in mins.

Fig. 31 The effect of cardiac arrest on the clearance of Xe^{133} from the cord. The normal clearance of Xe^{133} ceases at cardiac arrest and the level of isotope remains constant showing that clearance is by the bloodstream and not by tissue diffusion.

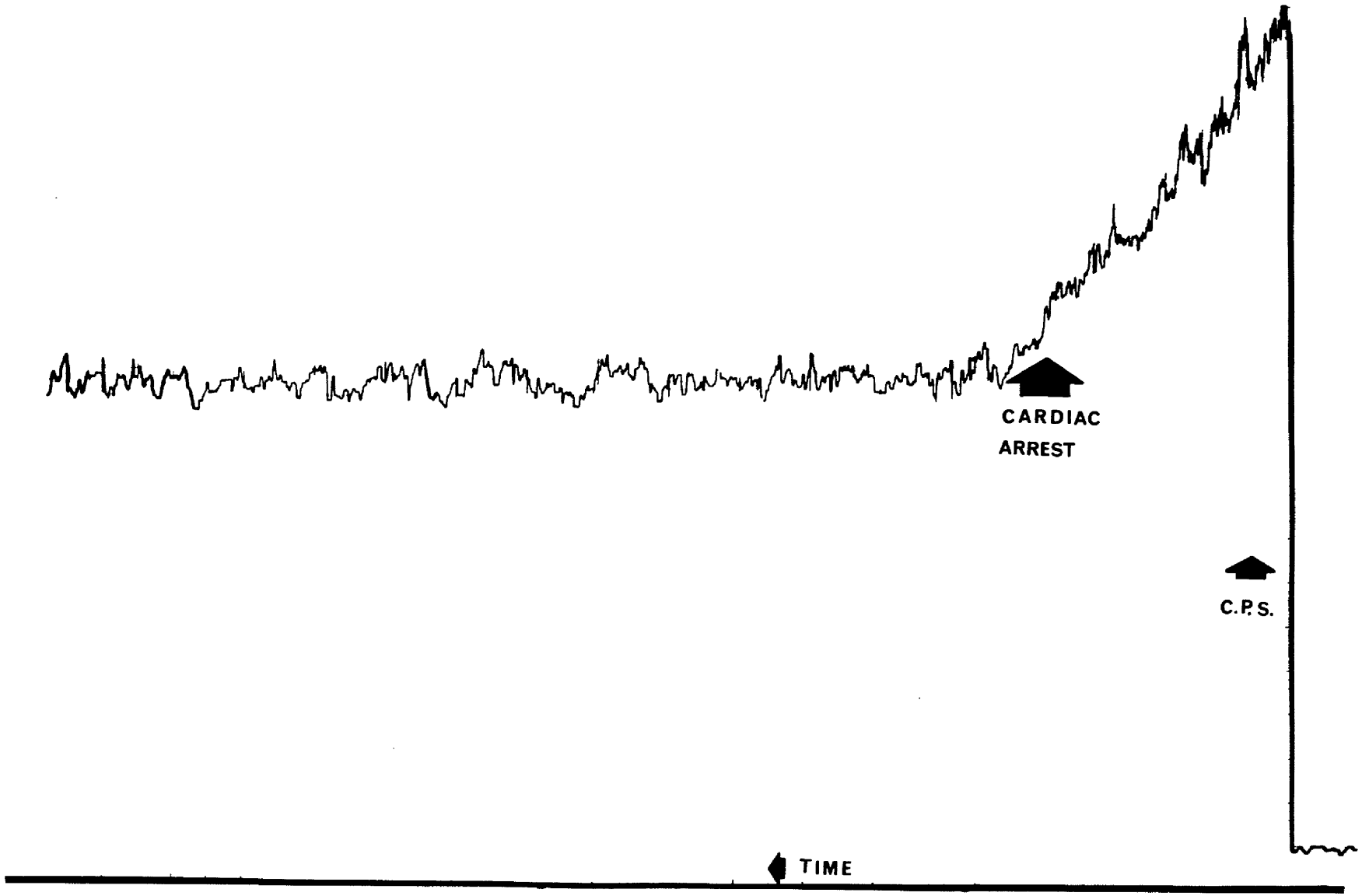

CARDIAC
ARREST
C.P.S.
TIME

Fig. 32 The effect of the $paCO_2$ on the S.C.B.F. The percentage change in flow has been correlated with the $paCO_2$. The regression line ($r = 0.87$) is shown. The results from 9 dogs are included and in each case the flow at $paCO_2$ 40 mm.Hg. was taken as 100%.

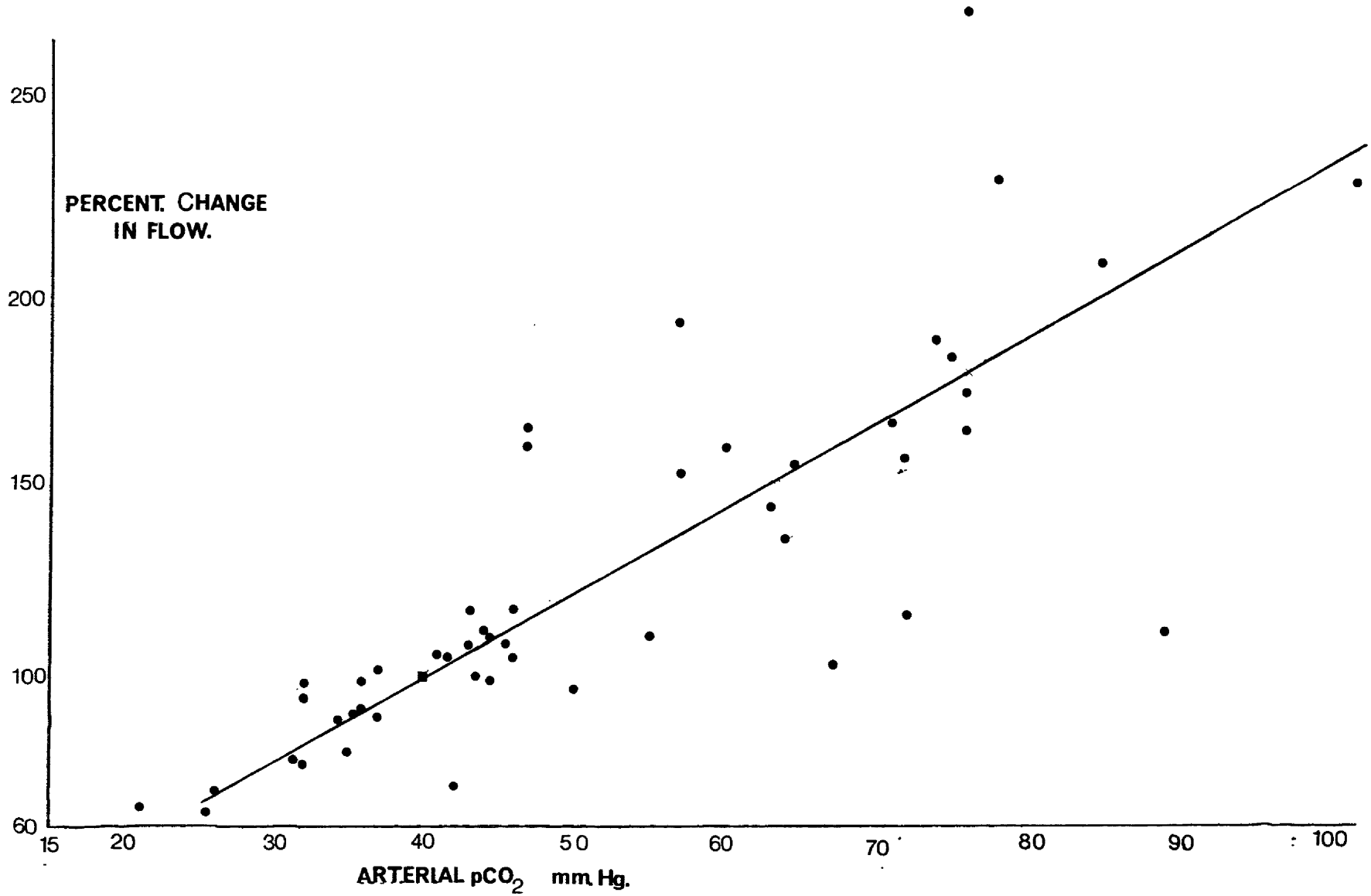

250
200
150
100
60
PERCENT CHANGE
IN FLOW.
15
20
30
40
50
60
70
80
90
100
ARTERIAL pCO_2 mm. Hg.

Fig. 33 The effect of paO_2 on S.C.B.F. is shown. The results from 9 dogs are presented and in each case the flow at paO_2 100 mm.Hg. was taken as 100%.

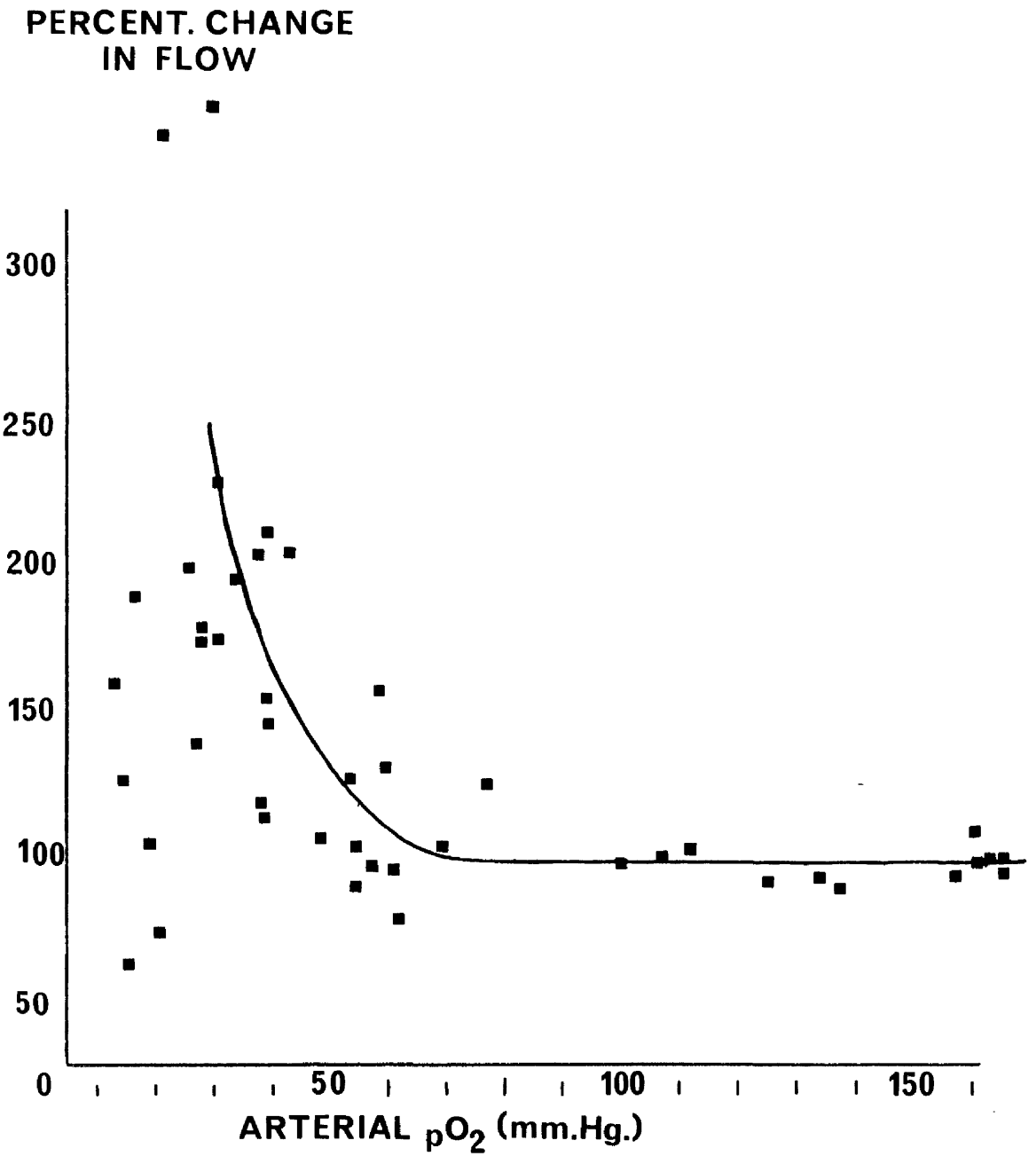

PERCENT. CHANGE
IN FLOW
300
250
200
150
100
50
0
50
100
150
ARTERIAL pO_2 (mm.Hg.)

Fig. 34 The effect of paO_2 on the absolute blood flow in 6 dogs is presented.

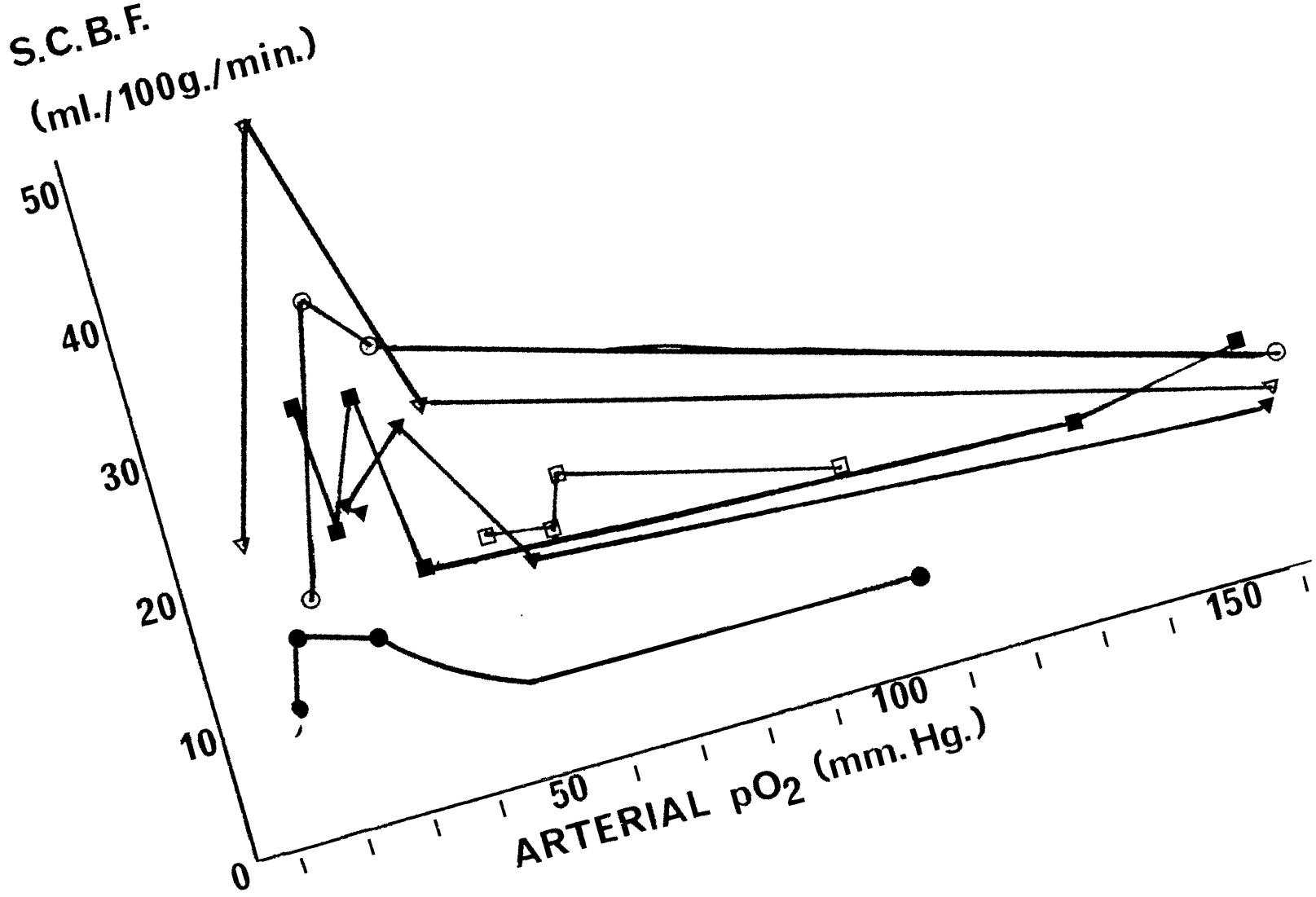

S.C.B.F.
(ml./100g./min.)
50
40
30
20
10
0
50
100
150
ARTERIAL pO_2 (mm.Hg.)

Fig. 35 The percentage change in S.C.B.F. with alterations of the mean arterial blood pressure under conditions of normoxia and normocarbia. The combined results from 8 dogs are shown. The S.C.B.F. at a pressure of 95 mm.Hg. was taken as 100%.

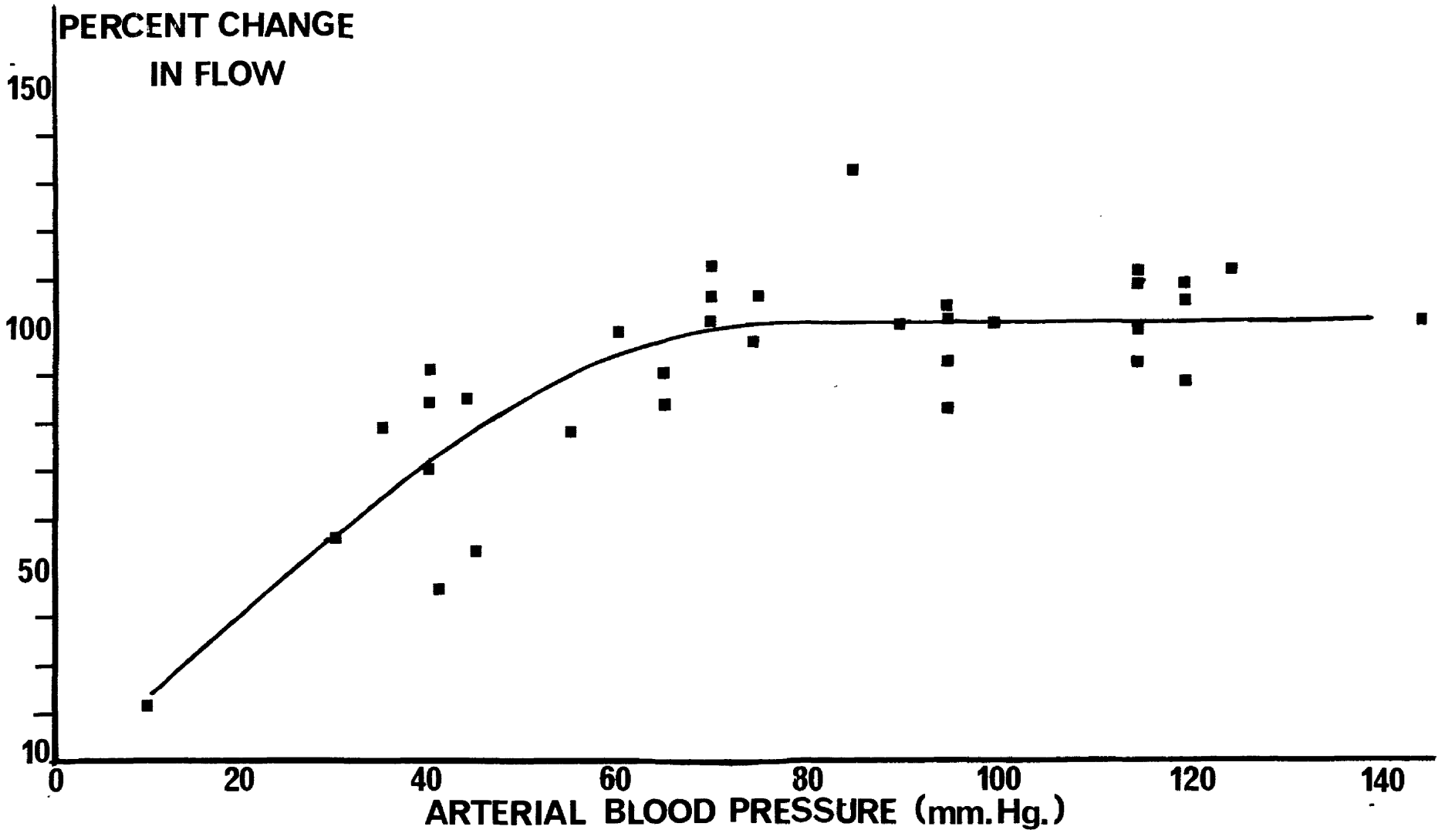

PERCENT CHANGE
IN FLOW
150
100
50
10
0
20
40
60
80
100
120
140
ARTERIAL BLOOD PRESSURE (mm.Hg.)

Fig. 36 The absolute change in S.C.B.F. with progressive hypotension. The results from 8 dogs are shown.

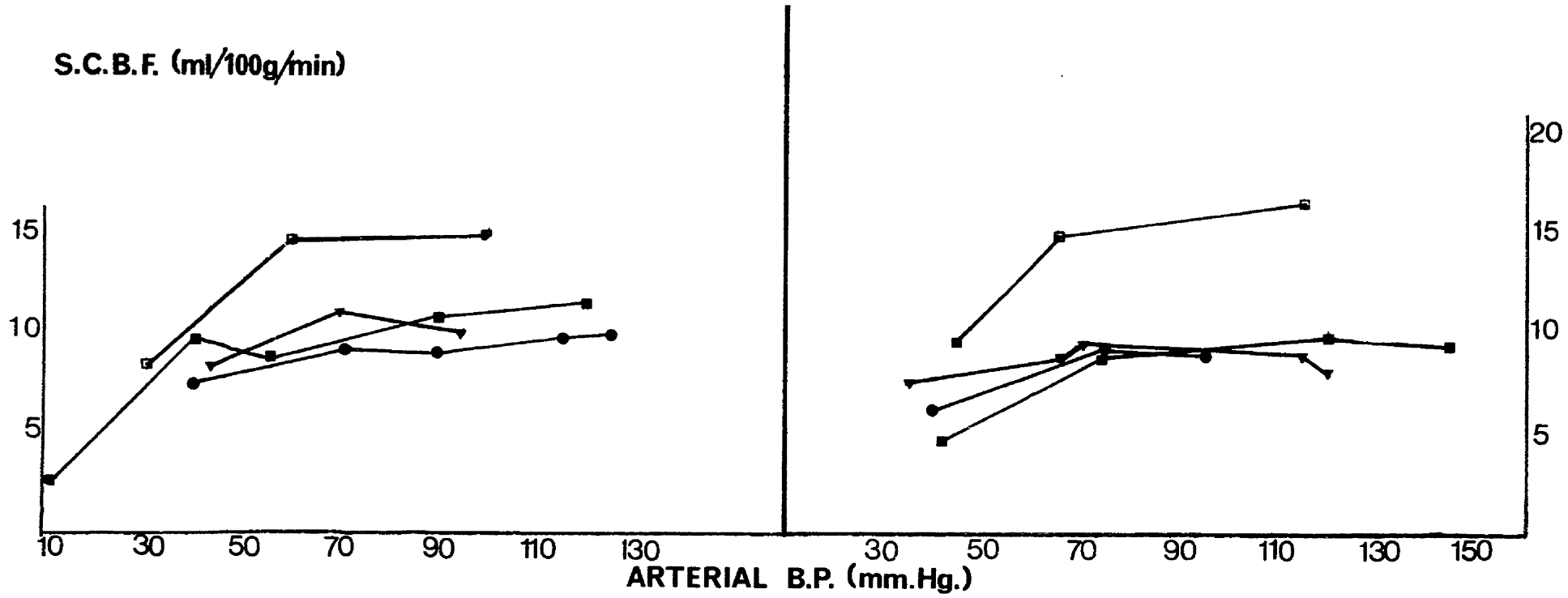

S.C.B.F. (ml/100g/min)
15
10
5
20
15
10
5
10
30
50
70
90
110
130
30
50
70
90
110
130
150
ARTERIAL B.P. (mm.Hg.)

Fig. 37 Two clearance curves from the same dog where the blood pressure was rapidly lowered by bleeding via an aortic cannula.

A. shows the semilogarithmic plot of a biexponential clearance curve. During the slow component the pressure was reduced from 145 - 110 mm.Hg. over 45 secs. as indicated by the arrows.

B. shows the semilogarithmic plot of a monoexponential clearance curve. The pressure was reduced from 90 - 60 mm.Hg. over 2 minutes.

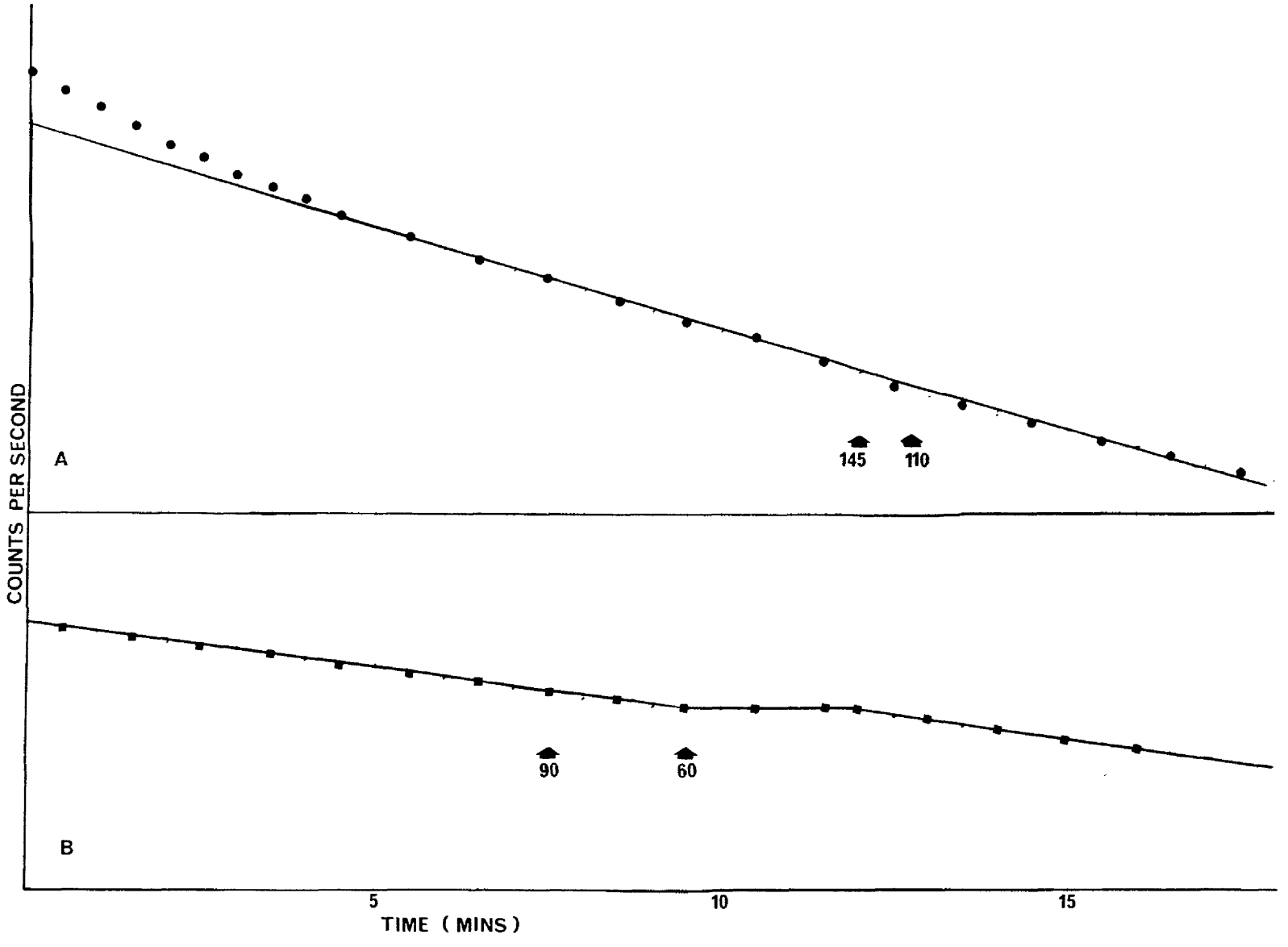

COUNTS PER SECOND
A
145
110
90
60
B
5
10
15
TIME (MINS)

Fig. 38 The percentage change in S.C.B.F. with alterations of mean arterial blood pressure under conditions of hypoxia and normocarbia. The combined results from 8 dogs are shown. The S.C.B.F. at a pressure of 100 mm.Hg. was taken as 100%.

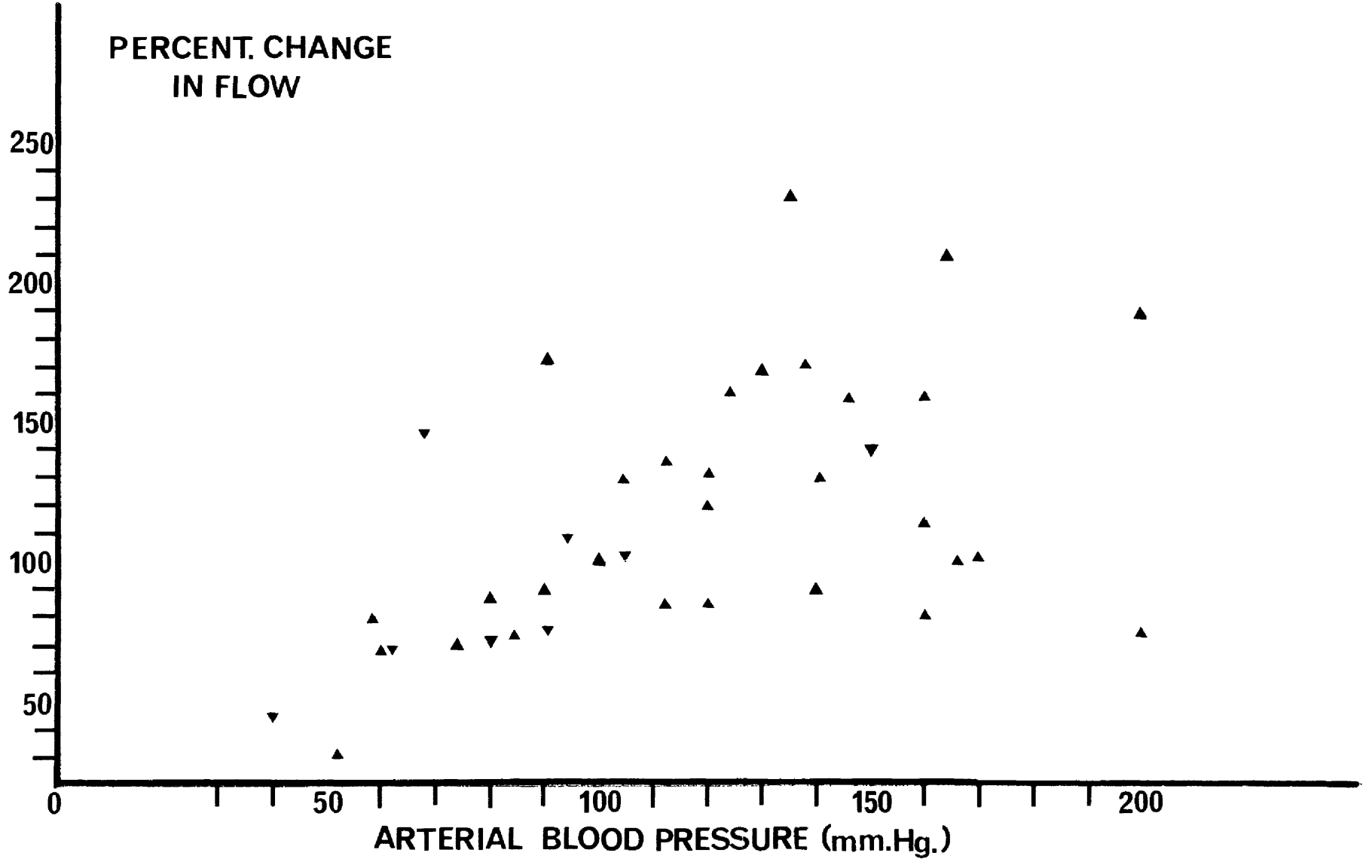

PERCENT. CHANGE
IN FLOW
250
200
150
100
50
0
50
100
150
200
ARTERIAL BLOOD PRESSURE (mm.Hg.)

Fig. 39 The absolute changes in S.C.B.F. with progressive hypotension in 6 dogs under conditions of hypoxia and normocarbia.

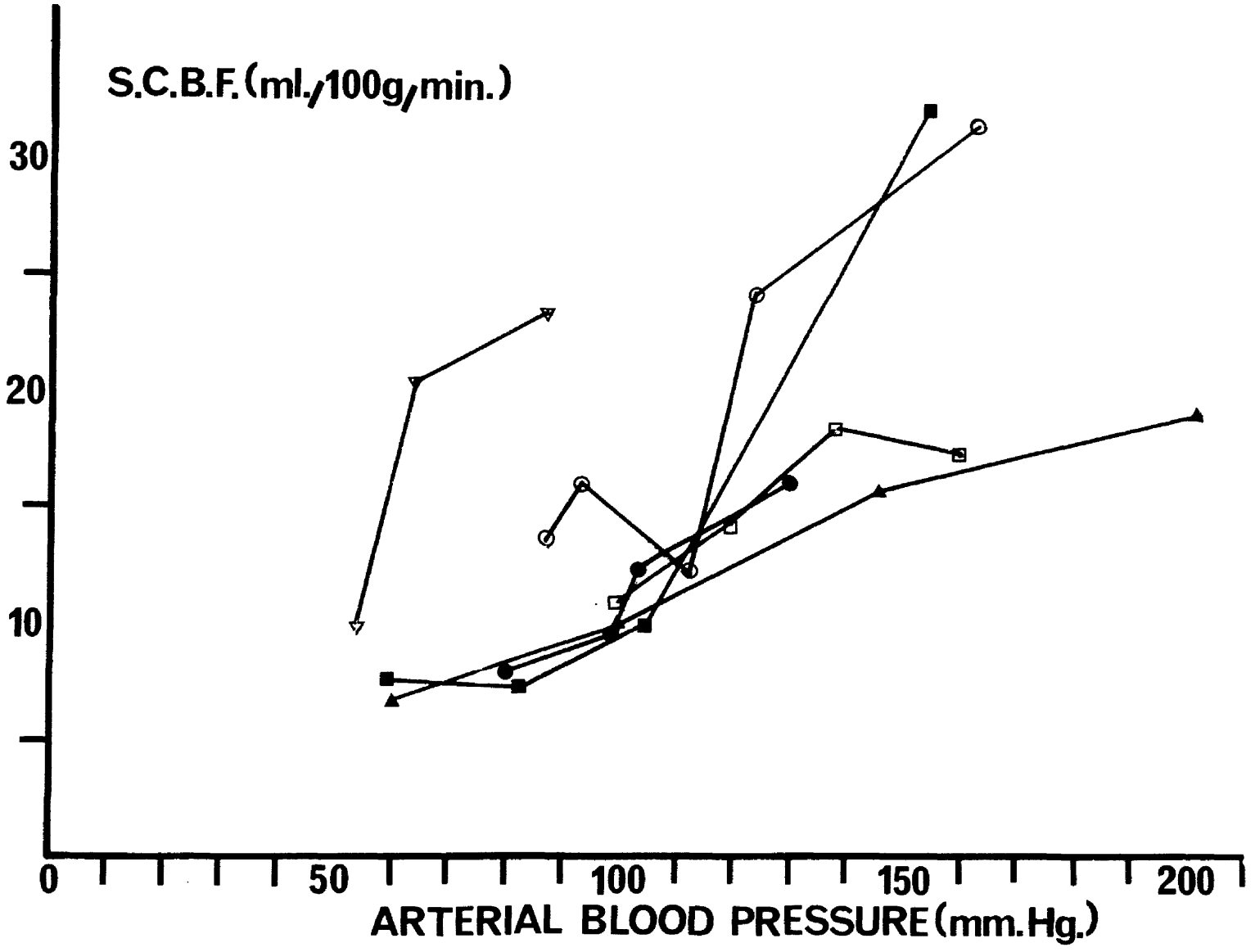

S.C.B.F.(ml./100g/min.)
30
20
10
0
50
100
150
200
ARTERIAL BLOOD PRESSURE(mm.Hg.)

Fig. 40 The percentage change in S.C.B.F. with alterations in mean arterial blood pressure under conditions of hypercarbia and normoxia. The combined results from 6 dogs are shown. The S.C.B.F. at a pressure of 90 mm.Hg. was taken as 100%.

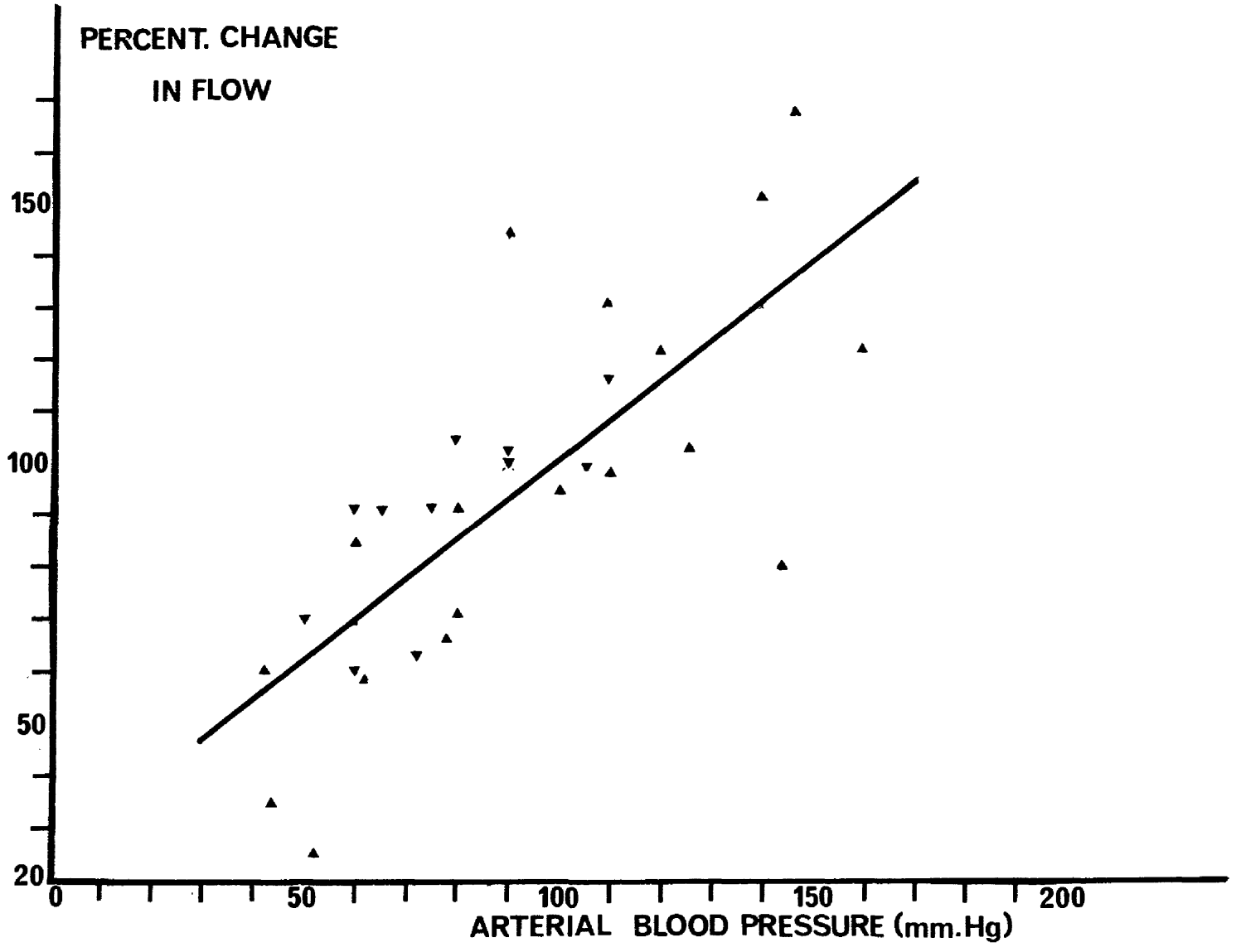

PERCENT. CHANGE
IN FLOW
150
100
50
20
0
50
100
150
200
ARTERIAL BLOOD PRESSURE (mm.Hg)

Fig. 41 The absolute changes in S.C.B.F. with progressive hypotension in 6 dogs under conditions of hypercarbia and normoxia.

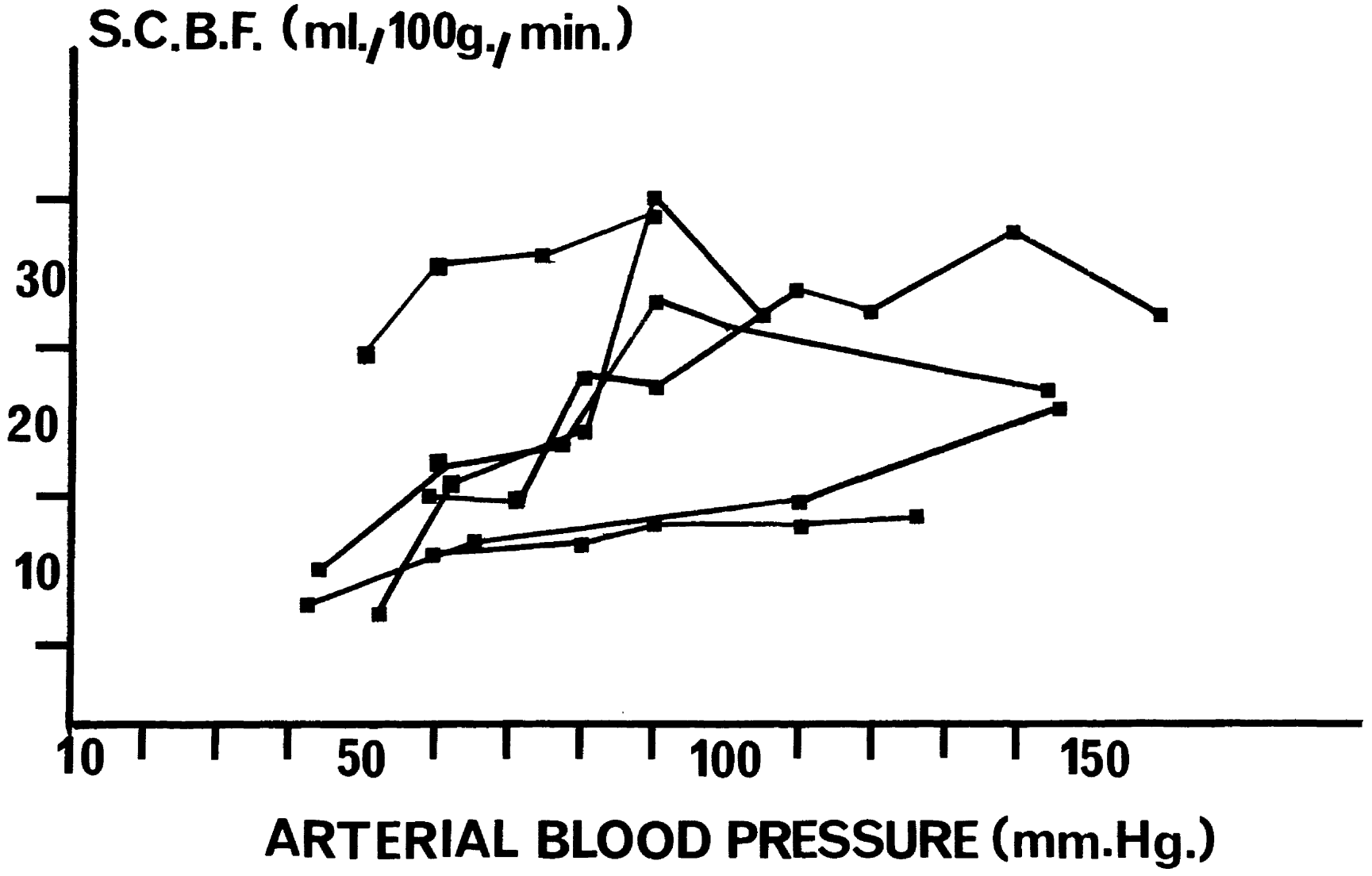

S.C.B.F. (ml./100g./min.)
30
20
10
10
50
100
150
ARTERIAL BLOOD PRESSURE (mm.Hg.)

TABLE I

Malacia alone	1	
Demyelination alone	3	
Compression alone	8	
Malacia & Compression	3	
Malacia & Demyelination	5	
Demyelination & Compression ...	2	
Demyelination, Compression & Malacia	3	
TOTAL	25	Cord lesions

TABLE 2

Case No.	Pro-truded Disc	Type	The rostro-caudal extent of the undermentioned processes			
		Funk-quist (1962)	Extra-dural mass	Meningeal Haemorrhage	Total & Sub-total necrosis	Lesser Damage
33352	L2/3	III	Post.Thoracic -mid-lumbar	Post.Thoracic -mid-lumbar	Mid.Thoracic -mid-lumbar	Ant.Thoracic segments & caudal lumbar segments
43598	L3/4	III	T11 - sacral segments	T4 - L3	T4 - L2	L2 - Sacral segments
43610	T13/L1	III	Mid.Thoracic -Sacral segments	Mid.Thoracic -Sacral segments	Ant.Thoracic-Sacral segments	Minimal
43973	T12/T13	III	T12 - L4	T5 - Sacral segments	T5 - Sacral segments	Ant.Cervical segments - T5
43826	T12/T13	III	T12 - T13	T13 only	T9 - T10	T6 - T9 and T10 - L2
33811	L1/L2	III	T12 - L4	Minimal	Mid.Thoracic - Sacral segments	Minimal
29012	L2/L3	II	L2 - L4	Minimal	T6 - post. lumbar segs.	Post.cervical segments - T6
47773	L4/L5	III	T9 - L3 L5 - Sacral	T2 - T12 L6 - Sacral	T2 - L3	C5 - T1 & L4 - Sacral segments

Post. = Posterior
Ant. = Anterior

Where levels are referred to as mid-lumbar etc., the exact cord segments was not determined.

TABLE 3

Dog. No.	Run	pCO_2	S.C.B.F.	S.C.B.F. corrected to pCO_2 40 mm.Hg.
		mm.Hg.	ml/100g/min.	
4	1	35.5	18.2	19.4
	3	32	19.1	21.0
	7	37	18.2	19.2
5	1	40	15.7	15.7
	2	36	12.4	13.4
	3	34.5	13.9	14.7
	7	42	11.21	10.8
13	1	48.5	12.75	11.48
	2	42	14.97	11.68
	3	46	11.17	10.39
	4	47	11.17	10.28

TABLE 4

Blood Flow in white matter standardised to a pCO_2 of 40 mm. Hg.

Dog	No. of estimations	S.C.B.F. ml/100g/min. M ± S.D.	Cord segment
3	3	13.8 ± 0.92	L_1
4	3	19.8 ± 0.98	T_{13}
5	4	13.6 ± 2.12	T_{13}
6	4	15.2 ± 2.5	L_2
7	3	29.4 ± 3.3	L_3
9	2	11.1 ± 0.84	T_{12}
10	2	11.25 ± 0.5	L_1
13	4	10.95 ± 0.72	T_{13}

TABLE 5

Flows in the W.M. at different segments in the same dog.

Dog.	Segments	No. of estimations	pCO_2 mm.Hg. M ± S.D.	S.C.B.F. ml/100g/min. M ± S.D.	P
22	T_{12}	3	45.5 ± 3.2	9.2 ± 1.2	< 0.05
	L_3	3		20.5 ± 5.3	
23	T_{12}	4	45.0 ± 4.9	16.7 ± 1.3	N.S
	L_2	4		15.0 ± 2.5	
24	T_{13}	4	36.5 ± 1.6	14.92 ± 2.2	N.S
	L_4	4		17.6 ± 5.3	
32	T_{13}	4	49 ± 7.8	23.4 ± 6.9	N.S
	L_3	5	52.0 ± 8.3	18.6 ± 3.8	

P = significance of difference in flows.

N.S = not significant.

TABLE 6

Comparison of S.C.B.F., in W.M. using Trichlorethylene, Halothane and Pentobarbitone as anaesthetics. Segments T12/T13.

Anaesthetic	No. of observations	pCO_2 mm.Hg. M ± S.D.	S.C.B.F. ml/100g/min. M ± S.D.	B.P. mm. Hg. M ± S.D.	
Trichloreth-ylene (0.5 - 1%)	17	38 ± 5.9	16.9 ± 8.0	140 ± 12	*
Pento-barbitone (25 mg/Kg)	14	40.6 ± 3.6	14.7 ± 5.3	138 ± 24	*
Halothane (0.5%)	13	42.9 ± 4.6	14.8 ± 4.0	114 ± 17	

* $P < 0.01$

TABLE 7

	Blood Flow calculated from the Fast component			
Dog	No. of estimations	Arterial pCO_2 mm.Hg. M ± S.D.	S.C.B.F. ml/100g/min. M ± S.D.	Segment
2	4	33 ± 1.4	86 ± 20	L_5
3	1	37	85	L_1
5	3	39 ± 3.0	31.5 ± 4.2	T_{13}
6	3	35.3 ± 2.0	51 ± 8.8	L_2
7	3	46 ± 1.0	84 ± 24	L_3
10	1	36	74	L_1
13	5	45.7 ± 2.0	26.7 ± 2.0	T_{13}

TABLE 8

Summary of Previous Quantitative Investigations of S.C.B.F.

Author	Method	Species	S.C.B.F. ml/100g/min	Area of cord
Landau et al 1955	auto-radiography	Feline	14	white matter
Flohr et al 1969	particle distribution	Feline	20.3 16.5 23.7	cervical thoracic lumbo-sacral
Smith et al 1969	Xe^{133} clearance	Caprine	17.6	lumbar

TABLE 9

The effect of Hypercarbia on S.C.B.F.

Anaesthetic	No. of observations	pCO_2 (mm.Hg.) M ± S.D.	B.P.(mm.Hg) M ± S.D.	S.C.B.F.(ml/100g/min.) M ± S.D.
Trilene	17	38 ± 5.9	140 ± 12.32	16.9 ± 8.0
	7	66 ± 9.6	152 ± 11.49	29.8 ± 15.2*
Halothane	13	42.9 ± 4.6	114 ± 17.5	14.8 ± 4.0
	13	80 ± 21.4 ***	121 ± 24.2	23.3 ± 9.8**

* $P < .02$

** $P < .01$

*** $P < .001$

TABLE 10

Dog 25 Segment T13

Time	Run	$paCO_2$ mm.Hg.	S.C.B.F. ml/100g/min
11.15	1	25.5	7.76
12.10	2	31.5	9.45
1.05	3	57	18.27
1.50	4	74	22.41
2.25	5	44.5	13.2

TABLE 11

The absolute sensitivity of the S.C.B.F. to $paCO_2$.

	Normocarbia	Hypocarbia			Hypercarbia		
Dog	S.C.B.F. at pCO_2 40 mm.Hg	pCO_2 mm.Hg	S.C.B.F. ml/100g/min	Sensitivity ml/100g/min mm.Hg.	pCO_2 mm.Hg	S.C.B.F. ml/100g/min	Sensitivity ml/100g/min mm.Hg.
4	20.25	21	13.4	0.36	76	55	0.96
					78	46	0.67
5	15.7	26	11	0.33	75	28.7	0.37
					60	25	0.46
9	11	32	10.8	0.02	57	21	0.58
25	12	25.5	7.76	0.29	57	18.2	0.36
					74	22.4	0.39
16	13.2	32	10.2	0.37	63	19	0.25
12	14.5				85	32	0.38
					64	19.6	0.21
15	11.5				76	18.8	0.2
					102	26.13	0.23
27	13.8				76	23.3	0.27
10	11				64.5	17	0.24
				Mean 0.27			Mean 0.39
				S.D. 0.14			S.D. 0.21

TABLE 12

The effect of combined hypoxia & hypocarbia on S.C.B.F.

Dog	Run	S.C.B.F. ml/100g/min	$paCO_2$ mm.Hg.	paO_2 mm.Hg.
40	1	15.2	42.5	134
	2	31.6	47	35
	3	18.2	26	22
	4	11.5	24.5	192
41	1	17	40	160
	2	39.2	36	31.5
	3	29.7	21.5	52
	4	12.6	27.5	162
44	1	13.4	38	168
	2	23.78	37	31.5
	3	24.8	20	22
	4	12.4	24	59
	5	6.7	21	138
45	1	14.6	45	163
	2	30	45	44
	3	19.1	20.5	56