of these experiments. Better results were obtained when the interferon was injected by the intramuscular route.

A single dose of interferon afforded protection to mice when injected at times between 30 and 3½ hours before infection with virus, but not when given 48 hours before infection. Some protection was obtained when a large dose of interferon was given three hours after infection.

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Neurogenic Intermittent Claudication

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Intermittent claudication, pain in the legs produced by exercise and relieved by rest, is a well-known manifestation of peripheral or aorto-iliac obstructive vascular disease. It may also be a prominent feature of anaemia, McArdle's (1951) disease, the pre-infarctive anterior tibial syndrome (French and Price, 1962), and as a complication of vasoconstrictive drugs (Graham, 1960). It is less well known as a symptom of a "neurological" lesion.

Lewtas and Dimant (1957) described the case of a man of 62 with an eight-year history of pain, numbness, and tingling in the legs produced by exercise associated with hypertrophic interstitial polyneuritis (Dejerine–Sottas disease) of the cauda equina. Blau and Logue (1961) described a similar symptom-complex occurring in six patients with midline protrusions of a lumbar disk with an associated arachnoiditis. Four similar cases have been seen in the departments of neurology and neurosurgery of the United Oxford Hospitals within a year—three with a protrusion of a lumbar disk and one with an adhesive arachnoiditis of the cauda equina without a disk lesion.

The distribution of symptoms in the four men and the C.S.F. findings are summarized in Fig. 1 and the Table; only one of the cases is reported in detail.

C.S.F. Findings[1]

	Protein (mg./100 ml.)	Cells (per ml.)
Case 1	180	8
Case 2	70	0
Case 3	?	37
Case 4	110	0

[1] All samples obtained above the level of myelographic obstruction.

Case 2

A 60-year-old yarn-spinner presented with a four-year history of cramp-like pain in the antero-lateral aspects of his legs brought on by walking. Initially the pain would occur after a quarter of a mile (400 metres) of moderate walking, but by the time of admission he could only walk 200 yards (180 metres) before the pain became so severe that he was forced to stop. If he then stood still the discomfort would diminish in a quarter of an hour. The story seemed so suggestive of vascular insufficiency that his general practitioner had treated him with tolazoline hydrochloride for a year without success. Six months before admission he noticed pins-and-needles in both feet associated with the pain in the legs. There had been no sphincter disturbance, and there was no history of lumbago, back injury, or sciatica.

On examination all peripheral pulses were of good volume and remained so after sufficient exercise to bring on the pain. There was diminished power of dorsiflexion of the left foot, more noticeable after exercise. The left knee-jerk was less brisk than the

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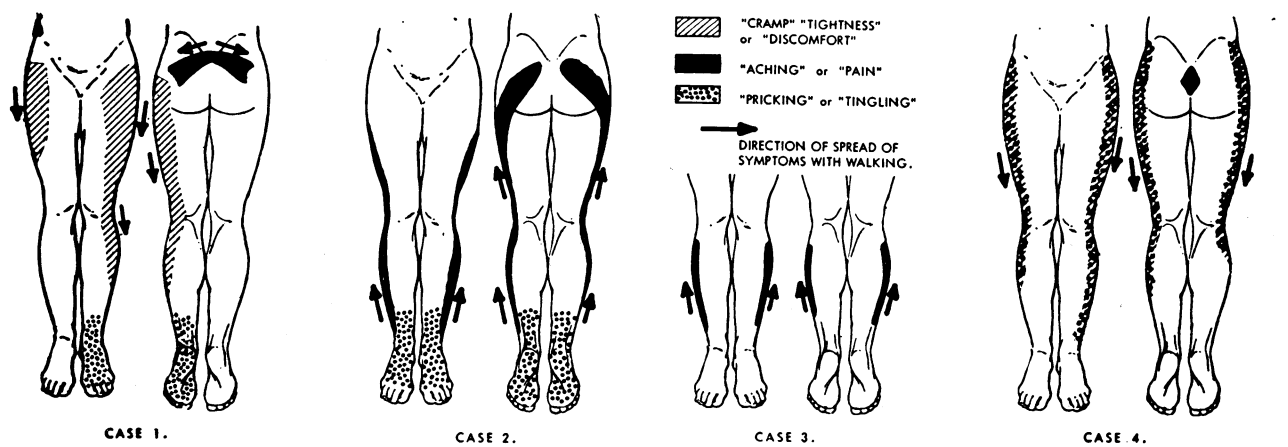

FIG. 1.—Distribution of symptoms

right, but both ankle-jerks were present. Vibration sense was absent from the feet and lowest third of both shins, but there was no other sensory abnormality. Spinal mobility and straight-leg raising were normal. Exercise of the gastrocnemius and soleus on a foot ergometer reproduced his symptomatic pain, not, it was noted, in the maximally exercised muscles, but over the peroneal region, corresponding to the fifth lumbar dermatome.

The blood picture and serum vitamin B_{12} were normal. *X*-ray examination of the lumbar spine revealed six lumbar-type vertebrae and some narrowing of the L 4/5 disk space. Lumbar puncture performed at the L 3/4 interspinous space produced clear cerebrospinal fluid under normal pressure and with a free rise and fall on jugular compression. It contained 70 mg. of protein per 100 ml., but no cells. Iophendylate was instilled and was found to lie above a block of the subarachnoid space at the L 4/5 level. The picture (Fig. 2,A) was interpreted as showing a disk protrusion with thickening of the roots and dilatation of the blood-vessels.

At lumbar laminectomy by Mr. J. Pennybacker the roots bulged through the incised dura but were normal in appearance, and there was no sign of the expected arachnoiditis. A small midline protrusion of the L 4/5 disk was exenterated. Ten months later he claimed to be symptom-free.

In none of the three disk lesions was there any evidence of the arachnoiditis which was a prominent feature of Blau and Logue's cases. In Case 4, however, the myelographic findings of which (Fig. 2B) seemed similar to those of Case 2, lumbar laminectomy revealed that the iophendylate was trapped above an adhesive arachnoiditis of the cauda equina, but there was no disk protrusion. Apart from the separation of the roots consequent on the exploration no definite treatment was feasible, and this man was the only one of the four not to benefit from his operation.

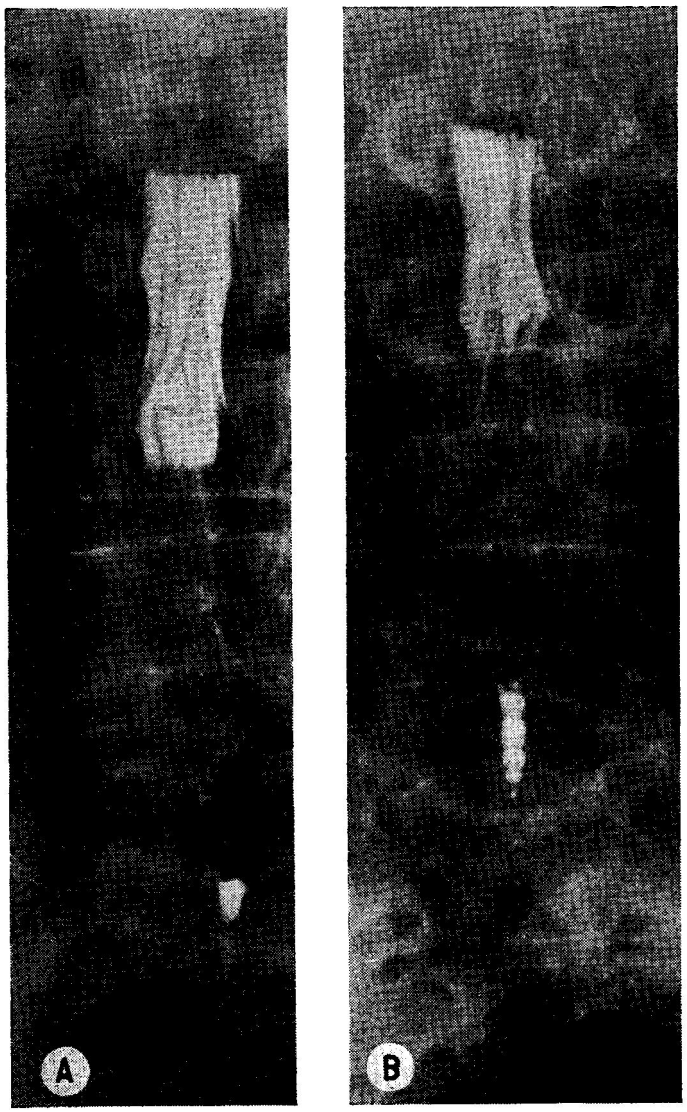

FIG. 2.—Myelograms in Case 2 (A) and Case 4 (B).

Diagnosis

The main problem is to separate these patients, none of whom showed impairment of straight-leg raising or other signs of the classical "slipped disk," from those with vascular disease. The dermatomal distribution of the symptoms, if distinct, will place the cause at root level rather than the periphery, but symptoms of cauda equina ischaemia, including paraesthesiae, sensory changes, and altered reflexes, may be prominent in disease of the aorto-iliac vessels. The presence of normal pulses, examined both at rest and after exercise (DeWeese, 1960), and the absence of abdominal or femoral bruit will exclude the great majority of patients with vascular disease, but inevitably there will be doubtful cases. It is obviously undesirable to perform a myelogram on a patient who is likely to come to aortography later, as the iophendylate shadows will confuse the picture. In order to reduce the number of patients unnecessarily subjected to both procedures, use may be made of the fact that seven of the nine patients with the "neurological" lesion so far described, in which the estimation was possible, had a raised C.S.F. protein. A lumbar puncture may be performed and the needle left *in situ* for the few minutes necessary for an assistant to measure the protein content of the C.S.F. If this is abnormal the iophendylate is instilled, but if it is normal or equivocal the aortogram can be performed first.

Comment

As in Blau and Logue's cases, it was impossible to relate the symptoms to mechanical factors such as increased protrusion of the disk or to minor spondylolisthesis occurring in the upright posture. Thus it was not possible to induce the pain by prolonged standing, and in two cases studied in detail (Nos. 2 and 4) it was consistently reproduced by ergometric exercise of the leg while lying in bed, and it was not affected in severity or time of onset by increasing or decreasing the lumbar lordosis by means of pillows. Moreover, it was easily demonstrated that the onset of the symptoms was related to the rate of exercise as well as to its duration.

The hypothesis was first entertained that the symptoms might be due to an increase in pressure on abnormally confined nerve roots during exercise, due to vasodilatation (Blau and Rushworth, 1958), together with the probably negligible increase in volume of the active nerve fibres (Hill, 1950). It was not possible, however, to cause radiation of pain to an inactive limb by exercising the opposite one, which could occur if this mechanism applied.

The possibility envisaged by Blau and Logue of intermittent nerve anoxia in these cases was investigated further in Case 4 by arranging a fixed rate of work on a foot ergometer and measuring the "claudication time"—that is, the time before pain appeared in the exercised limb, under different oxygen tensions. A translumbar aortogram previously performed in this patient had shown no abnormality of pelvic or peripheral leg vessels. The patient breathed through a modified air-crew mask fitted with a demand valve, and claudication times were measured after five-minute intervals while he breathed air, pure oxygen, or a mixture of nitrogen and 12% oxygen. The procedure was performed under continuous E.C.G. control and the patient reported no unusual symptoms. The results (Fig. 3) showed that the claudication time varied directly with oxygen tension but demonstrated a lag before the effect of a change in the respired gas became apparent. (This is not

apparent between runs 4 and 5 because, owing to technical difficulty, the interval between these was prolonged to 10 minutes.)

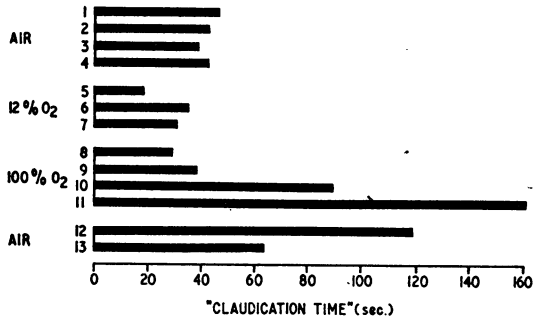

FIG. 3.—Variation of "claudication time" with oxygen content of respired gas (Case 4).

The metabolic rate of peripheral nerves is low compared with grey matter and other tissues, and is probably only about 1/10 of that of muscle weight for weight (Larrabee, 1958). It is established that oxygen uptake of a peripheral nerve trunk in the rat varies directly with the frequency of stimulation (Cranefield *et al.*, 1957). It may be predicted, therefore, that the oxygen tension in the interstices of a nerve trunk will be lowered during exercise if a simultaneous increase in the blood supply through the vasa nervorum is prevented. In this partially anoxic state the condition of the nerve will be comparable with that in the experiments of Lewis *et al.* (1931) when the blood has been allowed to return to a temporarily ischaemic nerve, the fibres near the blood-vessels being better oxygenated than those further away. In these circumstances sensation of tinglings and "pseudo-cramp" occur, probably due to impulses arising at the site of anoxia in touch-fibres and muscle-afferents respectively (Cobb and Marshall, 1954; Nathan, 1958). Thus a relative ischaemia of active cauda equina roots during exercise seems the likeliest explanation of the symptoms in our patients.

Summary

Attention is drawn to the production of intermittent claudication in four patients by a prolapsed lumbar disk or an arachnoiditis of the cauda equina. The problem of distinguishing such cases from those of aorto-iliac vascular disease, which can give a closely similar clinical picture, is discussed. The probable mode of production of the symptoms is briefly examined.

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Treatment of Herpes Simplex Lesions of the Face with Idoxuridine: Results of a Double-blind Controlled Trial

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After Kaufman's (1962a) report of successful treatment of experimental herpes simplex keratitis in the rabbit with 5-iodo-2'-deoxyuridine (idoxuridine) and his optimistic report of its value in the same disease in man (Kaufman, 1962b) it was obvious that the possible therapeutic effect of I.D.U. on herpes simplex of the skin should be investigated. Burnett (1962) in the U.S.A. reported no therapeutic benefit, but Hall-Smith *et al.* (1962), who used a 0.1% solution applied topically or 0.5% in an ointment in a small uncontrolled group, thought their patients had benefited. As Luntz and MacCallum (1963) reported less favourably than Kaufman on the value of I.D.U. when it was compared with neomycin ointment in the treatment of keratitis in man it seemed imperative to examine its effect on skin lesions in a double-blind controlled trial. The type of ointment and its source was the same[1] as that used by Hall-Smith *et al.* (1962).

Methods

Recurrent herpes lesions of the face in different patients are of variable duration. They may last from 2 to 20 days, and attacks may occur every few weeks or as rarely as once or twice a year. The history of patients with herpes suggested that the duration of the untreated attack was fairly constant in the individual. It therefore might be possible to measure the efficacy of treatment by the shortening of the duration of the lesion. However, if the patients' estimates of the normal duration of the untreated lesion were relied upon an avoidable error would be introduced into the trial. Verifying the alleged duration by observing untreated attacks in propositi would have taken an unreasonable length of time. We therefore decided to compare the time taken for complete healing in patients who were treated with I.D.U. cream and inactive base.

The patients in the trial were drawn from the staff of the United Oxford Hospitals. Herpes sufferers were asked to report as soon as possible after the onset of the first symptoms, usually prickling and tingling of the skin. A careful history was taken, including the duration of previous attacks. Only patients with

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[1] Smith Kline and French Laboratories Ltd.