Current Practice

PRACTICAL NEUROLOGY

Neurological Complications of Systemic Diseases—I

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This review is intended as a brief examination and description of the commoner neurological syndromes which may complicate systemic diseases encountered routinely in clinical practice. It is in no sense comprehensive. A disturbance of function of some part of the central nervous system, particularly the higher centres, is an almost invariable accompaniment of most serious illnesses. On the other hand, there are not so many conditions in which the neural lesions may obscure the systemic disease by drawing attention to a complication rather than to the primary disorder. At the expense of what might seem more logical classifications, these will be considered here in the order in which they are most likely to be seen in practice.

Diabetes Mellitus

Estimates of the frequency with which neuropathy complicates diabetes vary widely between 4% and 93%, reflecting the differences in the criteria for diagnosis and selection of the population studied. What is certain is that with a prevalence rate of diabetes in the community of about 2%, and an increasing prevalence of diabetes with age, there are very many patients at risk for diabetic neuropathy.

A number of clinical syndromes have been described. There is often considerable overlap between them, and it seems probable that the underlying pathological process is similar in the majority of cases, merely varying in intensity and distribution within the nervous system. By far the commonest clinical manifestations reflect a chronic *sensory polyneuritis*, which may be confined clinically to the legs. Paraesthesiae, often nocturnal and described as burning or cramp-like, and sometimes relieved by walking, may be the only symptoms in a patient in whom the only signs are depressed or absent tendon-reflexes at the ankles and impaired perception of vibration below the knees. Often such signs are found in diabetics who are without symptoms referable to their central nervous systems.

A *mononeuritis* of almost any nerve in the limbs, though commonly peroneal, ulnar, or median, may cause foot-drop or weakness of grip and paraesthesiae of the hands. This may develop in isolation or in the setting of an extensive asymmetrical *sensorimotor polyneuritis* affecting the arms and legs.

Though muscle weakness is less common as a manifestation of diabetic neuropathy than sensory disturbances, the syndrome described as *diabetic amyotrophy*, which often presents with severe pains in the legs mimicking the root pains of degenerative lumbar disc disease, may be seen. Wasting and weakness of thigh and pelvic muscles of one or both legs is found, with absent tendon reflexes—yet little in the way of detectable sensory deficit.

Sensory defects and distressing paraesthesiae and clumsiness reflecting extensive damage to peripheral nerves or posterior roots and cord may be associated with a profound impairment of joint position sense, causing unsteadiness which is worse in the dark. This syndrome used to be called *diabetic pseudotabes*. Irregular pupils reacting sluggishly to light, shooting pains in the calves, neuropathic perforating ulcers of the feet, and a swollen painless destructive arthropathy of the tarsal joints in the feet may complete the picture.

Acute *cranial nerve palsies* are not uncommon. The oculomotor and abducent nerves are most often affected, and the lesions may be painful. The pupillary reflexes are usually spared, and the prognosis is good, recovery usually occurring within a few months. Autonomic denervation in some form or another is also common, and may be associated with distressing symptoms. Diarrhoea, intermittent and frequently nocturnal, may cause malabsorption and be associated with faecal incontinence; an atonic bladder may encourage infection and cause urinary incontinence; impotence, probably reflecting a disturbance of autonomic function, occurs in a large proportion of male diabetics; postural hypotension and persistent tachycardia indicate impaired cardiovascular reflexes; and peripheral vasodilatation and absent sweating are a common manifestation of diabetic sympathectomy.

Treatment

Treatment is directed towards maintaining control of blood sugar levels. This may be best achieved by insulin or oral hypoglycaemics; but high renal thresholds for sugar excretion occasionally make blood sugar estimations essential for good control. There is no doubt that poor control of the diabetes—in the sense of persistent hyperglycaemia—is a more frequent accompaniment of neuropathy in diabetics than normal blood sugar levels. Unfortunately, poor control does not appear to be the sole factor in the aetiology of diabetic neuropathy, and though in general acute or subacute episodes of neurological disability clear up with good management, some do not, and in the occasional paradoxical case the institution of adequate control is accompanied by the development of a neuropathy for the first time.

Symptomatic treatment is often rewarding, in that instruction on care and cleanliness of the feet, and a careful look at the shoes for nails and rough edges, may prevent or result in the healing of perforating ulcers; adequate analgesia may relieve distressing paraesthesiae; testosterone is worth a trial in cases of impotence; and a course of tetracycline and the prescription of atropine may improve nocturnal diarrhoea.

This is not the place for a discussion of diabetic coma, and iatrogenic hypoglycaemia is common enough to need no review of its neurological complications. But in recalling the

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features of disturbed cerebral function, which do not provide a problem in diagnosis in the context of treated diabetes, it is worth mentioning that the identical symptoms of episodic irritability or unexplained aggressive behaviour, or even short-lived confusional states, may be the presentation of an insulinoma. Pallor, sweating, nausea, and vomiting, and the occurrence of the episodes before breakfast or other meals, may suggest the diagnosis, but transient strokes or unremarkable epileptic attacks may obscure it. The rarity of pancreatic insulinomas and the unexpected ways in which hypoglycaemia may affect the higher centres of the central nervous system no doubt account for the number of cases in which the diagnosis continues to be missed in this eminently treatable condition.

Malignant Neoplasia

Lesions of the central nervous system associated with carcinoma or malignant neoplastic proliferation of reticuloendothelial tissue resolve themselves into two types: those due to metastatic deposits, and those due to a number of mechanisms as yet incompletely understood, including immunological, metabolic, and nutritional aberrations. In Britain deaths from neoplastic malignancy exceed 100,000 a year. Though there is no general agreement on the incidence of non-metastatic complications directly attributable to the neoplastic process rather than secondary to cachexia, 6% has been suggested as the figure.

Carcinoma.—The commonest metastatic and remote complications affecting the central nervous system are provided by carcinomas of the bronchus, breast, stomach, and ovary. Metastatic deposits in the hemispheres may present with an epileptic attack and a rapidly developing dysphasia or one-sided disturbance of motor or sensory function in the limbs, clearly calling for urgent investigation in hospital. Metastases in relatively silent areas may present less obviously; in the right parietal lobe merely by spatial disorientation, which may show itself surprisingly early in difficulties while driving, or in the case of the frontal lobe by an unexplained but persisting alteration in behaviour, fluctuating confusion, or insidious dementia. Headache, nausea, unsteadiness, and nystagmus often reflect the predilection of both bronchial and breast metastases for the posterior fossa; and headache with evidence of lower cranial nerve palsies may signify secondary deposits at the base of the skull. Complaints of suddenly developing disturbed bladder function associated with tingling and heaviness in the lower limbs, which may start jerking unexpectedly at night, with or without localized backache to indicate vertebral deposits, should always raise the question of urgent investigation for possible cord compression.

Of the non-metastatic complications, an early sign may be proximal muscle wasting and weakness, with or without striking fatigability indicating a *myasthenic* component, in which there is difficulty getting out of a chair or bed, climbing stairs, shaving, or doing the hair. It is not altogether clear what proportion of those patients whose weakness appears to be primarily myopathic can be considered to have a specific *myopathy* related to the carcinoma rather than the associated cachexia. In some few cases, muscle tenderness and violaceous rash on face and arms will be evidence of an inflammatory *dermatomyositis* apparently directly attributable to the neoplastic process. A similar proximal muscle weakness of limb girdles may also indicate the presence of a mixed *sensory and motor polyneuritis* and be associated with paraesthesiae and defective sensory perception in hands and feet, together with absent tendon reflexes. A less common subacute inflammatory lesion of posterior roots and ganglia gives rise to the more dramatic *sensory neuropathy*, in which distressing paraesthesiae in hands and feet are associated with a progressively disabling ataxia of gait and limbs, absent tendon reflexes, yet normal power.

A subacute *cerebellar degeneration*, in which there is cellular dissolution in the cerebellar cortex, may occur in isolation and cause a severe and rapidly progressive ataxic syndrome superficially resembling that due to sensory radiculopathy. A slowly developing spastic tetraparesis associated with wasting and fasciculations, brisk tendon reflexes, and extensor plantar responses, with or without a bulbar or pseudobulbar palsy, may indicate degeneration of motor nuclei and tracts in a syndrome almost indistinguishable from the *amyotrophic lateral sclerosis* variant of motoneurone disease.

Less common are the *encephalopathies*. A subacute inflammatory limbic encephalitis causing amnesia, confusion, and progressive dementia may occur in isolation or together with brain stem encephalitis or the sensory radiculopathy described above; and a patchy demyelination of cerebral tissue termed multifocal leukoencephalopathy may cause progressively disabling visual defects, hemipareses, epilepsy, and confusion over the course of a few months.

Reticuloses.—Those found most frequently to involve central nervous tissue by direct invasion, usually infiltration outside or through the dura, are myelomatosis and the more sarcomatous variants of Hodgkin's lymphoma. In both these conditions spinal cord compression or obstruction to the blood supply of the cord causes a rapidly progressive paresis of legs or all four limbs, with sensory loss and disturbance of bladder function, and requires urgent diagnosis and treatment. Intracranial deposits giving rise to epilepsy or focal limb weakness are rare in both these conditions, and indeed the only lymphoma in which intracerebral deposits occur with other than extreme rarity is lymphosarcoma.

Leukaemias, on the other hand, are more often associated with intracerebral complications. These may present with epileptic attacks, hemiplegia, or confusional episodes, due either to metastatic deposits or haemorrhages, the latter often multiple and a terminal event. Symptoms of raised intracranial pressure with headache, vomiting, and drowsiness, secondary to meningeal infiltration with leukemic tissue, tend to complicate these diseases with increasing frequency as effective cytotoxic therapy, which fails to cross the blood-brain barrier, prolongs life.

Local infiltration or haemorrhage into nerves and roots in leukaemia and the lymphomas, particularly in the case of myelomatosis, gives rise to an asymmetrical mixed *sensory and motor peripheral neuropathy* or mononeuritis multiplex, or an isolated cranial nerve lesion, most commonly facial suggesting a simple Bell's palsy.

As in the case of carcinoma, neural complications occur which are neither infiltrative nor metastatic. Unlike those in carcinoma, the pathogenesis appears more clearly explicable on the basis of disturbed immunological mechanisms. In the case of *herpes zoster*, which most frequently involves one of the thoracic dermatomes, and in the case of multifocal leukoencephalopathy, which leads to death within a few months and is more frequently seen with the lymphomas than associated with carcinoma, as described above, viruses are evidently implicated. Other manifestations of immunological paresis, often related to steroid therapy, are the frequent bacterial and fungal meningitides and occasional intracranial abscesses which complicate the terminal stages of these diseases. Less clear is the aetiological explanation of the occasional case of sensorimotor polyneuropathy due neither to infiltration with neoplastic tissue nor to the abnormal proteins which these cells may produce. These complicate only myelomatosis and the macroglobulinaemias with any frequency.

Treatment

Most of these neural complications may precipitate the initial presentation of the primary disease, especially in the case of bronchial carcinoma, though admittedly they occur more usually in patients in whom the primary diagnosis has already

been established. Treatment is principally that of the underlying condition and has often been instituted before the neural complication makes its appearance. Surgical decompression or, in appropriate cases, irradiation alone is urgent in any of these conditions in which spinal cord compression occurs. Even in the case of secondary carcinomatous deposits these measures may provide rewarding palliation if instituted early enough. The spectre of the potentially treatable solitary intracerebral secondary remains, despite the well-recognized fact that its occurrence in post-mortem material declines in proportion to the thickness of the brain slices examined. The removal of a bronchial carcinoma has not been shown to result in improvement in the non-infiltrative polyneuropathies, but has been followed by regression of cerebellar degeneration. Oral steroids have been reported to relieve the distressing paraesthesiae and even the motor and sensory deficits in a very small number of these cases.

Metabolic disturbances due to the production of hormone analogues by bronchial carcinoma may respond to relatively simple palliative measures, making the terminal stages of this disease less intolerable. Hypercalcaemia, may cause a syndrome indistinguishable from that seen in parathyroid hyperfunction in which muscle cramps and weakness of limb girdles and trunk give rise to difficulty getting out of a chair and a waddling lordotic gait yet brisk tendon reflexes; this may be relieved with oral steroids. Irradiation of an inoperable tumor which is producing a corticotrophin-like substance may relieve, for a short period, the disabling myopathy due to adrenal hypercorticism.

(This article will be concluded next week with a review of the neurological complications of disorders of connective tissue and endocrine glands.)

TODAY'S DRUGS

Antacids

With the help of expert contributors we print in this section notes on drugs in current use.

Antacids are drugs which neutralize or reduce the acidity of the gastric contents. The digestive properties of gastric juice are mainly due to pepsin. The function of gastric acid is considered to be the maintenance of an optimal pH for the action of pepsin (1.5-3.5). Pepsin has very little activity at pH 4.0 and none at pH 5.0. Acid and pepsin are secreted in response to stimuli from the parasympathetic nervous system and from the hormone gastrin, which is released from the gastric antrum in response to a number of stimuli, including a fall in gastric acidity.

Our knowledge of the aetiology of peptic ulceration is still very incomplete. Modern opinion accepts the importance of acid secretion, but a number of other factors contribute to the susceptibility of the gastric and duodenal mucosa to the irritative and erosive effect of gastric juice. In fact, acid secretion may be normal or low in some patients with peptic ulceration—which emphasizes the importance of mucosal resistance. Aspirin, alcohol, and bile acids can all alter the physiological properties of the gastric mucosa and may predispose to erosion or ulceration. Relatively little is known, however, of the factors which affect mucosal resistance, and so treatment has mainly been directed at reducing gastric acidity. There is no doubt that antacids relieve the pain of peptic ulceration.

Pharmacology

The gastric juice normally contains approximately 0.5% hydrochloric acid, and about 1,500 ml. is secreted over 24 hours. Most of the available drugs have little effect on the volume of gastric secretion, but theoretically it is relatively simple to neutralize the hydrochloric acid. The ideal antacid should effectively neutralize the acid and have a prolonged action in the stomach without producing a systemic alkalosis or other unwanted effects.

All the common gastric antacids are weak bases, and all indirectly suppress the activity of pepsin when given in sufficient doses to elevate the pH above 4. Aluminium hydroxide has a direct effect of inhibiting pepsin as well. No harmful effects appear to result from the suppression of the activity of pepsin, since protein digestion proceeds in the intestinal tract.

The secretion of gastric juice and the output of hydrochloric acid is in fact increased by the presence of an antacid in the stomach;¹ this effect is particularly marked in patients with duodenal ulcers. The "acid rebound" is probably due to gastrin release, and it explains the need for continuous antacids if a high intragastric pH is to be maintained. Calcium salts have recently been shown to produce marked acid rebound.²

Antacids can be considered as absorbable or non-absorbable; some also adsorb acid in addition to simple neutralization. Sodium bicarbonate is a constituent of a large number of proprietary antacid mixtures. It is highly soluble and rapidly effective in reducing the pain of peptic ulceration; for the same reason it has a short duration of action. The released carbon dioxide causes eructation of gas, which gives a sensation of relief to some patients. Even if given in doses which only partly or intermittently neutralize gastric acid, sodium bicarbonate can alter the pH of the extracellular fluid, producing a metabolic alkalosis and an alkaline urine. This may be particularly harmful if calcium is being taken (as milk) in excess when chronic hypercalcaemia, metastatic calcification, and uraemia may result—the milk-alkali syndrome.³ In conditions in which sodium retention occurs sodium bicarbonate can contribute to oedema and must, therefore, be avoided.

Magnesium hydroxide is practically insoluble and does not produce systemic effects. It is not effective until it has been converted to magnesium chloride by the action of gastric acid; hence it has a slower onset and a longer duration of action than sodium bicarbonate. The soluble but unabsorbed magnesium ion accounts for its laxative action, which is shared by all the compounds containing magnesium. Calcium salts, which tend to constipate, are often given in combination with magnesium salts to offset this effect. A small proportion of magnesium ions is absorbed, but this is unimportant unless there is renal impairment.

Calcium carbonate is also an effective antacid. It is of low solubility and tends to precipitate in the intestine to form insoluble calcium soaps in combination with fatty acids. A small fraction of the calcium ions may be absorbed and may similarly result in the milk-alkali syndrome if excess quantities of milk are being taken, but this is more often a complication of the use of sodium bicarbonate. However, an acute reversible form with hypercalcaemia and uraemia may follow the use of calcium carbonate alone.⁴