NEUROLOGICAL ASPECTS OF THE SYSTEMIC DISEASES

1. Radiation damages

Following irradiation of cerebral tissue, delayed necrosis appears in a proportion of cases, determined by the dose of radiation and its duration. The majority of cases appear within 2-3 years of therapy. The necrosis affects all the brain components, but especially blood vessels. Vascular proliferation and occlusion result in secondary infarction while a direct effect on glial tissue culminates in demyelination and cavitation of the white matter. The area of radiation necrosis is associated with oedema and may be difficult to distinguish radiologically from a primary neoplasm. The CT changes are nonspecific, with mass effect, oedema and patchy enhancement. On the T2-weighted MRI sequences the lesions are hyperintense and may show a sharp cut off at the boundary of the irradiated area. Corticosteroids are sometimes helpful in relieving symptoms related to the oedema but in many cases surgical excision is necessary both for diagnosis and for relief of symptoms. PET scanning may be the best means of distinguishing between radiation necrosis and neoplasm. Virtually all patients receiving non-trivial doses of irradiation develop some demyelination and gliosis with hyalinized vessels.

Radiation damage to extracranial vessels

Radiation induced occlusive disease of the carotid and vertebral arteries in the neck has been reported in patients treated with radiotherapy for a variety of carcinomas or lymphomas affecting the neck area. Typically, there are often multiple sites of arterial narrowing or occlusion with a distribution differing from that seen with atheromatous disease. The patients present with a variety of cerebrovascular syndromes. Where the carotid artery is substantially stenosed, but not occluded, surgical intervention is usually indicated.

DRUG INDUCED DAMAGE

A vast array of therapeutic and chemical agents are known to be potentially toxic to either the peripheral or central nervous system. A leucoencephalopathy is recognized to complicate methotrexate therapy, particularly when combined with prior cranial irradiation. The clinical and pathological features resemble those seen with irradiation necrosis, though fibrinoid necrosis of the blood vessels is usually lacking. In some cases the spinal cord bears the brunt of the process. Cyclosporin is capable of provoking seizures, coma, and pyramidal dysfunction. Pathological studies in fatal cases have demonstrated areas of cerebral oedema associated with evidence of breakdown of the blood-brain barrier. CT demonstrates transient low-density areas in white matter, while MRI reveals high signal intensity lesions on T2-weighted images. The encephalopathies associated with asparaginase and procarbazine can lead to a state of lethargy and confusion which slowly reverses when the offending drug is withdrawn. A cerebellar syndrome occurs with both 5-fluorouracil and cystosine arabinoside and again is usually reversible if the drug is withdrawn or its dosage reduced.

Peripheral nerve damage is encountered with many drugs, toxins and heavy metals. Well-documented examples are those encountered during therapy with cis-platinum and vincristine. In both instances a mixed or predominantly sensory neuropathy is found based principally on axonal degeneration. Other drugs having a harmful effect on peripheral nerve function include phenytoin, nitrofurantoin, isoniazid and ethambutol.

ALCOHOL AND THE NERVOUS SYSTEM

Quite apart from the effects of acute intoxication, various central and peripheral nervous system disorders are associated with chronic alcohol abuse. CT scanning of some alcoholics reveals ventricular dilatation and enlargement of the cortical sulci, changes which may, at least, be partly reversible following a period of abstinence. Better defined both chemically and pathologically is a cerebellar syndrome in which there is depletion of Purkinje cells predominantly in the anterior and superior vermis. Either CT or MRI demonstrate the distribution of the atrophic process. Typically, the patient presents with a gait ataxia with relatively normal upper limb coordination. Nystagmus is not conspicuous.

The Wernicke-Korsakoff syndrome is particularly associated with alcoholism, though the same disorder can result from a deficiency of thiamine, induced, for example, by prolonged vomiting. In the acute stages the lesions, sometimes haemorrhagic, are distributed in the mammillary bodies, the

peri-aqueductal grey matter of the mid-brain, the floor of the fourth ventricle and in the paraventricular parts of the thalamus and hypothalamus. The maximal changes are found in the mammillary bodies which later become atrophi accompanied by atrophy of the peri-aqueductal grey matter and other structures. Microscopic features include patchy cell necrosis, but with some sparing of neuronal cell bodies, astrocytic and microglial proliferation, haemorrhages and, in some cases, vascular proliferation.

Typically, the condition combines three clinical components: ophthalmoplegia, ataxia and a disturbance of orientation. The ophthalmoplegia consists of lateral rectus or horizontal gaze palsies, combined with nystagmus in both the horizontal and vertical planes.

The ataxia predominantly affects gait and reflects a pathological process which, like the isolated alcoholic cerebellar syndrome, principally affects the superior cerebellar vermis. Typically, the patient is drowsy, confused and amnesic. With recovery a more classical Korsakoff psychosis emerges in many, characterized by a profound impairment of short-term memory coupled with loss of memory for remote events. A confabulatory element has been over-emphasized. Early, vigorous, treatment with thiamine is particularly successful in reversing the ophthalmoplegia but less so in returning cognition to normal. CT identifies the haemorrhagic lesions in some cases.

Central pontine myelinolysis can occur in a number of conditions though the early reports were confined to alcoholics. Important, though not inevitable, in the pathogenesis of the condition is a hyponatraemic state which has been over-rapidly corrected. Post-mortem examination demonstrates discoloration of the basis pontis microscopy of which reveals demyelination with relative axonal sparing and an absence of any inflammatory reaction. The condition occurs both in alcoholics and in individuals with serious medical disorders or substantial malnourishment. Clinical features other than a depression of the conscious state include tetraparesis, anarthria and defects of horizontal eye movement. Some patients survive only to enter a locked-in state.

In Marchiafava-Bignami disease there is demyelination of the central section of the corpus callosum. The condition is virtually confined to male alcoholics. No single clinical picture corresponding to the pathological change has been established though frontal lobe features are often prominent.

The peripheral nerve and muscle disorders associated with alcoholism have been described elsewhere.

THE NEUROLOGY OF ENDOCRINE DISEASE

Pituitary disorders

The visual symptoms associated with pituitary tumour have already been considered. Patients with acromegaly eventually develop muscle weakness and wasting though muscle biopsy changes are often not conspicuous. The CK activity may be mildly elevated. Carpal tunnel syndrome is a recognized complication of acromegaly. Infrequently a diffuse hypertrophic demyelinating neuropathy is encountered.

Adrenal disorders

The myopathy associated with Cushing's disease (or steroid therapy) is considered in Chapter 3. At least 50 per cent of patients with Cushing's syndrome have muscle weakness. In patients who have had bilateral adrenalectomy for Cushing's syndrome, a marked elevation of serum ACTH levels may follow, associated with hyperpigmentation and proximal muscle weakness. In Cushing's syndrome itself, the myopathy is of gradual onset in the majority, though a variant with acute onset and muscle pain is recognized. Typically, the pelvic girdle muscles are those principally affected. Though muscle weakness is a prominent feature of Addison's disease, a specific myopathy has not been described in that condition.

Thyroid disorders

Thyrotoxicosis is associated with muscle weakness in about three-quarters of the patients. Distal muscles are affected as well as proximal in a minority. Light microscopy changes on muscle biopsy are often inconspicuous and more evident abnormalities on EM are not specific for this condition.

Many patients with hypothyroidism complain of muscle cramps or weakness. A true myopathy is rare and is reversed by treatment of the thyroid deficiency. Hoffman's syndrome consists of muscle

hypertrophy, pain and slowness of movement in adults with hypothyroidism. The muscles dimple excessively on percussion in a manner resembling myotonia.

A diffuse neuropathy has been rarely described in thyrotoxicosis but more frequently in hypothyroidism taking sometimes the form of a predominant sensory loss associated with demyelination of peripheral nerve and slowed conduction velocities. Hypothyroidism is also associated with carpal tunnel and, less commonly, with tarsal tunnel syndrome.

Dysthyroid eye disease is alleged to be the commonest cause of diplopia in middle-aged individuals. The patient has evidence of either lid retraction or lid lag. Typically, there appears to be a defect of elevation, suggesting a superior rectus palsy. Further assessment reveals that the apparent palsy is due to tethering of the inferior rectus within the orbit. Less commonly, other muscles are involved in the fibrotic reaction. Tests of thyroid function frequently reveal a euthyroid state. The abnormally expanded muscle is readily demonstrated by CT or MRI scanning of the orbit.

Parathyroid disorders and abnormalities of calcium metabolism

No clear association has been established between hypoparathyroidism and primary muscle disease. Proximal, often painful, muscle weakness is a recognized feature of primary and secondary hyperparathyroidism and osteomalacia. Patients with osteomalacic myopathy have muscle and skeletal pain, proximal muscle weakness and bony tenderness. The alkaline phosphatase level is markedly elevated with a normal or depressed calcium concentration. X-rays of the pelvis may reveal Looser zones.

Pancreatic disease

Insulinomas are rare, with an incidence around 1 per million of the population. Symptoms are likely to appear when plasma glucose levels fall below 2.5 mmol/l. Neurological symptoms, which are typically episodic, include drowsiness, altered behaviour, brain stem manifestations, seizures and focal defects suggesting a cerebrovascular event. Many patients develop symptoms after an overnight fast and virtually all become symptomatic during a 72 hour fast. The consequent hypoglycaemia is accompanied by inappropriately high insulin levels.

The tumour is best localized using coeliac axis angiography. Distal pancreatectomy is performed if the tumour is in the tail of the gland.

In Pagetÿs disease, abnormal osteoclastic activity leads to both increased bone resorption and secondarily, increased new bone formation. Neurological complications follow bone fracture or result from direct compression of neural tissue by either abnormal bone or bone which has undergone malignant transformation. The skull is affected in about half the cases, the changes being earlier and more readily detectable by isotope bone scan than conventional radiology. Cranial nerve palsies result from compression within the skull exit foramina and particularly affect the eighth nerve. Deformity of the skull base, with softening, leads to invagination of the odontoid process and secondary compression of the brain stem and cerebellum. Hydrocephalus follows in some cases. Spinal involvement is usually multifocal.

NEUROLOGICAL FEATURES OF VASCULITIS

In vasculitic disorders there is evidence of inflammation and necrosis of blood vessels. Both the peripheral and central nervous system can be affected by an ischaemic process though the pattern of involvement varies between individual conditions included within this group. Some of the vasculitic syndromes are associated with granuloma formation.

Systemic necrotizing vasculitis

This group includes polyarteritis nodosa (PAN), allergic angiitis with granulomatosis (Churg-Strauss syndrome) and an intermediate form. In PAN there is inflammation of small and medium-sized arteries in many different organs. Histological features include inflammatory cell infiltration, internal elastic lamina proliferation and fibrinoid necrosis of the vessel wall. Neurological complications occur in at least 50 per cent of PAN patients and include mononeuritis multiplex, sensorimotor neuropathy, radiculopathy and brachial plexopathy. Some of these reflect the consequence of occlusion of the vasa nervorum. CNS involvement takes the form of infarction of the brain and spinal cord, or an encephalopathic syndrome embracing altered cognition with seizures.

Involvement of the visual pathway by the ischaemic process is common. The neurological features of the Churg-Strauss syndrome are similar.

Hypersensitivity vasculitis

Conditions in this group include serum sickness and some cases of essential mixed cryoglobulinaemia.In serum sickness, the neurological complications include peripheral and brachial neuropathy, seizures and encephalopathy. Peripheral neuropathy is a recognized complication of the vasculitis accompanying cryoglobulinaemia.

Wegener's granulomatosis

In Wegenerÿs granulomatosis, granuloma formation with arteritis is found in various systems including the respiratory tract and the kidneys. The condition typically begins in the upper respiratory tract with a nonspecific granulomatous rhinitis or sinusitis. The condition progresses to bony destruction of the nasal bones, sinuses and sometimes the orbits. Focal extension of these granulomatous masses into the orbit, middle or posterior cranial fossae account for many of the neurological complications. Saddle-nose deformity is common associated with abnormalities on bone scanning. At this stage of the disease, granulomatous masses are often visible on chest X-ray. Neurological complications appear in up to half the patients. In addition to the effect of direct invasion by granulomatous tissue, remote granulomas may appear in individual cranial nerves or within the cerebrum itself. Vasculitis accounts for the other neurological complications. Typically, the peripheral nervous system is affected in the form of mononeuritis multiplex, polyneuritis or radiculitis. Focal infarction of the CNS or subarachnoid haemorrhage is less common. Antibodies to anti-neutrophil cytoplasmic antigen (of the anti-alpha granule type) -C-ANC A are found in about three-quarters of cases, but only rarely in patients with polyarteritis nodosa. The condition often responds dramatically to cyclophosphamide.

Granulomatous angiitis

This is a rare disorder sometimes triggered by zoster infection, characterized by an inflammatory reaction confined to vessels of the central nervous system. Leptomeningeal arterioles and venules are particularly affected, by an often patchy inflammatory process containing lymphocytes, plasma cells and granulomas associated with multinucleate giant cells. Clinical features include headache, intellectual decline and focal neurological deficit associated with small vessel infarcts and meningeal infiltration. The ESR is sometimes elevated and the CSF almost inevitably abnormal. Angiography may demonstrate focal areas of narrowing and dilatation of the intracranial vessels (beading). The condition may respond to a combination of cytotoxic therapy and corticosteroids.

Behçet's disease

Behçet's disease is diagnosed on the basis of recurrent orogenital ulceration occurring in association with evidence of ocular inflammatory disease. Neurological complications occur in up to a quarter of the cases, though headache alone is more common. Virtually all patients with neurological involvement have evidence of an aseptic meningitis accompanied by apleocytosis and an elevated protein concentration. Focal neurological features include seizures, motor and cerebellar signs, paraplegia, pseudo-tumour cerebri and ocular palsies. The brain stem is the site most often affected by focal disease. Typically, the neurological syndrome follows a remitting and relapsing course.

CT is virtually always abnormal in cases with neurological disease. Findings include focal areas of low density, cortical and cerebellar atrophy and evidence of sagittal sinus thrombosis. Patchy or homogeneous enhancement of the focal lesions is usual in the active stages of the disease. The radiological changes tend to resolve as the symptoms lessen. MRI is an alternative technique for demonstrating the lesions.

Systemic lupus erythematosus

Microinfarction is an important component of the neurological damage found in systemic lupus erythematosus (SLE). The hyalizination of small blood vessels with perivascular inflammation, endothelial proliferation and secondary thrombus formation is quite commonplace. Additionally, immune complex deposition in the choroid plexuses has been considered relevant in the development

of neurological complications associated, perhaps, with the formation and consequent access of anti-neuronal antibody into the CNS. Neurological findings include headaches, psychiatric disorders, seizures, cranial or peripheral nerve disorders, spinal cord syndromes and movement disorders. The movement disorders encountered include a Parkinsonian-like state, hemiballismus and chorea. Motor deficit can result from hemisphere or spinal cord infarction. The peripheral nerve syndromes are similar to those seen in pan, though in addition a Guillain-Barrй syndrome has been described. In patients with neurological disease,abnormalities include an elevated cell count and protein concentration, abnormal IgG indices, oligoclonal IgG and decreased C4 levels.

Some patients with SLE, but also others without that disease, have evidence of circulating antiphospholipid antibodies. The best characterized of these are the lupus anticoagulant and anticardiolipin antibodies. Associated findings include a positive VDRL test (in about a quarter) and a prolonged partial thromboplastin time. Clinical syndromes described in association with antiphospholipid antibodies include retinal or optic nerve ischaemia, a migraine-like condition, brain infarction and an ischaemic encephalopathy.

Scleroderma

A close association exists between progressive systemic sclerosis (PSS) and the crest syndrome - calcinosis, Raynaudўs phenomenon, oesophageal motility disorder, sclerodactyly and telangiectasiae. The cardiac, renal, skeletal and gastrointestinal complications are similar in both but pulmonary involvement is less common in crest patients. A primary muscle disorder, at least in terms of EMG abnormalities and elevated CK levels is commoner in PSS.

It has been suggested that CNS involvement does not occur with either condition. However, a CNS vasculitic process has been described with, in some cases, evidence of an arteritic process on angiography. CT or MRI in these patients establishes the presence of one or more areas of cerebral infarction. Immunosuppressive therapy in any of these autoimmune disorders predisposes the individual to opportunistic CNS infection. PML, for example, is a recognized complication of SLE or its treatment.

Conversion hysteria

Though the very existence of conversion hysteria has been questioned, it is the experience of all neurologists to encounter individuals who show clear signs of a nonorganic disability. The debate as to whether the elaboration of a disability is conscious or unconscious tends not to be fruitful. Paralysis in varying degree is the most frequently encountered conversion reaction. The weakness may be confined to one limb, to one side of the body, or be global in its distribution. Typically, within a limb, all muscle groups are affected roughly to an equal extent. There is a characteristic variability in performance during muscle testing which should seldom cause diagnostic confusion with myasthenia gravis. A more fixed posture of the limb, of the type described by Charcot and others, is decidedly rare though some patients with a conversion reaction hold the limb in an altered posture which can, however, be overcome by passive movement.

Syphilis of the nervous system

At neurosyphilis the various structures of the NS are affected. It is impossible to understand, what damages are caused by the penetration of the microorganism (T. pallidum) and what damages depend on immune disturbances. Vasculitis and meningitis are observed more often. Less often they observe progressive paralysis.

Pathomorphology Meningitis with lymphoid infiltration of the meninges and affection of the endothelium of brain vessels develops at early stages of disease. Similar changes occur in brain cortex at chronic stages. One observes infiltration and atrophic changes with proliferation of glia cells. The degeneration of dorsal roots and posterior funiculi of the spinal cord take place after the inflammatory phase at chronic course of neurosyphilis.

Clinical forms.

1) Asymptomatic neurosyphilis. They find specific changes in CSF only (positive Wassermann reaction).

2) Syphilitic meningitis develops within one year after infection. Clinically one observes acute or subacute serous meningitis.

3) Endarteritis of brain vessels. Clinically they observe subacute focal symptoms.
4) Syphilitic gumma of the brain or the spinal cord. The clinical course reminds the tumor.
5) Tabes dorsalis develops at the disorder of the meninges of the spinal cord. Inflammatory - dystrophic changes of dorsal roots and posterior funiculi takes place. Clinically they observe lower extremity pains and ataxy.
6) Progressive paralysis develops owing to chronic specific meningoencephalitis. The clinic is various, but dementia with criticism disturbance dominates. Then paralyses and epileptic seizures develop.
Diagnostics. Lymphocytic pleocytosis (200-300 per mm3), positive Wassermann reaction and positive immunofluorescence reaction one observes in CSF.
Treatment. It is necessary to consider penicillin in a dose of 200 000 10 unit of activity every 3 hours intramuscularly. The course dose: 40 000 000 unit of activity. One administers potassium iodide for 2-4 weeks then they prescribe preparations of bismuth such as biiochinolum and bismoverol. Most physicians recommend 1 to 2 months treatment cessation between courses of treatment by antibiotic and bismuth preparations. One administers symptomatic therapy and therapy by biogenic stimulators.

Human Immunodeficiency Virus Infection

Ethiology and pathogenesis. AIDS is the final stage of the infection, caused by human immunodeficiency virus. HIV is human nononcogenic retrovirus, slow virus, which causes chronic demyelination. The incubation period is prolonged; HIV persists into the nervous system and disturbs the immunity. HIV has the tropism to macrophages, lymphocyte and cerebral cells. Hematogenic and sexual transmission of infection is typical for HIV. There are no preventive and medical measures and it threatens by pandemia. More than 100 persons infected with the human immunodeficiency virus in Smolensk. HIV transmits from mother to child.
Clinic and diagnostics. In the clinical finding they emphasize 3 stages: 1) latent (incubation period), 2) pre-AIDS (generalized lymphadenopathy) and 3) full-scaled
(comprehensive) picture.Disorder of the CNS is observed in 60 per cent of cases; in 10-20 per cent of cases CNS affection is the first symptom. Acquired immunodeficiency syndrome (AIDS) dementia complex and sensory polyneuropathy are the most often manifestations.Progressive multifocal leukoencephalopathy and multifocal giant cell encephalitis is the reason of AIDS dementia complex. The onset of disease is characterized by sleepiness, disturbance of attention and memory. Then muscular tonus increase, sucking reflex and grasping reflex, adiadochocinesis, apathy, bradykinesis and tremor are added. Full-scaled picture is characterized by the development of mutism, paraplegia and disorder of pelvic functions on the background of dementia. The syndrome of sensory polyneuropathy is manifested by pains and paresthesia of inferior limbs and loss of knee reflex.
It is possible the combination of sensory polyneuropathy and AIDS dementia. Tumors (Kaposi's sarcoma), pathology of oral cavity and other organs are developed as the complication of AIDS. V and VII nerve disorder is the variant of demyelinating polyneuropathy and debut of mononeuropathy.
Treatment is not developed.