practitioner without an ophthalmic opinion. Nor should treatment be repeated or renewed by general practitioners without regular ophthalmic review to eliminate the possibility of steroid induced glaucoma or the onset of an unsuspected secondary infection. Unfortunately, those most in need of instruction will probably not be reading this journal. The task falls, therefore, on ophthalmologists—who have the problem thrust on them—to reinforce education at a local level.[4] They will have to try and try again to prevent the misappropriate use of topical steroids—an iatrogenic cause of great visual disability.[4]

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Peripheral neuropathy associated with dysproteinaemia, skin changes, and endocrinopathy

Connoisseurs of bizarre multisystem syndromes will be delighted by a little known gem from Japan, which is characterised by progressive polyneuropathy, diffuse hyperpigmentation, scleroderma, hypertrichosis, anasarca, various endocrine changes, hepatosplenomegaly, lymphadenopathy, and dysglobulinaemia, usually associated with plasma cell dyscrasia. More than 150 cases of this distinctive disease have now been described under a variety of names, including Shimpo's syndrome,[1] Takatsuki syndrome,[2] PEP syndrome (progressive polyneuropathy associated with pigmentation, oedema, and plasma cell dyscrasia),[3] POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes),[4] and Crow-Fukase syndrome.[5] Although most reports have come from Japan, several isolated cases or small series have been reported from the United States and Europe.[6-12]

A recent review of 102 Japanese cases showed that 56 of the patients had multiple myeloma, usually associated with osteosclerotic bone lesions and a circulating λ light chain.[5] Of the remaining 46 patients, two had an extramedullary plasmacytoma, 33 had only a serum monoclonal protein, and 11 a raised serum concentration of a polyclonal protein. The clinical features of the syndrome were the same whether multiple myeloma was present or absent.

The age at onset ranged from 27 to 80, with a male to female ratio of about 2:1. Most patients presented with chronic progressive polyneuropathy, peripheral oedema, or a combination of the two. The neuropathy was of the distal, symmetrical, sensorimotor type, with gradual proximal spread, and in many cases severe weakness prevented the patient from walking. Nerve conduction studies showed that both motor and sensory conduction were slow, and biopsy specimens showed a mixture of axonal degeneration and segmental demyelination. The cranial nerves were almost always spared, but the protein concentration in the cerebrospinal fluid was increased in 94% of cases, and papilloedema was present in 62%. Anasarca was often present with dependent oedema (91%), ascites (62%), and pleural effusions (40%). Diffuse pigmentation occurred in 93% of patients, and hypertrichosis, thickened skin, and hyperhidrosis were also common. Most of the men had gynaecomastia and impotence, and many of the women were amenorrhoeic. Less common endocrine disturbances included glucose intolerance and hypothyroidism. Most patients had enlargement of the liver and spleen or generalised lymphadenopathy, and the lymph nodes showed a peculiar histological change known as Castleman's angiofollicular hyperplasia with proliferating arborising capillaries, spindle cell proliferation in the follicle centres, sheets of mature plasma cells in the interfollicular tissue, and clear cut lymph sinuses with sinus histiocytosis. Other common clinical features included mild fever and finger clubbing.

Most patients in this large series were treated with prednisolone, cyclophosphamide, or irradiation; they showed some initial improvement, but many eventually deteriorated and died of the disease. Most deaths were due to heart failure; the mean survival was 33 months from the onset of the symptoms.

Peripheral neuropathy is a rare complication of plasma cell neoplasia, occurring in less than 1% of all cases,[12] but at least 170 cases of polyneuropathy associated with dysproteinaemia have been reported outside Japan.[5 12 13] Only about one third of these have had the cutaneous and endocrine features of the full blown POEMS syndrome, and it is still not certain whether the full syndrome is a separate entity from the peripheral neuropathy alone. In a review of 56 reported cases of neuropathy due to IgM paraproteins Driedger and Pruzanski found evidence of the full syndrome in only six cases, but they commented that features such as mild oedema, scleroderma, pigmentation, hypertrichosis, hyperhydrosis, impotence, and amenorrhoea may go unnoticed or unreported.[12] This suggestion is supported by the data of Kelly *et al*, who carefully studied 16 non-oriental patients with multiple myeloma and peripheral neuropathy and found that only one had none of the other features of the syndrome and that 12 patients had three or more of the other features.[13]

The pathogenesis of this syndrome is puzzling. It seems likely that the abnormal protein is implicated in the nerve damage, and binding of immunoglobulin to nerve and myelin sheaths has been reported in some patients, but the importance of this is uncertain, since the same finding may occur in patients with myeloma without neuropathy.[14] Mice repeatedly injected with the monoclonal protein from patients with myeloma do, however, develop a demyelinating polyneuropathy.[15] Some of the features of the syndrome such as water retention, pigmentation, gynaecomastia, impotence, and amenorrhoea might be explained by increased oestrogen production. Urinary oestrogen concentrations were increased in 11 of the 19 patients in whom they were measured,[5] and two patients have recently been shown to have an increased rate of conversion of androgen to oestrogen.[16] A similar acceleration of exogenous androgen conversion occurs during normal pregnancy and has been used as a test of placental function. Further investigation of this syndrome may thus throw unexpected light on other topics, including the control of sex hormone metabolism.

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Regular Review

Differential diagnosis of dementia

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Between 3% and 5% of people aged over 65 have severe impairment of memory, intellect, orientation, and personality and a similar proportion have milder dementia.[1 2] Dementia is no longer considered to be caused by "senility": though it is increasingly common with advancing age, 80% of people over the age of 80 are not demented. Nor can degenerative arterial disease always be incriminated[3]: 20-30% of demented patients have a vascular basis for their symptoms but most patients who become demented do not do so as a result of atherosclerosis.[4] Dementia is not a diagnosis but a syndrome whose aetiology must be ascertained in order to recognise the reversible or modifiable causes. Let us review those conditions which should be considered when a patient over 60 develops intellectual impairment and assess the usefulness of investigations.

The two most important aspects of the clinical assessment of an apparently demented person are, firstly, the mode of onset and progression of the symptoms, and, secondly, the presence or absence of focal neurological symptoms and signs. Dementia is a chronic disorder developing over many months. "Acute dementia" resulting from profound cerebral anoxia is uncommon.

Confusion coming on abruptly may be the result of head injury—but apparent confusion of sudden onset may be caused by jargon dysphasia due to a stroke. If cognitive impairment develops over days or weeks and the patient's consciousness is clouded the diagnosis is of an acute or subacute confusional state (delirium); this has many causes including chest infection, adverse drug reactions, metabolic disturbances, or dehydration with constipation.[5]

Intellectual impairment which comes on insidiously and gradually worsens over months or years without any associated neurological features suggests several diagnostic possibilities.

Alzheimer's disease

The most common cause of dementia is Alzheimer's disease, in which initially there is loss of memory for recent events and impaired cognitive function. Together these symptoms impair the patient's ability to do everyday tasks. Often she (or he) has no insight into her decline. Only late in the course of the illness do neurological signs appear: the presence of fits or a disturbance of gait in the early stages makes the diagnosis unlikely.[6] Dysphasia and parietal lobe signs (agnosia and apraxia) also occur: Alzheimer's disease is therefore sometimes described as a "cortical" dementia. Those dementias in which cortical features are absent (for example, normal pressure hydrocephalus, Huntington's chorea, the dementia of Parkinsonism) have been labelled as "subcortical" dementias—but doubt has been cast on the validity of this distinction.[7 8]

Alzheimer's disease is a pathological diagnosis based on the presence of neurofibrillary tangles and plaques throughout the cerebral cortex. Unfortunately there is no laboratory test for Alzheimer's disease, and some patients in whom it has been diagnosed clinically prove to have other conditions at necropsy. The clinical diagnosis may be made only after other conditions have been excluded: the three disorders most important to exclude are benign forgetfulness, depression, and drug toxicity.

Benign forgetfulness, depression, and drugs

Occasional inability to recall names or relatively unimportant past events is a common experience which is more prevalent in men over 60.[9] The person with "benign senescent forgetfulness" may recall things on one occasion