Although the importance of humoral agents has been suggested (Marie, 1890; Mendlowitz, 1942; Hall, 1959; Ginsberg and Brown, 1961), the neurogenic theory for the production of hypertrophic osteoarthropathy is currently favoured. This arose after finding in man and in dogs that when the osteoarthropathy occurred in association with lung neoplasms thoracic vagotomy produced an immediate fall in blood flow to the affected limbs, with subsequent relief of symptoms (Flavell, 1956; Holling *et al.*, 1961).

The evidence from this case report suggests that the substance which causes hypertrophic osteoarthropathy either is produced by vascular tissue in response to specific infections or tumours or is present in the blood in a precursor state and is activated by contact with abnormal vascular tissue. For the effect of this substance to be localized it must be metabolized in the periphery or in the lungs.

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Brain Stem Encephalitis Caused by *Herpesvirus hominis*

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Herpesvirus hominis (herpes simplex) encephalitis typically presents in the adult as a temporal lobe disturbance and it is not generally known as a cause of brain-stem disorders. The recent introduction of antiviral preparations such as idoxuridine has made it important to delineate the clinical effects of this virus as an aid to its speedy diagnosis and treatment. We wish to report two cases of brain-stem encephalitis due to herpes simplex infection in which we used an immunofluorescent technique to help in the rapid identification of the pathogenetic agent.

Case 1

Three weeks before admission to hospital a 14-year-old schoolboy had had a febrile illness with a sore throat and mild nasal congestion from which he rapidly recovered. Ten days later he complained of mild headache which increased during the course of the day. By evening he was vomiting and had great difficulty in remembering the earlier part of the day. The next day he was lethargic and delirious, with a temperature of 102°F (38.9°C); he complained of double vision and his speech was slurred. He was admitted on the third day. By then he was unable to clear his throat; he dribbled saliva, tended to choke and cough while eating, was very restless, and failed to recognize members of his family.

Neurological examination showed a confused, febrile boy with a slurring dysarthria and incontinence of urine. There was first-degree nystagmus to right and left. The palate elevated very poorly. There was no definite limb weakness or ataxia. All the tendon reflexes were depressed. Both planter responses were flexor. There was no sensory loss.

Over the next 48 hours, as his level of consciousness fell, he developed mild bilateral facial weakness and his tendon reflexes

disappeared. He had two brief episodes of coma associated with divergent upward gaze, very small pupils, and flaccidity of the limbs. Two days later his respiration became irregular and periodic and there were frequent extensor spasms. After tracheostomy his spontaneous respiratory pattern varied between central neurogenic hyperpnoea, Cheyne-Stokes, and regular breathing. After nine days a flaccid right hemiplegia appeared. His conditions then deteriorated, he became hypotensive, and he died on the 16th day of the illness.

The cerebrospinal fluid contained 50 lymphocytes/mm³. 55 mg protein/100 ml, and 62 mg glucose/100 ml; culture was sterile. Serum complement-fixing antibody titres to *H. hominis* rose from 1:4 on the day of admission to 1:128 on day 15. The electroencephalogram showed diffuse, irregular, slow-wave background activity with anterior left hemisphere and mid-temporal focal slow-wave abnormalities. The slow waves had a repetitive pattern which changed in periodicity between day 4 and day 10.

Intravenous idoxuridine 3 g daily was given without discernible clinical effect between day 10 and day 15 of the illness.

At necropsy there was extensive patchy haemorrhagic infarction of both cerebral hemispheres, maximal in the temporal lobes, and small haemorrhagic softenings were scattered throughout the cerebral peduncles, pons, and medulla. Microscopical examination showed necrotizing encephalitis in the cerebral cortex, more severe and diffuse throughout the tegmentum, pes pontis, and floor of the fourth ventricle. Inclusion bodies were not seen.

Cryostat sections from many areas of the brain were examined by the indirect immunofluorescent technique, using rabbit anti-herpes and swine anti-rabbit sera. Neurones and glial cells in the cerebral cortex and brain stem contained herpes-virus antigens, and so did a few macrophages in the perivascular infiltrates.

Case 2

A 48-year-old pattern cutter was admitted to a regional hospital with a one-week history of progressive vertigo, headache, hiccup, and photophobia. He was febrile and had a stiff neck. Over the next week he became increasingly drowsy and developed dysarthria before transfer to this hospital.

On admission he was afebrile, drowsy, and confused. He had neck stiffness. His speech was so disturbed that conversation was impossible. Both pupils were pin-point in size but reacted to light and accommodation. There was bilateral ptosis, gaze paresis, first-degree nystagmus to the right, and failure of adduction of the left eye. Upward gaze was limited and convergence absent. There was weakness of the right masseter. The right corneal reflex was absent. Pin-prick sensibility was impaired over the left side of the face. A lower motor neurone facial weakness was present on the left. He had mild left pyramidal signs with ataxia and was unable to stand because of severe dysequilibrium. Adequate sensory testing was not possible.

Over the next two days his condition deteriorated and he became more drowsy and developed some limitation of abduction of the left eye. Thereafter his condition remained static and then began gradually to improve. He became more alert, and many of the

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abnormal signs resolved in part during the next two months, after which he was discharged to another hospital.

The cerebrospinal fluid on day 7 contained 30 lymphocytes/mm³, 2,200 R.B.C./mm³, and 70 mg protein/100 ml; on day 19, 263 lymphocytes/mm³ and 130 mg protein/100 ml; and on day 102, 8 lymphocytes/mm³ and 80 mg protein/100 ml.

Cells from the lumbar cerebrospinal fluid were examined for *H. hominis* antigens and immunoglobulins by indirect immunofluorescence. In the first sample (day 31) there were plentiful mononuclear cells; about 15% contained *H. hominis* antigens and 20% contained IgG or IgM. A subsequent specimen (day 53) showed only small numbers of IgG-containing cells, and no *H. hominis* antigens were detected.

H. hominis was isolated from the cerebrospinal fluid taken on day 7; this finding was not available until late in the illness. The serum titre to *H. hominis* rose from 1:8 on day 3 to 1:80 on day 53.

On admission to this hospital the electroencephalogram was diffusely slow without periodic complexes. Over the next three days it deteriorated as the small amount of alpha rhythm disappeared; it then slowly improved, to become normal two months later.

Comment

Both these patients suffered from *H. hominis* encephalitis. The first had an appropriate serum antibody response, changes in the electroencephalogram which may be diagnostic of this condition (Upton and Gumpert, 1970; Illis and Taylor, 1972), and typical pathological changes at necropsy (van Bogaert *et al.*, 1955). The second patient had a similar antibody response, cells in the cerebrospinal fluid contained herpesvirus antigens, there were other typical changes in the fluid, and the virus was isolated from it. Clinically, this diagnosis seemed unlikely at first because both patients presented with brain-stem disorders, which are not usually thought to be associated with herpes encephalitis. The first patient had clinical and pathological evidence of generalized encephalitis which had

caused particularly severe damage to the brain-stem. In the second patient the clinical lesions were even more strikingly confined to this region. Brain-stem encephalitis is an ill-defined entity, and patients suspected of suffering from it are commonly found to have other conditions. It is very unusual for any aetiological agent to be isolated (Bickerstaff, 1957).

With the development of effective antiviral chemotherapy it is becoming increasingly important to identify the aetiological agents in cases of encephalitis. There is some evidence that idoxuridine is at least partly effective in the treatment of *H. hominis* encephalitis (Nolan, *et al.*, 1970), especially if it is given early in the course of the disease. A prerequisite for the rapid diagnosis of infection by a specific virus is to regard it as a possibility. The speediest laboratory investigations likely to be of help are probably electroencephalography, which may be diagnostic under certain circumstances, and the immunofluorescent detection of viral antigens in cells from the cerebrospinal fluid (Sommerville, 1968; Dayan and Stokes, 1970). The latter technique is limited by the availability of suitable antisera, but it can be of particular value in diagnosing or excluding those few viruses for which there are specific treatments.

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Progressive Kidney Damage after Non-obstructive Urinary Tract Infection

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Most cases of chronic pyelonephritis in adults are the result of urinary tract infection in childhood (Asscher and Waters, 1971). Bailey, Little, and Rolleston (1969) reported a case in which a kidney diminished in size after an attack of acute pyelonephritis. In the present patient progressive shrinkage of both kidneys occurred over three years. This shrinkage was associated with persistent pyuria and a *Streptococcus faecalis* infection.

Case History

A 39-year-old housewife attended hospital in November 1967 with a three-month history of four attacks of bilateral loin pain associated with rigors, frequency, and dysuria. Each of these attacks responded to ampicillin but they recurred within days after stopping the drug.

In October 1965 urine analysis had shown nothing abnormal and her blood urea was 18 mg/100 ml.

On examination in November 1967 there was tenderness of both loins and above the pubic arch. The blood pressure was 150/100 mm Hg, haemoglobin 12.4 g/100 ml, W.B.C. 16,300/mm³ (polymorphs 83%), E.S.R. (Westergren) 40 mm in the first hour, and blood urea 19 mg/100 ml. Urine analysis showed protein +, urine deposit contained numerous pus cells, and a midstream specimen of urine was sterile. An excretion urogram (Fig. 1) showed slight dilatation of upper pole calyces, with loss of renal substance from the right upper pole and a scar at the left lower pole.

In June 1968 she was admitted because of loin pain, fever, and dysuria. Numerous urine cultures, including cultures for acid-fast bacilli, were sterile although pyuria persisted. The blood urea was 22 mg/100 ml and the creatinine clearance varied between 54 and 62 ml/min. Repeat urography showed the dilatation of upper pole calyces to be a little more prominent. By October 1968 the blood urea had risen to 53 mg/100 ml and the creatinine clearance had fallen to 37 ml/min. A micturating cystogram was normal. Renal biopsy showed interstitial fibrosis with tubular atrophy alternating with areas of tubular dilatation. The dilated tubules contained proteinaceous casts. The glomeruli were well preserved. She was started on long-term treatment with ampicillin 500 mg four times daily. The attacks of loin pain and fever abated but sterile pyuria persisted.

In July 1970 ampicillin was stopped. In December the loin pain and

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