Gangrene in Behçet's Syndrome

SIR,—We should like to report a case of Behçet's syndrome in which gangrene of the forefoot was considered to be a manifestation of the disease.

The patient, aged 35 when first seen in 1955, has had symptoms since the age of 16. Mouth ulceration has been a recurrent problem, but genital ulceration occurred only once at the age of 38. Iritis occurred in 1957 and 1961 and left no residual damage. Arthralgia and stiffness, features since the age of 17, have been controlled by analgesics and physiotherapy. Skin nodules, appearing at intervals, have shown a nodular vasculitis on biopsy. Since 1957 ulcers of the lower legs have been slow to heal even with intensive therapy. Acneiform eruptions and local pyoderma of the chest and thighs have always responded to antibiotic therapy.

He was admitted to hospital in January 1967 with a 10-day history of constant right forefoot pain, aggravated by leg elevation. The foot, initially cold and white, had become blue-black in colour. He gave no history of Raynaud's phenomenon, claudication, or angina. There was gangrenous change with a demarcation line just proximal to the metatarsal heads and there was delayed filling of the veins on the dorsum of the foot. The peripheral pulses were easily palpable, though a right femoral bruit was audible. Shallow, clean ulcers were present on the left foot and leg, and there was an acneform eruption on his thighs and buttocks. No other abnormality was found. Investigations revealed: haemoglobin 14·4 g./100 ml.; E.S.R. 51 mm./hr.; W.B.C. 11,000; prothrombin activity and glucose tolerance test normal; and fasting serum cholesterol 135 mg./100 ml. No cold agglutinins were found and oscillometry was normal. Radiographs showed some sclerosis of the sacroiliac joints which had not progressed. There was no evidence of vascular calcification.

When conservative therapy followed by right lumbar sympathectomy was unsuccessful, amputation of the forefoot had to be carried out. Recovery from these operations has been uneventful.

Behçet's[1] original description included the triad of relapsing iritis with recurrent ulceration in the mouth and on the genitalia. Many other apparently associated systemic manifestations have been added to the syndrome,[2 3] including vascular disorders. Thrombophlebitis is common, and arterial involvement, usually associated with aneurysm formation, has been described.[4] Gangrene has been reported only once, by Pallis and Fudge,[5] who described minimal finger-tip lesions.

The basic pathological process in this condition is probably a vasculitis.[6] In the absence of larger vessel involvement the gangrene in this case was presumably due to lesions of the small vessels of the forefoot. The cause of this disease is not known. The administration of corticosteroids appears to suppress some of the systemic symptoms in a small number of patients, but there is no evidence that they halt, or even alter, the underlying pathological abnormality.

We wish to thank Dr. R. J. G. Sinclair for permission to publish details of this case, and Mr. A. I. S. Macpherson for undertaking the surgical management.

—We are, etc.,

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REFERENCES

1 Behçet, H., *Dermatologische Wochenschrift*, 1937, **105**, 1152.
2 Dowling, G. B., *Proceedings of the Royal Society of Medicine*, 1961, **54**, 101.
3 Strachan, R. W., and Wigzell, F. W., *Annals of the Rheumatic Diseases*, 1963, **22**, 26.
4 Hills, E. A., *British Medical Journal*, 1967, **4**, 152.
5 Pallis, C. A., and Fudge, B. J., *Archives of Neurology and Psychiatry*, 1956, **75**, 1.
6 Mamo, J. G., and Baghdassarian, A., *Archives of Ophthalmology*, 1964, **71**, 4.

Anticonvulsant Therapy, Folic Acid Deficiency, and Neuropsychiatric Disorders

SIR,—I would like to comment on the conclusions made by Drs. N. Weckman and R. Lehtovaara,[1 2] who concluded that there was no relation between anticonvulsant therapy, folate deficiency, and neuropsychiatric disorders.

The association of megaloblastic anaemia and anticonvulsant therapy has been the subject of many publications and is recognized by most physicians. The anaemia responds to folic acid, and several authors[3 4] have independently described low serum folate activity in drug-treated patients. These have been large and detailed surveys. Furthermore, since our original report[5] I have had the opportunity of witnessing low C.S.F. folate activities in treated epileptics, which was significantly different from that of a control group irrespective of whether the results were analysed using a log-normal or a gaussian distribution.

It is difficult to explain the discordant results obtained by Drs. Weckman and Lehtovaara, and I think there must be a systematic difference in technique in carrying out the folate assays. With particular reference to the C.S.F. folate activity it is of note that the mean C.S.F. folate of their control groups is well below the range found by Herbert.[6] Furthermore, I believe when designing such a study it is important that the parameter being studied should be compared with as normal a section of the community as possible. With regard to the C.S.F. folate activity the moral objections of performing lumbar punctures on normal healthy subjects is self-evident. Clearly a compromise must be made, and perhaps I can suggest certain criteria that can be applied to these hospital control subjects:

(1) A normal serum folate.

(2) The C.S.F. should be normal with respect to the total protein, cell count, Pandy, Nonne-Apelt, and Lange tests.

(3) The patient should not have suffered from any recent neurological catastrophe and should have no progressive neurological illness.

(4) The patient should be receiving no drug therapy.

(5) The specimens should be taken while the patient is fasting.

If these criteria are not fulfilled a falsely high proportion of "control subjects" will have a low C.S.F. folate activity.

Prolonged intoxication with the anticonvulsant epanutin is a recognized cause of permanent dysfunction of the central nervous system both in the experimental animal and in man.[7] More recently neuropathy has been described as a complication of prolonged anticonvulsant therapy.[8] The relationship of anticonvulsant-induced folate deficiency to neuropsychiatric disorders has also been the subject of several detailed studies.[9–11] The increase in fit frequency following folate therapy in folate-deficient anticonvulsant-treated epileptics can in some instances be dramatic,[12] which, together with neurological and psychiatric improvement,[10 13] lends support to the concept that anticonvulsants act by interfering with folate metabolism, and in occasional cases result in severe neuropsychiatric sequelae.—I am, etc.,

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REFERENCES

1 Weckman, N., and Lehtovaara, R., *Scandinavian Journal of Clinical Investigation*, 1968, Suppl. No. 101, p. 210.
2 Weckman, N., and Lehtovaara, R., *Lancet*, 1969, **1**, 207.
3 Klipstein, F. A., *Blood*, 1964, **23**, 68.
4 Malpas, J. S., Spray, G. H., and Witts, L. J., *British Medical Journal*, 1966, **1**, 955.
5 Wells, D. G., and Casey, H. J., *British Medical Journal*, 1967, **3**, 834.
6 Herbert, V., and Zalusky, R., *Federation Proceedings*, 1961, **20**, 453.
7 Kokenge, R., Kutt, H., and McDowell, F., *Neurology*, 1965, **15**, 823.
8 Horwitz, S. J., Klipstein, F. A., and Lovelace, R. E., *Lancet*, 1968, **1**, 563.
9 Hansen, H. A., Nordqvist, P., and Sourander, P., *Acta Medica Scandinavica*, 1964, **176**, 243.
10 Anand, M. P., *Scottish Medical Journal*, 1964, **9**, 388.
11 Reynolds, E. H., *British Journal of Psychiatry*, 1967, **113**, 911.
12 Wells, D. G., *Lancet*, 1968, **1**, 146.
13 Reynolds, E. H., Chanarin, I., and Matthews, D. M., *Lancet*, 1968, **1**, 394.

SIR,—The reversible acute symptoms and signs of cerebellar dysfunction in epileptic patients on treatment with hydantoinates are well known. It is also well established that large doses of hydantoinate may cause parenchymatous cerebellar degeneration.[1 2]

In recent times peripheral neuropathy and myelopathy have been reported as complications of anticonvulsant therapy, and are believed to be due to antifolate activity of the anticonvulsant drugs[3]—which also accounts for the megaloblastic erythropoiesis which occurs in association with administration of anticonvulsants. Psychiatric disturbances have occurred in the presence of low serum folate concentrations suggesting a causal relation.[4–6] The mechanism by which the neurological complications are produced is controversial, however. Antifolate activity may not account for all the known facts. I report here a case of acute reversible neuropathy complicating treatment of epilepsy with phenobarbitone and phenytoin.

A 15-year-old girl presented with a six-month history of generalized (idiopathic) epilepsy. Detailed clinical examination showed no neurological defect. Investigations including plain radiographs of chest and skull, fasting blood sugar, serum calcium, phosphate and alkaline phosphatase, serum urea and electrolytes, and blood Kahn test were normal. She was treated with phenobarbitone 30 mg. and phenytoin 100 mg. three times daily. Four weeks after commencing treatment she developed stomatoglossitis, dizziness, ataxia of gait, and a diffuse maculopapular rash.

Neurological assessment showed horizontal jerky nystagmus on lateral gaze in either direc-