of the care taken. In retrospect, moderate inclination of the upper trunk would probably have been wise.

When operations on the stomach were done urgently not long after gastric cooling had been under way there were no untoward findings in the gross or microscopical appearances of the stomach. Nor was there any evidence that postoperative healing was prejudiced by gastric cooling.

Discussion

In this study gastric cooling was carried out for a 24-hour period in all but a few of the cases so treated. This was because a review of the duration of treatment used by other workers (when they stated this) suggested this to be a reasonable time to control haemorrhage and minimize the chance of its immediate recurrence. It proved satisfactory to adhere to this period as a basis for comparative study, but probably a shorter period could be effective in some cases.

The definition of "massive" haemorrhage in terms of the blood loss, the patient's condition, and haemoglobin and haematocrit levels was arbitrary. It would not allow strict comparison with other reported series, but was a good practical guide for inclusion of patients in this series. Only after the patient had been accepted was the card indicating the method of treatment consulted.

Comparison between the two groups by examination of the "degree of arrest of haemorrhage" (Tables IV and V) would suggest that gastric cooling (three recurrences or failures) had a better success rate than the conservative group (seven failures), but statistical evaluation of these data (Table VI) indicates that any difference in the arrest of haemorrhage is not significant. Moreover, Table II shows that the eventual outcome (four deaths) was the same for each group.

TABLE VI.—Statistical Evaluation of Data from Tables IV and V

		Gastric Cooling	Conservative Management	Total
Permanent arrest		19	15	34
Degree of cooling		3	7	10
Total		22	22	44

$$\chi^2 = 2.07, \quad P > 0.10.$$

In Fig. 4 the volume of blood transfused and the degree of anaemia show some minor differences (the conservative group had marginally lower haemoglobin levels at the start and throughout the period of review; less blood was transfused to those under 50 years—conservative group), but the overall similarity of the figures is striking. In particular an average of 8.6 units of blood was given to the gastric cooling group, while an average of 8.3 units was given to the controls.

It is evident that there is no significant difference between the two groups.

Summary

In a prospective study gastric cooling was used as an adjunct to initial conservative management of patients with serious upper gastrointestinal haemorrhage.

It has been shown that this method conferred no benefit on this group of patients compared with a similar group managed by expectant measures only.

This relative failure was not due to technical deficiencies; the hypothermia apparatus functioned smoothly and appeared to be superior to most earlier units.

The overall experience with this technique suggested that it may be useful when haemorrhage is persisting and there are strong reasons for avoiding operation.

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Lactobacillus casei C.S.F. Folate Activity

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Folic acid derivatives are essential components of enzyme systems required in the synthesis of several key precursors of both protein and nucleic acids. The effects of folate deficiency on human metabolism are potentially extremely severe (Woods, 1964).

It is known that the C.S.F. concentrates folate (Herbert and Zalusky, 1961). As the explanation for this is not understood and because of the recent interest in the relation between folate deficiency and neurological disease (Hansen *et al.*, 1964; Anand, 1964; Grant *et al.*, 1965), it was decided to study the C.S.F. folate activity in patients with neurological disease.

Materials and Methods

Samples of cerebrospinal fluid were obtained from patients in the following groups:

(1) *Hospital Controls*: The 30 patients in this group were admitted for investigation of neurological or psychiatric symptoms.

However, in no instance was there evidence of active neurological disease. Several patients who had cerebrovascular accidents some months before admission were included in the control group. The C.S.F. was normal in respect of the total protein, cell count, and Pandy, Nonne-Apelt, and Lange tests.

(2) Patients with miscellaneous neurological diseases including: those with epilepsy being treated with anticonvulsants and those with multiple sclerosis and varied tumours of the nervous system.

The C.S.F. was centrifuged and the supernatant taken for analysis. Blood for the serum folate estimation was taken while the patient was fasting. The serum was separated within two hours from the time of venesection. Ascorbic acid (5 mg./ml.) was added to the C.S.F. and serum. Specimens were stored at -20° C. until analysis.

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The serum folate levels were measured by microbiological assay with *Lactobacillus casei* (Waters and Mollin, 1961). The normal serum folate range is 5.9–21 $\mu\text{g./ml.}$ A serum folate of 4 $\mu\text{g./ml.}$ or above excludes severe folate deficiency. The C.S.F. folate levels were determined similarly, but the final dilution of the C.S.F. was one part in 160 as compared with one part in 80 for the serum folate estimation. If the colorimeter reading of the test sample did not correspond with the sensitive part of the pteroylglutamic acid curve the assay was repeated at an appropriate higher or lower dilution. Duplicate assays were performed on each C.S.F. and serum specimen, the mean figure being taken.

Results

Group 1

The range of C.S.F. folate activity in the 30 hospital control subjects was 12.6–67 $\mu\text{g./ml.}$ The mean C.S.F. folate level was 23.6 $\mu\text{g./ml.}$ (± 2.0 $\mu\text{g./ml.}$ S.E.). The mean serum

Relation between C.S.F. and serum *L. casei* folate activity.

folate was 5.4 $\mu\text{g./ml.}$ (± 0.46 $\mu\text{g./ml.}$ S.E.). The correlation between the C.S.F. and serum folate levels is shown in the Chart ($r = +0.7$; $P < 0.001$). The calculated regression line has been drawn ($y = 3.1 \times + 7.0$).

Group 2

(A) *Epileptics Treated with Anticonvulsants* (10).—The mean C.S.F. folate level in 10 epileptic patients on anticonvulsant therapy was 16 $\mu\text{g./ml.}$ (± 2.1 $\mu\text{g./ml.}$ S.E.), which was significantly different from the mean C.S.F. folate level of the control subjects ($P < 0.05$). The mean serum folate level was 4.7 $\mu\text{g./ml.}$ (± 0.57 $\mu\text{g./ml.}$ S.E.). One-third of the patients had a C.S.F. folate level below 12.6 $\mu\text{g./ml.}$ Despite the effect of the anticonvulsants a correlation persisted between the serum and C.S.F. folate levels ($r = 0.627$; $P < 0.05$). The calculated regression line was $y = 2.3 \times + 5.3$. Perhaps the most interesting epileptic patient studied was a woman who developed a cerebellar disorder with ataxia, nystagmus, and dysarthria while being treated with Epanutin and phenobarbitone. Intensive investigation (including air-studies) failed to suggest an alternative diagnosis to Epanutin intoxication. However, when the Epanutin therapy was curtailed no improvement resulted. Her serum and C.S.F. folate levels were 1 $\mu\text{g./ml.}$ and 4.2 $\mu\text{g./ml.}$ respectively. The serum vitamin B_{12} level was normal. Treatment with folic acid resulted in no objective improvement.

(B) *Multiple Sclerosis* (12).—The range of C.S.F. folate activity in the 12 patients with multiple sclerosis was 16–43 $\mu\text{g./ml.}$ The mean C.S.F. and serum folate levels were 21.6

$\mu\text{g./ml.}$ (± 1.7 $\mu\text{g./ml.}$ S.E.) and 6.0 $\mu\text{g./ml.}$ (± 0.83 $\mu\text{g./ml.}$ S.E.) respectively. The mean C.S.F. folate level was not significantly different from that of the control subjects ($P > 0.05$). The correlation between the serum and C.S.F. folate activity in this small group was poor ($r = 0.28$; $P > 0.05$). Several of the patients were being treated with vitamin B_{12} injections and/or corticosteroids. This therapy or the underlying pathology may have been responsible for the lack of correlation.

(C) *Tumours of the Nervous System* (10).—The C.S.F. folate range in 10 patients with varied tumours of the nervous system was 7–27 $\mu\text{g./ml.}$ The mean C.S.F. folate level was 19 $\mu\text{g./ml.}$ (± 1.9 $\mu\text{g./ml.}$ S.E.) while the mean serum folate level was 5.9 $\mu\text{g./ml.}$ (± 1.1 $\mu\text{g./ml.}$ S.E.). The mean C.S.F. folate level was not significantly different from that of the control subjects ($P > 0.05$). This group included patients with benign tumours and also those with malignant lesions. A patient with a low C.S.F. folate of 7 $\mu\text{g./ml.}$ and serum folate of 3.9 $\mu\text{g./ml.}$ had a spinal block due to metastases. When a laminectomy was performed tumour tissue was found invading the theca. In view of the known ability of tumour cells to metabolize folate it is not surprising that the correlation between the serum and C.S.F. *L. casei* folate activity was poor ($r = 0.32$; $P > 0.05$).

(D) *Miscellaneous Neurological Diseases*.—Smaller groups of patients suffering from polyneuritis (5), Parkinsonism (4), motor neurone disease (4), Friedreich's ataxia (1), tabes dorsalis (1), syringomyelia (1), trigeminal neuralgia (1), and acute necrotic myelitis (1) were also studied. Their C.S.F. folate levels with one exception fell within the range seen in the control subjects. The patient with a low C.S.F. folate of 12 $\mu\text{g./ml.}$ was an alcoholic with a peripheral neuropathy. His admission to hospital was prompted by the development of bilateral optic neuritis. A patient with neurological symptoms in whom no definite diagnosis could be made is of interest because she had a low C.S.F. folate level. She had pulmonary tuberculosis and was being treated with antituberculosis drugs (isoniazid, para-aminosalicylic acid, and streptomycin). She gave a short history of paraesthesia of her hands and feet, suggesting an early peripheral neuropathy. However, electromyographic studies showed no evidence of peripheral neuropathy. Her C.S.F. folate was 8 $\mu\text{g./ml.}$ and the serum level 1.3 $\mu\text{g./ml.}$ The serum B_{12} level was 660 $\mu\text{g./ml.}$ When her drug therapy was curtailed and her diet improved her symptoms were alleviated.

Discussion

It remains unexplained why folate deficiency does not cause a clearly defined neurological picture allied to that of subacute combined degeneration of the cord. Neurological disease associated with folate deficiency has now been documented by a few authors (Anand, 1964; Hansen *et al.*, 1964). Grant *et al.* (1965) have discussed this association and described three cases with mainly sensory signs and symptoms which improved after oral folic acid.

There is a positive correlation between the serum and C.S.F. folate activity. Despite this correlation it is reasonable to assume that the C.S.F. folate level will more accurately reflect the folate content of the nervous system than the serum level. It is therefore advantageous to assay the C.S.F. folate activity when investigating the relation between disorders of the nervous system and folate deficiency.

The major difficulty of investigating such a relation is that folate deficiency may be coincidental and quite unrelated to the nervous disorder. Therefore, before attributing a neurological disorder to folate deficiency it is essential to exclude other aetiological factors, including deficiency of vitamin B_{12} , pyridoxine, and thiamine.

As a group the epileptics showed the largest proportion of subnormal folate levels. Mannheimer *et al.* (1952) and Badenoch (1954) were the first to note the occurrence of megaloblastic anaemia in epileptic patients who were being treated with anti-convulsant drugs. More recently there have been reports of folate deficiency in many non-anaemic drug-treated epileptics (Hawkins and Meynell, 1958; Klipstein, 1964; Malpas *et al.*, 1966; Reynolds *et al.*, 1966). The findings in our small group of epileptics are in agreement and also show that evidence of disturbed folate metabolism may be detected in the C.S.F. This is of interest, as Reynolds *et al.* (1966) have postulated that the interference with folate metabolism may be related to the therapeutic action of anticonvulsants, and at the same time may be responsible for some of the mental symptoms that occur in these patients.

One of the epileptic patients being treated with phenobarbitone and Epanutin subsequently developed a cerebellar syndrome which failed to resolve when the Epanutin was curtailed. Permanent neurological dysfunction resulting from Epanutin has been described by several authors, including Morris *et al.* (1956) and Putnam and Rothenberg (1953). Rats and cats when subjected to prolonged intoxication showed the loss of the Purkinje cells and degenerative cell changes in the cerebellum (Kokege *et al.*, 1965). The patient, described above, was found to have a C.S.F. folate level of 4.2 $\mu\text{g./ml.}$ It is suggested that the toxic effect of Epanutin is due to its interference with folate metabolism.

Sobotka *et al.* (1958), by means of a microbiological assay utilizing a thermophilic bacillus, found raised C.S.F. folate levels in 34 out of 42 cases of multiple sclerosis studied. The C.S.F. folate levels in the 12 multiple sclerosis patients studied all fell within the range seen in the control subjects. Of 10 patients with varied tumours of the nervous system, only one had a low C.S.F. folate level. This patient had a spinal block due to metastases. It is probable that the tumour cells were metabolizing the C.S.F. folate.

The C.S.F. folate level in five patients with polyneuritis of different aetiology with one exception fell within the range seen in the control subjects. The exception was an alcoholic with a severe peripheral neuropathy and evidence of an early hepatic cirrhosis. Folate deficiency in combination with a deficiency of other vitamins has already been noted in cases of alcoholic peripheral neuropathy by Fennelly *et al.* (1964). No improvement resulted when the patient was given oral folic acid.

The association of folate deficiency and tuberculosis has been noted by Roberts *et al.* (1966). They concluded that folate deficiency was not due to the chemotherapy but to the disease process itself, or a poor diet. Whether the paraesthesiae and

dysaesthesia in the case described were due to the folate deficiency cannot be answered, as the symptoms may have been the presenting feature of a disease, such as multiple sclerosis, which spontaneously remitted.

Summary

The serum and C.S.F. *Lactobacillus casei* folate activity has been assayed in 30 hospital control patients. A positive correlation between the C.S.F. and serum folate activity has been shown to exist.

The C.S.F. folate activity has been assayed in miscellaneous neurological diseases. Drug-treated epileptic patients showed a high proportion of subnormal C.S.F. levels. Groups of patients with multiple sclerosis, miscellaneous tumours, etc., were found to have a mean C.S.F. folate level which did not differ significantly from that of the control group.

The association between neurological disorders and folate deficiency is discussed.

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