ml. compared with a mean level of 4.3 m\(\mu\)g. for the latter group. In a population in the tropics where folate deficiency was common sprue might also be expected to be common.

**Summary**

The clinical and pathological findings in 42 patients with "military tropical sprue" from South-east Asia are described. In the early stages intestinal malabsorption of fat, xylose, and vitamin \(B_12\), mild jejunal change, and folate deficiency were found. In patients seen after two months these abnormalities were more severe. After four months the intestinal mucosa, both jejunal and ileal, had the appearance of partial villous atrophy, megaloblastic anaemia due to folate deficiency occurred, and there was a considerable fall in the serum vitamin-\(B_12\) concentration. The regular clinical and pathological pattern was found helpful in diagnosis.

Both folic acid and a mixed antibacterial course were effective in causing a remission of intestinal malabsorption and a return of the intestinal mucosa to normal. The symptomatic and haematological responses to antibiotics were slow. Antibiotics appear to improve intestinal absorption of folic acid.

These findings are in accord with the hypothesis that temporary intestinal malabsorption arising from non-specific causes may be maintained by secondary folate deficiency and bacterial proliferation in the small bowel. In a population in the tropics where folate deficiency is common sprue might also be expected to be common.

We thank Lieutenant-General Sir Robert Drew for his active interest and the Wellcome Trust for generous financial support. We are particularly indebted to Professor D. L. Mollin for constant help and advice throughout this work. We also thank Dr. Leon Ellenbogen, of the Lederle Laboratories, Pearl River, N.Y., for the supply of intrinsic factor.

**References**


Many descriptions of tropical sprue have been published, but several aspects of the disease are inadequately documented or the subject of dispute, and four of these form the subject of this paper. First, the fully developed clinical picture is easily recognized, but the diagnosis may be missed in the early stages because the significance of certain initial symptoms is not appreciated. Secondly, while antibacterial therapy produced an excellent response in British patients treated in England by French et al. (1956), it is not known whether similar subjects respond so well when treated in the tropics. Thirdly, folic-acid therapy usually corrects the anaemia which is a common feature of tropical sprue, but its effect on the intestinal lesion is less certain: Gardner (1956) obtained a reasonably good response in United States Service men in Puerto Rico, but Sheehy and Floch (1964) concluded from experience in the same area that folic acid rapidly alleviated the haematopoietic but not the intestinal lesion, and although previous reports from Hong Kong on the effects of folic acid in sprue (Rosenthal, 1952; Webb, 1956) have been favourable, more detailed data are desirable. Finally, remarkably little is known about the fate of expatriate patients who remain in the tropics after treatment.

--- Webster, M. C., M.D., M.R.C.P.E.D.; B. SIMPSON, M.R.C.P.E.D.

**Material and Methods**

Our series comprises 21 men aged 18 to 38 and nine women aged 18 to 50; they belonged to a closely knit community and rarely left Hong Kong. Parasitic infestation and bacterial infection of the gastrointestinal tract were excluded by stool examination.

**Haematological methods** were as described by Dacie (1956). Serum folate levels were estimated by the method of Waters and Mollin (1961), the normal range being 6 to 21 m\(\mu\)g./ml., and serum vitamin-\(B_12\) levels by the method of Hutter et al. (1956), the lower limit of normal being 140 m\(\mu\)g./ml.; these tests were performed in the laboratory of Dr. D. L. Mollin at the Hammersmith Hospital.

**Gastric Function.**—In anaemic patients the fasting aspirate was tested for free acid, and if none was present an augmented histamine test meal examination was made (Kay, 1953). **Faecal fat excretion** was measured in at least three consecutive 24-hour specimens of stool by the wet method of van de Kamer et al. (1949), 6 g./day being taken as the upper limit of normal.

**Glucose absorption** was assessed by using an oral dose of 50 g. of glucose, capillary blood specimens being taken and the total reducing substances present being estimated. A rise in
the blood-sugar level of less than 40 mg./100 ml. was taken to indicate defective absorption.

D-Xylose absorption was assessed by the method described by Santini et al. (1961): normal subjects excrete at least 25% of an oral dose of 5 g. in the urine over five hours.

Radiological examination of the small intestine was made with non-flocculable barium (Raybar).

Small-intestinal biopsy specimens were obtained from either the second or third part of the duodenum by means of a Shiner (1956) tube, or from the upper jejunum with a Crosby capsule (Crosby and Kugler, 1957); the specimens were fixed in 10% formalin, and sections were stained with haematoxylin and eosin.

Clinical Findings

Some patients became ill within a month of their arrival in Hong Kong, but in others it was up to two years before symptoms appeared; the duration of illness before admission to hospital was generally between two and six months.

Mode of Onset.—Lassitude and anorexia were the sole initial symptoms in 10 patients, and it was one to four months later before any disturbance of the bowels was noticed. The lassitude was striking, and some of these patients were at first thought to be neurotic. All except one of this group became ill at the beginning of the hot season (April to June), a time when reacclimatization takes place after the cool winter. It is probable that the symptoms were in part due to the stress of reacclimatization, but, in retrospect, their severity suggested that the disease had already started. In five other patients the onset was quite different; they suddenly developed vomiting and watery diarrhoea, suggesting an infective cause, and after antibacterial therapy they seemed to improve temporarily in that their stools decreased in frequency but became more bulky and sometimes frankly steatorrhoeic. In the remaining 15 patients there was an insidious onset of looseness of the stools, which was either constant or intermittent, with tiredness and loss of appetite. Whatever the mode of onset all the patients lost a considerable amount of weight, sometimes as much as 20 kg. This could occur surprisingly quickly, and reflected the severity of their anorexia. Soreness of the tongue was complained of by more than half of the patients and was most common in those who were anaemic.

Physical Examination.—The patients looked thin, pale, and weary, and abdominal distension was common; a few had a frank glossitis, but more often the tongue was furred, with red papillae at the edges. None was severely hypotensive or dehydrated (Fig. 1).

Results of Investigations

Haematological Findings.—The Table shows that 10 of the men were anaemic (Hb<13.5 g./100 ml.) and six of the women (Hb<11.5 g./100 ml.) in six of the men and five of the women the sternal marrow was examined and showed megaloblastic change in the red-cell precursors in each instance. The serum folate level was estimated in three anaemic and four non-anaemic patients and was low in each instance, being in the range 0.7-3 mµg./ml.; the serum vitamin-B12 level was low, but not in the pernicious anaemia range, in three mildly anaemic subjects (140, 145, and 150 µµg./ml.), the duration of symptoms being 1, 12, and 6 months respectively, and was 295 µµg./ml. in one non-anaemic patient who had been ill for two months.

Gastric Function.—Free acid was present in the gastric aspirate of each anaemic patient.

Small-intestinal Function.—The Table shows that faecal fat excretion was above normal in every patient, the range being 6.3 to 38 g. a day. Glucose absorption was below normal in 16 out of 23 patients, and D-xylose absorption in 15 out of 20; even when glucose absorption was in the normal range on admission a substantial improvement was seen after successful treatment.

Small-intestinal Anatomy.—The radiological appearances were abnormal in 17 of the 18 patients who had been ill for three months or more, but were normal in 5 of the 12 with a shorter history. Biopsy specimens were obtained from the upper small intestine in 23 patients, and 18 of these showed partial villous atrophy and five were normal; duodenal (14) and jejunal (nine) specimens gave similar results (Fig. 2).

Treatment and Progress

Three patients (Cases 1-3) recovered on a standard hospital diet which did not contain liver or Marmite, and one of them (Case 3) had a reticulocytosis coincident with her clinical

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**FIG. 1.—Case 14. Left, before treatment. Right, after treatment.**

**FIG. 2.—Example of partial villous atrophy. (Jejunal biopsy from Case 27.)**
Improvement; one still had mild steatorrhoea (see Table) one and a half months later, but none required specific therapy. Signs of recovery were apparent within two weeks of their admission to hospital, whereas four other patients who were observed for over one month showed no similar improvement; we therefore kept all patients under observation for two weeks before beginning specific therapy.

### Antibacterial Drugs

Four patients (Cases 5-8) were treated with successive five-day courses of succinylsulphathiazole 10 g. daily, chlorotetracycline 1 g. daily, and chloramphenicol 1 g. daily. Three responded clinically and there was a marked improvement in absorption within a month, but none showed the immediate

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* Maximum rise in blood sugar per 100 ml. in glucose-tolerance test.  
D = Dilatation and abnormal mucosal pattern.  
M = Abnormal mucosal pattern.  
N = Normal.  
PVA = Partial villous atrophy.  
The results of investigations obtained when the patients were reassessed after treatment are given in parentheses.
improvement in well-being and appetite commonly seen when folic acid was given. The fourth (Case 8) deteriorated and his haemoglobin level fell from 12.2 to 9.9 g./100 ml.; faecal fat excretion declined, but this was probably due to a further decrease in appetite, as glucose absorption did not improve. This experience persuaded us to abandon the use of antibacterial agents as the sole form of therapy.

We found, however, that one patient (Case 13) who responded poorly to folic acid recovered when antibacterial drugs were given in addition, and four other patients (Cases 9–12, all of whom were severely ill) showed an excellent clinical response to this combined form of treatment, with a satisfactory improvement in absorption (see Table). The duration of symptoms in this group was longer than the average, being 4, 6, 12, 5, and 4 months respectively.

Folic Acid

Twelve patients (Cases 13–24) were treated with large amounts of folic acid, given either by mouth in a dose of 20–40 mg. daily for two to five weeks, or by intramuscular injection in a dose of 15 mg. daily for two weeks. In only one instance did this treatment fail (Case 13, described above), and the Table shows that in the others, among whom were the three patients treated in England (Cases 18–20), the clinical response was accompanied by marked improvement in small-intestinal function and anatomy, tests of which showed a return to normal in most instances. The parenteral route of administration appears preferable, for two patients in this group (Cases 23 and 24) responded imperfectly to folic acid by mouth but recovered when intramuscular injections were given.

When, however, a smaller amount of folic acid was given to six patients (Cases 25–30), the dose being 0.2 mg. daily for 14 days by intramuscular injection followed by 15 mg. daily for three days, there was no clinical or biochemical response in two (Cases 25 and 26), a limited response in two others (Cases 27 and 28, the former showing only clinical improvement), and recovery in only one patient (Case 29), whose small intestine was anatomically normal on admission. The sixth patient (Case 30) was not fully reassessed. When three of these patients (Cases 23–27) were given larger doses of folic acid the defects of absorption cleared, and the biopsy appearances returned to normal in the two who had shown partial villous atrophy on admission. These results suggest that the intestinal response to folic acid treatment is dose-dependent to the extent that 50 mg. over two weeks is insufficient, whereas four times this amount is usually effective.

The haematological response to 0.2-mg. doses was good in the two anaemic patients treated in this way (Cases 27 and 30), both having a reticulocytosis and rise in the haemoglobin level.

Follow-up

All the patients were symptom-free and had regained their lost weight when they returned to normal and often arduous work. Some then became tired and depressed, but three who were reinvestigated showed no evidence of anaemia or malabsorption, and these complaints gradually settled over a few months. Even though long-term treatment was not given, none of the patients relapsed during the remainder of their stay in Hong Kong, a period of up to two and a half years.

We cannot claim a certain cure, for malabsorption of vitamin B₁₂ was a constant feature in similar patients seen in Singapore by O'Brien and England (1964), and, as deficiency of this vitamin may become the dominant feature in chronic tropical sprue (Mollin 1961, reporting work done by Dr. C. C. Booth and himself), the restoration of normal absorption of this vitamin should be demonstrated before complete correction of the intestinal lesion can be accepted. In view of the other evidence, however, it seems unlikely that our patients will progress to the chronic stage of the disease.

Discussion

Our findings show that in Hong Kong the mode of onset of tropical sprue is variable. The patients in whom early diagnosis was most difficult were those who presented with lassitude and anorexia at the beginning of the hot season; it is important that the significance of these symptoms be appreciated, as treatment at this stage of the illness might result in a speedy cure. It is of interest that Ayre (1947) noted a similar occurrence in India when soldiers moved to a different climatic environment, whereas workers in countries which have a relatively stable climate, as in Puerto Rico, do not describe this type of presentation. The part played by climatic change in the causation of tropical sprue in these patients is uncertain.

Spontaneous remissions during the course of the illness have been well recognized since the time of Hillary (1766), and three of our patients (Cases 1–3) illustrate the fact that after admission to hospital a complete recovery may be seen; this means that a preliminary observation period of two weeks is necessary to establish a base-line before the effects of drug therapy can be validly assessed.

Our results with antibacterial therapy were clinically less striking than those obtained by French et al. (1956), who made a careful study of similar patients treated with the same drugs in England, and one patient (Case 8) deteriorated clinically and histologically during this therapy. One possible explanation is that if, in tropical sprue, the small intestine is invaded by pathogenic bacteria then these organisms may alter and become more susceptible to antibacterial drugs when the patient returns to a temperate climate. Alternatively, if the suggestion of Klipstein (1964) is accepted that this form of treatment is effective only when the patient receives an adequate amount of folic acid in his diet, it may be that our subjects were given less folic acid in their food, or ate less owing to a more severe loss of appetite.

We did, however, find that one patient (Case 13), whose symptoms had been present for four months, responded better to combined antibacterial and folic acid therapy after folic acid alone had failed; and four others, whose symptoms had been present for 4 to 12 months, responded very well to this regimen. In this regard it is of interest that Frazer (1958) reported that a third of the patients from Hong Kong responded only partially to folic acid and required antibacterial drugs in addition before a full recovery was obtained. Further, the results of Sheehy et al. (1965) in North American patients who contracted tropical sprue in Puerto Rico show that treatment with folic acid and vitamin B₁₂ was effective in those whose symptoms had been present for two months but not in those who had been ill for seven months. Thus it is possible that when the length of history exceeds three to four months antibacterial therapy may be needed in addition to folic acid if an optimal response is to be obtained.

Large doses of folic acid, amounting to a total of at least 200 mg. given over two weeks, reversed the intestinal lesion in nearly all of the 12 patients treated in this way, and this finding confirms the previous encouraging reports from Hong Kong by Rosenthal (1952) and Webb (1956). But when a total of less than 50 mg. was given there was a poor response as regards the small-intestine lesion, even though smaller doses than this are known to produce a haematological response (Sheehy and Floch, 1964; O'Brien and England, 1964) and did so in two of our patients. This suggests that the blood-forming tissues take up folate preferentially to the small-intestinal mucosa (assuming that the latter utilizes folate directly), or it may be that the needs of the intestinal epithelium are much greater.
Our results show that the prognosis of expatriate patients treated in Hong Kong and remaining there is excellent for at least two and a half years. Long-term follow-up studies in tropical sprue are rare. Hazari and Woodruff (1958) reported that 17 patients who had contracted tropical sprue in India 10 years previously and had been evacuated to Britain were all at full work, although some third of these had mild and intermittent symptoms but were not disabled by them. As more effective forms of treatment were available to our patients their outlook should be at least as good, but this point will need to be established.

Summary

Thirteen patients who contracted tropical sprue in Hong Kong are described. Nine of them became ill at the beginning of the hot season with initial complaints of lassitude and anorexia without disturbance of the bowels, and the significance of these early symptoms is stressed.

Treatment with antibacterial drugs was not as effective as treatment with large doses of folic acid, but it is suggested that some patients who have been ill for more than three months may require both forms of therapy before an optimal response is obtained.

It was confirmed that folic acid usually reverses the intestinal lesion in these patients provided an adequate amount of the drug is given; a total of less than 50 mg. was generally ineffective.

Twenty-six patients remained in Hong Kong for periods of up to two and a half years after treatment, and none relapsed.

We are deeply indebted to many medical and nursing colleagues who worked with us; to Professor A. C. Frazer, who advised on sprue research in Hong Kong and who has permitted us to include data on four cases which were transferred to his unit in Birmingham; and to Dr. A. C. Hobson (then Lieutenant-Colonel R.A.M.C.), who handed on the sprue project in Hong Kong to one of us (J. F. W.). We are also grateful to Lieutenant-Colonels S. A. Biggart and C. B. F. Downie, R.A.M.C., who were in charge of eight of the patients investigated. Dr. B. C. Morson and Lieutenant-Colonel N. W. E. J. Floch, R.A.M.C., have been most helpful in reviewing the small-intestinal biopsy specimens, and Professor D. L. Mollin and Colonel W. O’Brien, late R.A.M.C., have given us invaluable advice and helpful criticism throughout the preparation of this paper. Finally, we would like to thank the Director-General Army Medical Services for permission to use case notes and records for this publication.

REFERENCES


Hypoproteinaemia in Anaphylactoid Purpura

N. F. Jones,* M.A., M.B., M.R.C.P.; B. Creamer† M.D., F.R.C.P.; T. M. D. Gimlette‡ M.D., M.R.C.P.


Anaphylactoid (Henoch–Schönlein) purpura may produce a nephrotic syndrome and thus cause hypoalbuminaemia. However, some years ago we observed a patient with this disease in whom the serum albumin level was reduced at a time when urinary losses of protein were insignificant. Evidence of liver dysfunction was absent, but gastrointestinal complications of the disease were prominent. It was therefore suspected that the hypoalbuminaemia was due to abnormal losses of protein into the bowel. We here record observations on five patients with anaphylactoid purpura which suggest that protein-losing enteropathy may complicate this disease. This association does not seem to have been reported to date (Waldmann, 1966).

Methods

Loss of protein via the gut was assessed by measuring the radioactivity present in a five-day collection of faeces after the intravenous injection of 131-I-P.V.P. or 51CrCl2. The former was used according to the method of Gordon (1959) with 131-I-P.V.P. obtained from the Radiochemical Centre, Amersham. The use of 51CrCl2 followed the method of Rubini and Sheehy (1961).

Normal values obtained in this hospital for faecal excretion of radioactivity in these tests are given in the Table; they

<table>
<thead>
<tr>
<th>Serum Albumin Levels and Associated Features of Five Patients with Anaphylactoid Purpura</th>
<th>Gastro-intestinal Symptoms</th>
<th>Faecal Excretion (% of dose)</th>
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* Tr. = Trace with salicylsulphonic acid.
† Physician, St. Thomas’s Hospital, London.
‡ Chief Clinical Assistant, Radiisotope Department, St. Thomas’s Hospital, London.

Highest value in 7 control subjects | 0-0-28 | 0-28 |