- Starr, P. (1958). *Arch. intern. Med.*, **101**, 722.
 — (1959). *Proceedings of Symposium on Sodium Thyroxine*, Chicago, p. 49.
 — (1960). *J. clin. Endocr.*, **20**, 116.
 — (1961). *Proceedings of 4th International Goitre Conference*, 1960. In press.
 — and Lepp, A. (1960). *Proceedings of Symposium on Derivatives and Isomers of Thyroid Hormones*, Philadelphia, p. 49.
 — and Liebhold-Schueck, R. (1953). *Arch. intern. Med.*, **92**, 880.
 Tapley, D. F., Davidoff, F. F., Hatfield, W. B., and Ross, J. E. (1959). *Amer. J. Physiol.*, **197**, 1021.
 Zlatkis, A., Zak, B., and Boyle, A. J. (1953). *J. Lab. clin. Med.*, **41**, 486.

LONG-CONTINUED INHIBITION OF GASTRIC SECRETION BY POLDINE METHOSULPHATE IN PATIENTS WITH PEPTIC ULCER

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Antacids are widely used to control pain and promote healing in patients with peptic ulcer. Although antacids, provided they are taken often enough and in large quantities (Clark and Hunt, 1958), are unquestionably effective in maintaining a lowered acidity in the gastric contents during the day, they have no influence on the acidity of the gastric contents during sleep. Instead of neutralizing the acid after it is secreted, it would seem better to try to inhibit the secretion of acid continuously even when the patient is in remission. This paper is concerned with treatment of patients with peptic ulcer along these lines, using an anticholinergic substance, poldine methosulphate ("nacton"), which reduces by about one-half the gastric secretion of acid without producing noticeable side-effects.

Present Investigation

In-patients of a previous trial (Douthwaite and Hunt, 1958) and several new patients have been followed as out-patients for periods up to three years. All those studied were admitted to the wards under the care of the consultant physicians because a full course of medical treatment under the best conditions was necessary. With the permission of the clinicians concerned, the trial was discussed with the patients. All except one of those approached accepted the offer.

Relevant facts about the patients, who are all men, are summarized in Table I. The mean duration of their dyspepsia was 10 years, two patients had gastric ulcers and 14 had duodenal ulcers. For the most part the diagnosis rested on the clinical history and radiology. In two there had been a perforation and in two others melaena. Ten had lost more than five weeks from work.

Procedure.—The patients were studied in the wards with test meals first while on dummy tablets and then on poldine, the dose being slowly increased until the patients noted some side-effect attributable to anti-

cholinergic action. The amount was then reduced by 1 mg., or occasionally 2 mg., for each of the four daily doses, until the side-effect was abolished. During their treatment as in-patients they received in addition diets and antacids in accordance with the custom of the clinicians concerned. On their discharge, arrangements were made for the patients to attend for a test meal once a month, having taken their poldine on rising. On these occasions they were encouraged to report even mild dyspeptic symptoms that had occurred during the previous month. Their food was entirely of their own choosing, and antacids in the form of "prodexin" were made freely available.

Test-meal Method.—The method used for assessing the effect of poldine on gastric secretion has been described by Douthwaite and Hunt (1958). In essence it allows the total amounts of acid and chloride secreted in response to a test meal in 30 minutes to be measured by adding the amounts of acid and chloride recovered from the stomach to the amounts calculated to have passed into the duodenum. The amounts of acid and chloride can then be converted into the volumes of the acid component and the volumes of bicarbonate-containing secretion formed by the stomach (Hunt, 1954). The test-meal consists of 750 ml. of a solution containing 50 g. of glucose per litre, which is given down a tube into the stomach after an initial washout.

Dose of Poldine and its Side-effects

The dose of poldine was adjusted for each patient so that he did not notice any side-effects, such as dryness of the mouth, slowness in passing urine, or blurring of vision. As experience accumulated it became apparent that there were sometimes other side-effects that might indicate overdosage.

One patient took a double dose of poldine by accident and complained of severe headache, which ended very abruptly. One patient (Case 5, Fig. 2) noted eructations in the afternoon with an unpleasant odour after eating eggs. The symptom disappeared on reducing the dose. One patient reported reduced potency in the sexual act without loss of libido. As he was able to judge which of two lots of tablets were dummy, using his potency as an index, it was presumably a genuine side-effect. The other patients have not had the same experience. Potency was restored by a small reduction of the evening dose. One man, aged 35, noted slight breathlessness as a possible side-effect. No one noted constipation as a side-effect, although physicians using larger doses of poldine have reported it in their patients.

Tachycardia and extrasystoles, both unnoticed by the patients, have been found. It has been taken as a general rule, possibly overcautiously, that the heart rate should not be allowed to exceed 90 a minute at about two to three hours after the last dose of the drug. This has been made the limiting factor for 3 patients out of 16. In two patients extrasystoles were found occasionally, these were abolished by reducing the dose of the drug.

In one patient (Case 8), who had an excessive hypersecretion before treatment, it appeared that in spite of dryness of the mouth, the gastric effect of the drug was sometimes inadequate to relieve his symptoms. He was given his treatment in five divided doses instead of four, and in this way was able to take more poldine with fewer side-effects and with concurrent more effective control of his dyspepsia. Presumably, by giving the poldine more frequently the concentration at the

sites of action was kept more stable. Early experience with poldine given eight-hourly indicated that six-hourly doses were desirable even though the drug was clearly inhibiting gastric secretion eight to ten hours after the last dose. With the single exception of Case 8, it has never appeared that reducing the dose to eliminate side-effects has simultaneously caused an increase in gastric secretion of acid. Thus from experience we conclude that side-effects indicate that the dose is larger than need be. From time to time the dose for each patient has been raised, but in most instances it has been necessary to reduce it again because of side-effects. Thus, apart from the increase in tolerance noted during the first three weeks of treatment, there has been no significant change during the three years of this study.

Results

It may be seen from Table I that 14 out of the 16 patients taking a mean dose of 30 mg. of poldine a day have been followed for three years or more at the time of writing (February, 1961). The follow-up is complete except for three patients not referred to in Table I. The diagnosis for one of them was proved to be wrong. One patient followed the treatment for three months only, although dropping in afterwards from time to time to say that he was still having bouts of dyspepsia. Eventually he was admitted into the surgical wards for gastrectomy, but at the operation the stomach and duodenum were apparently normal, so that nothing further was done. When last seen he was well. One other patient was not followed because he did not take the drug regularly.

Column 8 of Table I shows a fraction, the numerator being the number of occasions on which the patient reported that since his previous visit there had been no dyspepsia, nausea, or any other symptom associated with his peptic ulcer. The denominator is the total number of visits. There were reports of complete freedom from dyspepsia in 83% of the 429 months at risk. This part of the study was started after the patients had been taking a placebo for one or two months in order that toxicity could be sought. For this purpose

comparisons were made between data for full blood counts, urine analyses, serum bilirubin, and blood urea after the patients had been taking poldine for periods of up to 12 months, and after they had been on dummy tablets for one to two months. A careful study of these data revealed no evidence of toxicity.

All the patients were convinced that they were much better while taking poldine than they were before. As objective evidence for clinical improvement, it may be seen from Table I that since the beginning of treatment the total loss of time from work with dyspepsia had been two days in Case 5, four days in Case 12, and 14 days in Case 13. This loss of working-time should be compared with that noted in the previous column: the mean loss of work before treatment was four weeks per annum per patient. The patients were advised to take antacids if they had even mild dyspepsia. On each visit they were offered a supply of prodexin, but the majority, Cases 3, 8, and 16 excepted, said that the supply they had at home remained untouched.

Fig. 1 contains the data for Case 14 on the gastric secretion of acid in response to test meals at about monthly intervals for the three years of treatment. This record is given because it shows the increase in gastric secretion of acid two days after the patient's father had died tragically. Shay, Sun, Dlin, and Weiss (1958) found that an anticholinergic drug blocked the response to stress. As the response of our patients to a comparable tragedy without poldine methosulphate is not known, our data are not relevant to this point. Fig. 2 shows similar data for Case 5. The pain in this patient seems to be related to his domestic circumstances and he shows rather regular changes of gastric secretion with time. When he began to complain of eructations it seemed possible that poldine was reducing the efficiency of the cardia, as does atropine (Bettarello, Tuttle, and Grossman, 1960). When the dose was reduced there was no corresponding increase in gastric secretion, but the eructations did not recur. So far as it goes, this sequence of events is consistent with the possibility that a suitable dose of poldine could reduce gastric secretion of acid without increasing oesophageal reflux in patients subject to it.

TABLE I.—*Clinical Data on Patients Taking Poldine*

Case No.	Age	Beginning of Dyspepsia	Duration of Longest Remissions before Treatment with Poldine	Diagnosis	Beginning of Treatment with Poldine	Dose of Poldine mg. day	No. of Months Free of Dyspepsia No. of Months at Risk	Patient's Comments	Time Off Work before Treatment with Poldine	Time Off Work after Treatment with Poldine
1	31	1957	1-8 weeks	D.D.	5/59	40	12/13 I	Completely unaware of digestive organs	20 weeks	Nil
2	39	1956	1 year	G.U.	9/57	28	22/27 I	One 14-day period with pain, 1960	3 "	"
3	47	1945	12 weeks	D.D.	12/57	24	22/32	Almost always free of pain. No trouble in cold weather	2-4 weeks/year	"
4	65	1956	3 days	D.D.	4/57	28	30/31	Free of trouble	9 weeks	"
5	31	1950	5 weeks	D.D.	9/57	32	22/32	Occasional mild pains only	At least 20 weeks	2 days
6	66	1955	Continuous	M. D.D.	9/57	16	26/29 I	Free of trouble	3 weeks	Nil
7	28	1955	4 days	Pyloric ulcer	5/59	38	10/12 I	No pain or sickness	Not assessable, because a casual worker	"
8	48	1954	3 years	P.D.U.	11/57	50	21/33	Occasional mild distress	210 days since 1954	"
9	48	1952	4 weeks	M. D.U.	7/57	24	29/30 I	No pain even on night shift	3 weeks	"
10	29	1953	2 "	D.D.	6/57	36	21/24 I	Almost always free of pain	5 "	"
11	35	1953	3 "	D.D.	2/58	24	19/23 I	Eats and drinks without fear. Never so well before	3 weeks/year	"
12	26	1951	3 weeks after perforation, then 18 months	P.D.U.	8/57	26	19/24	Some pain before marriage	100 days in hospital 1951-7	4 days
13	31	1946	12 weeks	D.D.	2/58	44	23/29	Pain on occasional days	100 days since 1956	14 "
14	32	1945	12 "	D.D.	8/57	44	24/28	Usually free of pain, occasional 2-day upsets	5 weeks	Nil
15	54	1926	2 years	G.U.	6/57	12	26/32	Usually free of pain	6-8 weeks/year since 1943	"
16	37	1953	12 weeks	D.D.	8/57	28	23/30	Occasional mild pain	10 weeks	"

D.D.=deformed duodenum. G.U.=Gastric ulcer. M.=Melaena. P.D.U.=Perforated duodenal ulcer. I=Recent radiological evidence of less deformity of duodenum.

Relation Between Radiological Studies and Clinical Response

Recently one of us assessed radiologically the change in the degree of deformity of the duodenal cap in the 14 patients with duodenal ulcer.

In six patients comparison of serial views taken before this trial was started showed that the degree of deformity of the duodenal cap had decreased. Presumably this was due to the fact that at least part of the initial deformity was caused by spasm associated with ulceration, and that this spasm was no longer present. It was therefore assumed that the above represented radiological evidence of an improvement. In eight cases

FIG. 1.—Case 14. Data on symptoms and gastric secretory responses to test meals at monthly intervals on poldine. P=Pain. O=Father died tragically. T=Tachycardia.

FIG. 2.—Case 5. Data on symptoms and gastric secretory responses to test meals at monthly intervals on poldine. E=Eructations. P=Pain. H=Heartburn. V=Vomiting.

there was no noticeable change, and it was therefore not considered possible to assess the true condition of the duodenal cap. If the initial deformity was in fact due to scarring, although the patient's present condition might suggest an improvement, the radiological findings were bound to remain unchanged. If ulceration and spasm played some part in the original deformity, the fact that this had persisted might suggest that spasm and/or ulceration were still present. There was no evidence of a crater or residual deformity in the two patients with a history of gastric ulceration.

Those patients in whom the deformity became less are marked in column 8 of Table I with the symbol I. It was found that those with radiological improvement in their duodenal caps had significantly more months free of dyspepsia—89% as compared with 77%—than those with duodenal caps unchanged. This difference is statistically significant at the one-in-fifty level. It may also be seen from Table I, column 9, that the patient's assessment of his response was particularly favourable in these six patients. There was, however, no evidence

that poldine was more effective in reducing the secretion of acid in these patients than in the others.

Studies of Gastric Secretion and Emptying

The method of studying gastric secretion allows the amount of two hypothetical components of gastric secretion—the parietal and non-parietal—to be assessed separately. The parietal component is regarded as containing 160 mN hydrochloric acid, which is the concentration at which it is supposed to be secreted by the parietal cells. The non-parietal component, formed by the mucus-secreting cells of the whole gastric mucosa, is thought to contain 45 mN bicarbonate. In effect this means that 3.6—160/45—parts of non-parietal component neutralize 1 part of parietal component. The result is that failure to recover acid from the stomach is assessed by this method as due to the secretion of some parietal component balanced by 3.6 times as much non-parietal component.

This report deals with 351 studies of gastric function during out-patient treatment and 58 control studies while the patients were taking dummy tablets as in-patients and out-patients.

It may be seen from Table II, columns 4 and 5, that there was about half as much secretion of the acid parietal component when the patients were taking poldine as when they were taking dummy tablets. It seemed possible that a selected group of the patients—for example, those with marked hypersecretion—would be specially sensitive to the action of poldine, so that their secretion would be more inhibited than that of patients with lower secretions of acid. To test this view the mean amount of parietal component secreted while a patient was receiving dummy tablets was plotted against the mean amount secreted while he was taking poldine tablets as an out-patient. The data for the 16 patients are shown in Fig. 3. It may be seen that the data fit reasonably well on to a straight line, so that there is no evidence that the drug is more effective in inhibiting secretion in hypersecretors than it is in those with lower rates of secretion. It may also be seen that the slope of the line is such that for each 2 ml. of secretion with dummy tablets there is 1 ml. while the patients are taking poldine.

On the other hand, the secretion of non-parietal component was reduced by only 22%, so that the acidity of the mixed parietal and non-parietal components, the gastric juice, fell from a mean of 100 mN without poldine to 74 mN with poldine.

TABLE II.—Effect of Poldine on Gastric Secretion and Emptying with Test Meals of 30 Minutes' Duration

Case No.	Volume of Gastric Contents (ml.)		Volume of 0.16 N HCl Secreted (ml.)		Volume of 0.045 HCO ₃ ⁻ Secreted (ml.)		Concentration of Acid in Gastric Juice (mN)	
	D.	P.	D.	P.	D.	P.	D.	P.
1	410	364	83	29	53	32	80	52
2	290	355	50	19	46	41	61	20
3	540	502	97	58	40	30	100	90
4	270	170	103	57	19	17	128	112
5	545	400	69	15	32	24	95	33
6	440	445	67	42	32	23	94	87
7	385	446	47	16	27	24	85	37
8	452	510	155	83	50	40	110	93
9	354	374	75	38	24	17	110	96
10	480	500	32	22	20	20	81	62
11	433	396	88	39	27	16	112	100
12	233	395	93	46	27	27	114	84
13	328	383	94	36	18	17	127	94
14	340	310	91	35	32	26	107	72
15	283	272	55	20	30	23	88	50
16	372	382	103	66	33	33	110	92
Means	384	387	81	39	32	25	100	73

D.=Dummy. P.=Poldine.

The mean volume of the gastric contents remaining in the stomach after 30 minutes, which may be regarded as an index of gastric emptying, was unchanged by the treatment with poldine.

Discussion

The main object of this trial was to determine whether poldine would be effective in reducing the gastric secretion of acid in patients with peptic ulcer going about their ordinary life. To judge from our data, poldine reduces gastric secretion by about one-half two to three hours after the drug is taken. In an earlier study of patients in hospital (Douthwaite and Hunt, 1958) it was found that the gastric secretion of acid was 45% of the control two to three hours after the dose and 60% of control 8 to 9 hours after the dose. From this finding and our current data, it is reasonable to assume that with four doses a day there will be a reduction of the secretion of acid at all times. This expectation is confirmed by the results of a few tests in our out-patients when they did not take their morning dose.

The data quoted above refer only to the reduction in the amount of parietal secretion formed in response to a glucose solution which probably stimulates by distension (Hunt and Macdonald, 1952). However, in further studies in conjunction with Drs. M. I. Grossman and R. D. Mitchell it has been found that there is with poldine a large reduction of the acidity of the gastric contents after an appetizing breakfast. In addition, Dr. Leonard Jones, in a communication to the Gastroenterological Society in 1960, reported that poldine caused a significant reduction of acidity in the gastric contents with meals of milk which were found by Douthwaite and Hunt (1950) to be powerful stimuli to gastric secretion in patients with duodenal ulcer. Finally, Seidelin (1961) has reported a reduction of about 50% in basal secretion and in the response to maximal stimulation with histamine in patients with duodenal ulcer receiving doses of poldine adjusted to give no side-effects. It is usually a fair generalization to say that any means which reduces the response to "maximal" doses of histamine will reduce the response to all stimuli. Thus Seidelin's report probably applies to secretion in response to food.

When a drug reduces the amount of acid parietal component secreted in response to a standard stimulus, a corresponding or greater reduction in the secretion of the alkaline non-parietal component may leave the concentration of acid in the mixed secretions—that is,

the gastric juice—unchanged or even increased. In our studies, however, the secretion of the non-parietal component fell by a smaller proportion than the secretion of parietal component, so that the mean concentration of acid in the gastric juice fell from 100 mN to 74 mN.

Poldine had no action on gastric emptying in our patients. However, this is no disadvantage, since it has not been possible to show that gastric emptying in patients with duodenal ulcer is different from that of healthy young persons (Hunt, 1957a, 1957b). The specificity of the action of poldine on gastric secretion is possibly an advantage, since slow emptying may increase the duration of gastric distension and contact of food with the antral mucosa, both of which may be expected to stimulate secretion.

Clinical Results of Treatment with Poldine

The clinical data in Table I show that our 16 patients lost a total of 20 days' work during the three years of the trial, while before they began treatment the mean absence from work was four weeks per patient per annum. Had our patients not improved clinically, we could have concluded that poldine was not useful in our context. The great reduction of loss of time from work does not logically allow us to conclude that the degree of reduction of acidity achieved with poldine is clinically useful. A full course of medical treatment in hospital followed by regular visits to an interested doctor, the continuous taking of tablets in an atmosphere of hope, and the knowledge that their gastric secretion was reduced, might all be expected to play a part in producing clinical improvement. However, some of these factors must always operate when patients with duodenal ulcer are given continuous medication.

Pharmacologically, poldine methosulphate was effective in reducing gastric secretion of acid without side-effects in out-patients for periods up to three years, since there was a return to control levels when dummy tablets were given for a month. Our clinical data are also consistent with poldine being therapeutically effective in reducing the duration and severity of dyspepsia in patients with duodenal ulcer and in greatly reducing the time they are away from work. However, the causal relationship between the reduction in gastric secretion of acid in patients with duodenal ulcer and the improvement in their clinical course remains open.

Clinical Use of Poldine

The following points are important in the effective use of poldine:

1. The dose should be given on rising, at 12 noon, at 6 p.m., and on retiring.
2. The dose should be built up gradually from 2 mg. per dose, and the total daily amount increased by 4 mg./day at four-day intervals.
3. Once definite side-effects are noted the dose should be reduced by 1 mg. or sometimes 2 mg. until they are no longer noted.
4. From our experience, a dose producing severe side-effects is not usually more effective in reducing gastric secretion of acid than a dose producing no side-effects.
5. Because poldine is pharmacologically active the dose should be carefully adjusted for each patient, and he should be seen at least at monthly intervals until it is clear that there is no undue tachycardia. Once the dose has been decided by trial, tolerance does not develop.

FIG. 3.—Comparison of gastric secretory responses to test meals by patients with and without poldine. Data based on 58 tests with dummy tablets and 351 tests with active tablets.

6. Should it be necessary to stop giving poldine for some days—for example, during pyrexia—it is important to build up the dose again gradually to avoid the possibility of marked side-effects on restarting with a full dose. In every instance the omission of one dose has abolished all side-effects.

7. The full effect of the drug on gastric secretion and on symptoms may take up to 21 days to appear. In the meantime the dyspepsia can be treated with antacids.

8. It is important to realize that poldine does not completely abolish the dyspepsia in all patients. In our experience it greatly reduces the number of occasions on which there is pain and it reduces the severity of the pain. However, overwork—for example, decorating a flat in the evening, long hours of overtime in a bank, or concreting a garden path—has raised the gastric secretion in response to test meals on the following day, and sometimes apparently caused dyspepsia in spite of continuous treatment with poldine. It is remarkable how slow even intelligent patients are in relating their symptoms to overwork. They have in our experience always responded to antacids.

Summary

Fourteen men with duodenal ulcers and two with gastric ulcers have been studied for a mean period of three years.

During this time they have been under treatment with four daily doses of poldine methosulphate ("nacton") just small enough to produce no side-effects. No tolerance developed.

The secretion of acid, as assessed at monthly intervals with test meals, was reduced by one-half by the drug as compared with the secretion with dummy tablets. There was no change in gastric emptying.

The patients were free of dyspepsia for four-fifths of the months of treatment. As compared with an average absence from work of four weeks per patient per annum before treatment, the mean loss of time from work was half a day per annum during the three years of the study. During this period the deformity of the duodenum was reduced in 6 out of 14 patients with duodenal ulcer. These six had less dyspepsia than the others.

The trial has established that poldine can reduce the secretion of acid by about one-half in out-patients with peptic ulcer. Simultaneously, dyspepsia and loss of time from work were much reduced. The trial does not establish that the reduction of secretion of acid and the clinical improvement are cause and effect, although the results are consistent with this view.

We thank Drs. C. G. Baker, E. R. Boland, R. Kauntze, K. S. Maclean, and W. N. Mann for their co-operation in our studies of patients under their care. We are indebted to Beecham Research Laboratories Ltd. for generous supplies of nacton (poldine methosulphate) and prodexin (aluminium glycinate and magnesium carbonate).

REFERENCES

- Bettarello, A., Tuttle, S. G., and Grossman, M. I. (1960). *Gastroenterology*, **39**, 340.
 Douthwaite, A. H., and Hunt, J. N. (1950). *Lancet*, **1**, 1019.
 — (1958). *Brit. med. J.*, **1**, 1030.
 Clark, T., and Hunt, J. N. (1958). *Practitioner*, **180**, 334.
 Hunt, J. N. (1954). *Guy's Hosp. Rep.*, **103**, 161.
 — (1957a). *Lancet*, **1**, 132.
 — (1957b). *Brit. med. J.*, **1**, 681.
 — and Macdonald, I. (1952). *J. Physiol. (Lond.)*, **117**, 289.
 Seidelin, R. (1961). In press.
 Shay, H., Sun, D. C., Dlin, B., and Weiss, E. (1958). *J. appl. Physiol.*, **12**, 461.

ORAL TREATMENT OF PERNICIOUS ANAEMIA WITH VITAMIN-B₁₂-PEPTIDE

BY

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The earliest treatment of pernicious anaemia was the inclusion of large quantities of liver or kidney in the patient's diet (Minot and Murphy, 1926; McCann, 1929). Oral administration of extracts and digests from these organs followed (Porter *et al.*, 1929; Davidson, 1932; Davis *et al.*, 1943), and remissions were also obtained by giving desiccated hog's stomach (Sturgis and Isaacs, 1929; Sharp, 1929; Wilkinson, 1930, 1949). All of these preparations, though effective, were unpleasant and could not be sterilized. They were therefore largely replaced by parenteral injections of liver extract and later of cyanocobalamin (vitamin B₁₂). Small amounts of the latter have been combined with extracts of desiccated hog's duodenal and pyloric mucosa to provide palatable oral substitutes, but in spite of good initial therapeutic results most long-term maintenance studies have shown high relapse rates (Adams, 1957; Bastrup-Madsen, 1957; Killander, 1957; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Berlin *et al.*, 1958; Pedersen and Ebbesen, 1958; Stokes and Pitney, 1958; Blackburn *et al.*, 1959; Ellenbogen *et al.*, 1960).

Orally administered crystalline vitamin B₁₂ alone, either in single massive doses of 3,000–9,000 µg. or in smaller daily doses of 5–50 µg., have been shown to produce rises in haemoglobin concentration, red-cell count, and packed cell volume when given to cases of pernicious anaemia in relapse (Chalmers and Hall, 1954; Estren and Wassermann, 1956). Clinical and haematological remissions have been maintained by giving orally 1,000–3,000 µg. every one to four weeks (Conley and Krevans, 1955; Reisner *et al.*, 1955; Unglaub and Goldsmith, 1955) or 50–500 µg. each day (Chalmers and Shinton, 1958; Brody *et al.*, 1959; McIntyre *et al.*, 1960). However, with doses less than 150 µg. daily or 1,000 µg. weekly the serum vitamin B₁₂ concentration remained abnormally low in some patients.

It has more recently been claimed that patients with pernicious anaemia can be adequately maintained on oral daily doses of 10 µg. of vitamin B₁₂ when the latter is combined as a peptide complex derived from fermentation (Heathcote and Mooney, 1958). This has since been disputed by Varadi and Elwis (1960). Having made a study of orally administered crystalline vitamin B₁₂ alone in cases of pernicious anaemia (Chalmers and Shinton, 1958), the opportunity was taken of making a comparison, using identical dosage and test methods, with this vitamin-B₁₂-peptide in similar patients.

Materials and Methods

Seventeen consecutive cases of pernicious anaemia in relapse were studied. The diagnostic criteria included macrocytic anaemia, megaloblastic erythropoiesis, histamine-fast achlorhydria, absence of steatorrhoea or other known cause of megaloblastic anaemia. All had serum-vitamin-B₁₂ concentrations below 100 µg./ml. At the start of the trial none showed any neurological mani-