marked nitrogen retention after the administration of H.G.H. to a patient with Cushing's syndrome.

There are conflicting reports on the usefulness of measuring the metabolic response to H.G.H. in predicting the growth response to long-term H.G.H. therapy. Prader *et al.* (1964), using a dose of 2 mg./sq. m. body surface area daily (Raben preparation), found that four primordial dwarfs sustained only slight nitrogen retention with H.G.H. and failed to respond to long-term therapy, while six out of nine hypopituitary dwarfs who all sustained marked nitrogen retention showed a satisfactory acceleration of growth with long-term H.G.H. therapy. The three exceptions were patients who developed high titres of antibody to H.G.H. in the course of treatment. We have followed the growth response of only four patients, but it did appear that, in them, the degree of nitrogen retention was related to their subsequent course. Wright *et al.* (1965), using a Wilhelmi preparation 5 mg. daily, however, were unable to find any parameter in the metabolic response which was of use in predicting subsequent growth response, with the possible exception of minimal nitrogen retention, which was associated with failure of acceleration of growth with chronic H.G.H. therapy.

Summary

The acute metabolic response to injected human growth hormone (H.G.H.) has been compared in seven patients with panhypopituitarism, six cases of idiopathic dwarfism, three cases of gonadal dysgenesis, three patients dwarfed as a result of chronic corticosteroid treatment, one case of Cushing's syndrome, and three adults without pituitary disease. Change in blood urea appeared to be the most sensitive factor.

The acute metabolic response was greater in patients with hypopituitarism than in those without primary pituitary disease.

Measurements of endogenous H.G.H. in response to insulin hypoglycaemia were made in 15 subjects. The acute metabolic response to injected H.G.H. was greatest in those with no measurable serum H.G.H. in response to insulin.

The relevance of the acute metabolic response to the linear growth response was examined in four patients who received long-term treatment with H.G.H. Growth was accelerated only in the three patients showing marked nitrogen retention during the acute metabolic test.

Under the Human Pituitary Subcommittee of the Committee of Clinical Endocrinology of the M.R.C. the H.G.H. was prepared by Dr. Anne Hartree, Department of Biochemistry, University of Cambridge, and ampouled, assayed, and tested for sterility and pyrogens by Drs. D. R. Bangham, P. M. Cotes, M. P. Stack-Dunne, and G. W. Bissett, Division of Biological Standards, Medical Research Council. Growth measurements were made by Professor J. M. Tanner and Mr. R. H. Whitehouse at the Institute of Child Health, University of London.

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Chronic Intestinal Ischaemia

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[WITH SPECIAL PLATE]

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When thrombosis of the superior mesenteric artery occurs with acute infarction of bowel the mortality rate approaches 100% in untreated cases and is over 90% in those treated surgically (Mavor *et al.*, 1963). The acute episode is preceded by prodromal symptoms of intestinal ischaemia in approximately 50% of cases (Dunphy, 1936). If these symptoms can be recognized, direct arterial surgery may avert the inevitable arterial occlusion and save life (Morris *et al.*, 1962). The provisional diagnosis of mesenteric ischaemia may be confirmed

by lateral aortography of the abdominal aorta, but the principal difficulty in diagnosis is a failure to suspect that the presenting symptom pattern may be due to ischaemia of small bowel.

In most cases of chronic intestinal ischaemia due to atherosclerosis at least two of the three principal arteries to the alimentary tract must be stenosed or occluded before symptoms result (Morris *et al.*, 1962), but Morris *et al.* (1966) reported 6 out of 31 cases in which a lesion of the coeliac axis alone was the cause of symptoms. Marable *et al.* (1966) reported three cases of stenosis of the coeliac axis caused by constricting bands without superior or inferior mesenteric abnormality. This was the cause of ischaemic foregut symptoms in one of our cases.

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We also report three cases of superior mesenteric occlusion and one case in which all three vessels were severely affected by atherosclerosis.

Case 1

A man aged 56 attended in October 1962 complaining of epigastric pain of one year's duration relieved by defaecation. He had occasional diarrhoea with yellow stools, and had lost 21 lb. (9.5 kg.) in weight. He had had coronary artery thrombosis in 1951 and 1954. Examination showed a thin, poorly nourished man with no specific findings, and a provisional diagnosis of malabsorption or alimentary carcinoma was made.

The principal laboratory investigations are listed in the Table. Test for faecal occult blood was negative, and barium-meal examination showed a malabsorption flocculation pattern on one film. Steatorrhoea was demonstrated, and jejunal biopsy by the peroral technique, using a Crosby capsule, showed changes in the jejunum corresponding to the group 4 lesion of Watson *et al.* (1965); that is, definitely abnormal but less severe than the changes found in adult coeliac disease.

A provisional diagnosis of mild adult coeliac disease was made, and after dismissal he improved slightly on a gluten-free diet. However, he became anaemic and was readmitted on 7 March 1963 for further investigation. One week later he had a mild cerebral attack with paresis but recovered rapidly. Faecal occult blood was present on two occasions, and radioactive chromium studies showed a daily alimentary blood loss of 5–6 ml.

At this point intestinal ischaemia or carcinoma was suspected, and at laparotomy on 1 April the small intestine was cyanotic and without detectable mesenteric pulsation. The ileocolic artery was exposed and divided, and the proximal end dilated by forcible saline injection to a calibre of about 4 mm. and anastomosed end-to-side to the right common iliac artery. On removal of the clamps mesenteric pulsation appeared and the previously cyanotic bowel became red and contractile.

His subsequent recovery was satisfactory, with relief of symptoms and gain in weight, and repeat jejunal biopsy 29 days after operation showed normal tissue. Three months after operation (Special Plate, Fig. 1) retrograde Seldinger catheterization of the right common iliac artery and injection of Urografin visualized the terminal mesenteric vessels. He thereafter remained well until December 1963, when he died from a coronary artery thrombosis.

Case 2

A man aged 54 presented on 26 February 1965 with loss of weight of two years' duration, loss of appetite for 10 months, and

Principal Laboratory and Other Investigations

	Case 1	Case 2	Case 3	Case 4	Case 5
Age in years	56	54	54	51	40
Height	4 ft. 11 in. (150 cm.)	5 ft. 3 in. (160 cm.)	5 ft. 3 in. (160 cm.)	5 ft. 2 in. (157 cm.)	5 ft. 5 in. (165 cm.)
E.S.R. (mm./hr.)	51	50	24	12	6
Hb (g./100 ml.)	10.7	13.2	15	15.5	14.7
Film	Anisocytosis	Anisocytosis	Anisocytosis	Normal	Normal
Albumin (g./100 ml.)	2.7	3.5	3.5	3.4	4.0
Globulin	4.9	2.7	2.6	2.8	2.5
Thymol turbidity (units)	0.2	6.3	0.8	1.8	0.6
Bromsulphalein excretion (% dye remaining at)					
25 minutes	—	—	25	23	15
45 minutes	—	—	15	22	8.5
Ca (mEq/l.)	4.5	—	4.7	4.6	4.7
P (mg./100 ml.)	3.0	—	3.0	3.8	—
Alkaline phosphatase (K.A. units)	14.5	9.8	22.0	15.5	11.5
Faecal fat (g./day)	9.8	—	19.7	5.2	9.2
Jejunal biopsy:					
Histology*	4	—	4	4	2
Maltase†	—	—	1.5	24.5	11.1
Sucrase†	—	—	0.3	5.1	2.9
Lactase†	—	—	0.1	0.9	0.8
Lactose tolerance test	—	—	Flat curve	—	Flat curve
E.C.G.	Normal	Normal	Normal	Posterior ischaemia	Normal
Chest x-ray film	—	Aortic calcification	Apical fibrosis, right	Normal	—

* Histological grading used by Watson *et al.* (1965).

† Lower limit of normal: maltase = 13.6; sucrase = 3.5; lactase = 1.7 units (Paton *et al.*, 1966).

a tendency to constipation. He had been treated in 1961 for intermittent claudication due to bilateral femoropopliteal occlusions.

Examination confirmed the severe weight loss, the liver was just palpable, and the colon was palpable in the left iliac fossa. A provisional diagnosis of alimentary carcinoma or mesenteric ischaemia was made, and he was admitted for investigation (see Table).

Barium enema was negative, and a barium-meal examination report stated: "Irritability of the duodenal cap and coarsening of its mucosa. An ulcer crater at the base of the cap cannot be entirely excluded." Faecal occult blood test was negative.

At operation on 7 April the abdominal aorta showed severe atherosclerosis, and there was no palpable arterial pulsation throughout the alimentary tract, in the viscera supplied by the coeliac axis and superior and inferior mesenteric arteries. Revascularization was not thought feasible and the abdomen was closed. He died suddenly three days later from coronary artery thrombosis.

Case 3

A man aged 54 was investigated in February 1965. He complained of abdominal pain of three months' duration, loss of 1 stone (6.4 kg.) in weight, occasional diarrhoea, and claudication of the left thigh and calf. Barium-meal examination showed a flocculation pattern suggesting malabsorption, and florid liver palms suggested liver disease (see Table).

Lateral aortography (Special Plate, Fig. 2) showed occlusion of the superior mesenteric artery and stenosis of the common iliac arteries. At operation on 25 April 1966 there was no pulsation in the branches of the coeliac axis and superior mesenteric artery. The latter was exposed at the root of the mesentery (where it was patent), divided, and reimplanted into the aorta at a convenient level. Vigorous pulsation was restored to the mesenteric vessels and the small bowel became red and contractile.

Postoperatively he developed diarrhoea (four stools daily), which persisted for several weeks but responded to Lomotil, and he began to gain weight.

Repeat jejunal biopsy showed regression of abnormal histological changes and intestinal disaccharidase levels improved but faecal fat remained high at 10 g./day. Repeat lateral aortography showed revascularization of the small intestine.

Case 4

A man aged 51 had a coronary artery thrombosis in 1961. In 1963 he developed claudication of the left calf, and an aortogram in 1965 showed narrowing of the left common femoral artery and a left superficial femoral occlusion. At operation on 15 March 1965 a large plaque was removed from the common femoral artery and a bypass vein graft inserted from this to the popliteal artery with complete relief of claudication.

Nine months later he developed a right femoropopliteal occlusion and also complained of poor appetite and loss of weight. Barium-meal examination showed some deformity of the duodenal cap and he was put on an ulcer regimen.

In March 1966 claudication recurred in the left leg with absence of the left femoral pulse, and aortography (Special Plate, Figs. 3 and 4) showed occlusion of the left external iliac artery, the vein graft remaining patent. The inferior mesenteric artery was hypertrophied and gave origin to a large marginal artery which supplied the colon and ileum. The marginal artery was larger than in the aortogram of 1965, and a provisional diagnosis of superior mesenteric occlusion or stenosis was made.

At this time he complained of persistent postprandial pain with flatulence, and abdominal distension and early liver palms were present (see Table).

At laparotomy on 27 June there was no detectable pulsation in the stomach and small-intestinal vessels, the small intestine was cyanotic, and the inferior mesenteric and marginal arteries were hypertrophied.

After splenectomy and mobilization of the pancreas the superior mesenteric artery was found to be obliterated at its origin, owing to atherosclerosis, and pulsation in the coeliac axis was poor. The superior mesenteric artery was exposed at the root of the mesentery

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FIG. 1.—Case 1. Seldinger catheter lies in right common iliac artery and injection of dye at this site has visualized the right iliac arteries. At the same time the terminal mesenteric vessels (1) can be seen, indicating that these have filled through a patent ileocolic to common iliac anastomosis. This film was taken three months after operation.

FIG. 2.—Case 3. Lateral aortogram showing dye in coeliac (1) and renal (2) arteries. Superior mesenteric artery is not visualized.

FIG. 3

FIG. 4

FIG. 3.—Case 4. Translumbal aortogram showing occlusion of left external iliac artery (1). The inferior mesenteric artery is hypertrophied and gives origin to a large marginal artery (2).

FIG. 4.—Case 4. Late film after the injection of dye illustrated in Fig. 3. Terminal branches to small bowel (1) derived from the superior mesenteric artery can be seen. As the level of aortic injection was well below the origin of the superior mesenteric artery, the terminal mesenteric arteries must have filled from the large marginal artery and superior mesenteric occlusion can be assumed.

FIG. 5.—Case 5. Early film of lateral aortogram showing dye in proximal portions of coeliac axis and superior mesenteric artery. There is a deep notch in upper border of coeliac axis (1) without evidence of atherosclerosis of aorta.

FIG. 5

and the distal normal artery reimplanted into the aorta with return of colour and pulsation in the small intestine.

Postoperatively he experienced diarrhoea for several weeks. Thereafter he was symptom-free and gained weight.

Case 5

A man aged 40 had had occasional abdominal pain for nine years, and for two and a half years had constant dull periumbilical pain with three motions daily. The pain was not related to meals but was relieved by defaecation and associated with abdominal distension. There was no loss of weight. He had previously been a heavy drinker.

Serum amylase was normal. Other investigations are listed in the Table. Lateral aortography showed narrowing of the coeliac axis (Special Plate, Fig. 5).

At operation on 31 May 1966 there was reduced pulsation in the stomach arteries and no hypertrophy of the pancreatoduodenal anastomosis. Numerous adhesions were present round the left lobe of the liver, and the coeliac axis appeared to be compressed by the median arcuate ligament and by fibrosis around the coeliac plexus. The ligament was divided, giving normal arterial pulsation. Biopsy of the liver showed a mild inflammatory infiltration round the portal tracts with lymphocytes and occasional eosinophils.

After a smooth convalescence he continued to complain of some mild abdominal pain, but faecal fat was 1 g./day and bromsulphalein clearance 10 days after operation was normal (1.5% dye remaining at 45 minutes).

Discussion

The characteristic presentation of persistent postprandial pain in an undernourished male patient who tends to eat small meals and who may be known to have atherosclerosis constitutes a syndrome which should be readily recognizable as due to ischaemia of the midgut. Dardik *et al.* (1965) collected accounts of only 18 cases successfully treated surgically (including cases reported by Morris *et al.* in 1962), but since then Morris *et al.* (1966) have reported 31 cases treated surgically without mortality, and Rob (1965) has reported 18 cases. This relatively small number of cases, most of which were treated in large centres, suggests either that the condition is rare or that recognition of the symptom pattern is difficult. Our own experience of five cases of chronic intestinal ischaemia operated on within three years (four successfully) suggests that it is not necessarily rare.

Difficulty in diagnosis is due to lack of awareness on the part of the clinician, who fails to include intestinal ischaemia in his differential diagnosis when a patient presents with atypical abdominal pain. Fry and Kraft (1963) analysed the prodromal symptoms of 20 patients who had died from acute infarction of bowel and stated that each had experienced abdominal pain and loss of weight but that the symptom pattern was not "stereotyped."

This is certainly true, and the middle-aged patient who presents with abdominal pain and severe loss of weight may be suspected of having an alimentary carcinoma. This diagnosis was thought to be a possibility in Cases 1 and 2, but barium studies were negative. From our experience we would strongly recommend that any patient with abdominal pain and loss of weight suggestive of carcinoma, in whom barium investigations prove negative, should be suspected of having chronic intestinal ischaemia. Evidence of atherosclerosis elsewhere enhances this suspicion and is an indication for lateral aortography.

Barium-meal examination showed minor abnormalities of the duodenal cap suggestive of ulcer in Cases 2 and 4, and ulcer was confirmed in Case 4 at operation. Such findings in patients with chronic intestinal ischaemia may lead to an erroneous diagnosis of duodenal ulcer and delay effective treatment. This sequence of events was observed in a patient who presented with an acute infarction of bowel, having attended elsewhere with his "ulcer" for six months.

Malabsorption is a common occurrence in visceral ischaemia. It occurred in Cases 1, 3, 4, and 5 and might have been discovered in Case 2 if the appropriate investigations had been carried out. Heard *et al.* (1963), who reported one case and reviewed 18 others from the literature, found that malabsorption was a feature in five (26%). Most of the case reports in the literature are poorly documented in this respect (Dardik *et al.*, 1965), and our experience suggests that malabsorption is commoner than the figures of Heard *et al.* indicate.

Small-bowel disease was demonstrated by steatorrhoea (Cases 1, 3, and 5), abnormal histology (Cases 1, 3, and 4), and low intestinal disaccharidase activity (Cases 3, 4, and 5). Abnormality of liver function was shown by impaired bromsulphalein excretion in Cases 3 and 4, though routine liver-function tests in these patients were normal.

Chronic ischaemia has therefore a functional effect on small intestine and liver. It may even cause abnormalities of pancreatic secretion, though we have no evidence to offer on this point. In addition to the loss of weight in these five patients, it was noteworthy that all were small, measuring from 4 ft. 11 in. to 5 ft. 5 in. (150 to 165 cm.) in height.

When mesenteric pulsation is found to be reduced or absent at operation, a variety of surgical procedures may be employed. Morris *et al.* (1966) prefer bypass Dacron graft, but employed endarterectomy in five cases. They performed single artery revascularization in 14 cases and revascularization of two arteries in 17 cases, but point out that full restoration of normal blood flow is not necessary for a good result, unlike revascularization in renal artery stenosis. Long-term survival of bypass grafts seemed good, and one had been successful for eight years.

Bypass saphenous-vein grafting (Fry and Kraft, 1963) and homografts (Mavor and Lyall, 1962; Heard *et al.*, 1963) have also proved successful.

Thromboendarterectomy is a logical procedure where the lesion is confined to the first centimetre or two of the main trunk, and this method was successfully employed in two cases by Shaw and Maynard (1958). Exposure of the origin of the coeliac axis and superior mesenteric artery from the aorta was easily achieved in Cases 4 and 5, without opening the chest, by mobilization of the splenic flexure of colon, splenectomy, mobilization of pancreas, and retraction of stomach and pancreas to the right. Occasionally stenosis may affect a longer segment of artery (Fry and Kraft, 1963—2 cases in 20) and this technique cannot be employed.

The possibility of direct arterial anastomosis between the aorta and the mesenteric vessels is illustrated by the successful result obtained by Ranger and Spence (1962) when a functioning side-to-side anastomosis was made between the aorta and ileocolic artery and by the successful result obtained in our first case by end-to-side anastomosis of the distended ileocolic artery to the right common iliac artery.

Mikkelsen (1957) advocated reimplantation of the distal portion of the superior mesenteric artery into the aorta. Experience of the satisfactory function of the reimplanted artery in cases of renal artery stenosis led to the reimplantation of the superior mesenteric artery in Cases 3 and 4. Brodin and Hansson (1964) have also reported the use of this method. The lumen of the anastomosis is not as large as that of a healthy superior mesenteric artery, but the efficiency of revascularization appears superior to that achieved by bypass grafting.

The assessment of the relative values of operative procedures to relieve chronic intestinal ischaemia will be possible only when sufficient cases become available for operation, and this requires the greater use of lateral aortography as a diagnostic procedure in suspected cases.

The prohibitive mortality of acute infarction emphasizes the necessity for early diagnosis at the stage of chronic ischaemia. Mavor and Lyall (1962) suggest that the period of prodromal symptoms is not necessarily prolonged, and in the collected

series of 19 cases of Heard *et al.* (1963) the mean duration of symptoms was four to five months. This suggests that prolonged investigation and indecision are undesirable in the management of these cases.

Summary

Five cases of visceral ischaemia are presented. Successful operative and clinical results were obtained in three of the four cases of chronic intestinal ischaemia and in one case of coeliac axis stenosis.

Malabsorption was a feature of four cases. Abnormalities of faecal fat, jejunal histology, disaccharidase activity, and bromsulphalein excretion were present, and improvement or reversion to normal followed successful operation.

Chronic intestinal ischaemia should be strongly suspected in middle-aged patients with atypical abdominal pain and loss of weight, especially when alimentary carcinoma is suspected and barium studies are negative. Successful revascularization of the abdominal viscera can be achieved when the diagnosis has been proved by lateral aortography.

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Controlled Trials of a Sulphonamide Given Weekly to Prevent Exacerbations of Chronic Bronchitis

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Purulent exacerbations are difficult to prevent in patients with chronic bronchitis. Trials of antibiotics administered continuously for long periods have given variable and often negative results (Elmes, 1962). Most of these studies have been in outpatients, in whom regular treatment and exact assessment are notoriously difficult (Porter, 1966). I present the results of a controlled trial of a new sulphonamide given weekly to hospital inpatients with chronic bronchitis.

Sulphormethoxine (Fanasil) is a sulphonamide with a half-life in the body of 100 to 200 hours, so that it is effective if given once weekly. In a preliminary study in this hospital it was found to have some effect in mild exacerbations of chronic bronchitis, especially when given in a 2-g. dose weekly. A weekly dose over long periods is so convenient that it seemed worth assessing the value of the drug in preventing purulent exacerbations of chronic bronchitis.

First Trial

Many of the patients in this hospital stay for long periods because of medical or social reasons, or both. Patients who suffered from chronic bronchitis were eligible for the trial if (1) they were going to stay for long periods; (2) had a history of at least one acute exacerbation during the previous 12 months as defined by hospital admission, treatment by antibiotics, or confinement to bed at home; and (3) had purulent sputum at the time of admission.

Plan of Trial.—In all patients the initial purulence of the sputum was cleared with courses of antibiotics. They were then divided into two groups by random selection, in a proportion of two treated to one control. Cards with treatment or control written on them were placed in sealed envelopes at

random and taken in strict order of entry into the trial. As it was anticipated that many of the controls would relapse, this ratio would allow more patients to be treated. The treated patients were given sulphormethoxine 2 g. once weekly. The control patients were given symptomatic treatment only. Because sulphormethoxine is a relatively new drug in this country, a double-blind trial with a placebo as well was not thought advisable, so that a close watch could be kept for any toxicity. No antibiotics were given to patients in either group unless a purulent exacerbation occurred. The patients were admitted to the trial from January 1964 until October 1964.

Patients.—All the patients were men. Most were aged from 40 to 70 (Table I). All had had symptoms of bronchitis for at least five years. Both groups were comparable in age (Table I) and in initial distribution of quantity of sputum (Table II). The method of allocation ensured that patients entered the trial in balanced proportions during each month of the year. Those

TABLE I.—Ages of Patients in First Trial

Age	Treated Patients	Control Patients
40–60 years	10	4
61–70	18	8
71–75	4	1
Total	32	16

TABLE II.—Results According to Initial Quantity of Sputum in First Trial

Sputum Quantity	Treated Patients		Control Patients	
	Success	Failed	Success	Failed
Less than 30 ml. daily	17	3	3	9
30 ml. or more daily ..	4	8	1	3
Total	21	11	4	12

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