Discussion

The demonstration by direct measurement that lysine is very poorly absorbed by the small intestine of a cystinuric patient confirms previous work which has indicated that in cystinuria the active transport system for dibasic amino-acids is defective (Milne *et al.*, 1961).

In cystinuria there is no clinical evidence of malnutrition despite this defect of intestinal transport, and despite the considerable renal loss of dibasic amino-acids and cystine. An alternative mechanism of absorption, perhaps by diffusion, would therefore appear to be likely. Plasma amino-acid levels after oral tolerance tests do indicate that some absorption of free lysine can occur (Hellier *et al.*, unpublished observations), but this method allows no assessment of its extent. The direct measurements reported in the present paper show that lysine absorption is in fact considerably greater when taken as a dipeptide, and it is very likely that in the cystinuric subject most dibasic amino-acid is absorbed in this way.

The extent to which amino-acids are absorbed as free amino-acids, after complete intraluminal hydrolysis of protein, or as oligopeptides after incomplete hydrolysis, has been a disputed question for many years. Recently, however, evidence has been accumulating that not only are dipeptides absorbed both in animals and in man, but that their absorption may be of nutritional significance (Craft *et al.*, 1968; Matthews *et al.*, 1968, 1969).

The inherited diseases in which defects of intestinal transport of specific amino-acids occur provide a unique opportunity for studying the mechanism of dipeptide absorption. Dipeptide absorption has not previously been studied in cystinuria, but Asatoor *et al.* (1970a, 1970b) carried out oral tolerance tests in two patients with Hartnup disease, a very rare condition in which clinically detectable malnutrition occurs due to defective small-intestinal transport of neutral amino-acids. They were able to show convincingly that while there was little or no absorption of neutral amino-acids when the free amino-acid was administered, various dipeptides containing the same amino-acids were readily absorbed. Our findings support their conclusion that in normal subjects amino-acids are absorbed by a dual mechanism either as free amino-acids or as dipeptides.

Free dibasic amino-acids are absorbed very slowly from the human jejunum, and as in animals very low transport constants (K_t and V_{max}) are found (Hellier *et al.*, unpublished observations). In the one normal subject studied lysine was better absorbed as the dipeptide than as free-amino acid, and it is quite possible that absorption of dibasic amino-acids as dipeptides might be of nutritional significance in normal subjects. In animals a very limited number of dipeptides have now been studied, but it would appear that the relative rate of absorption as free amino-acid or as dipeptide differs considerably for different dipeptides (Asatoor *et al.*, 1970b). The same is probably true in man, as Asatoor *et al.* (1970b) showed apparently better absorption of phenylalanine as free amino-acid than as dipeptide, a finding in contrast with our observations on lysine, and Matthews *et al.* (1968) showed diglycine to be absorbed more rapidly than glycine.

The site of hydrolysis of oligopeptides into the constituent amino-acids is unknown, though as only free amino-acids are found in portal vein blood it is reasonable to assume that the peptidases lie somewhere in the mucosal cell. It is of interest that during the dipeptide perfusion in the normal subject only very small quantities of glycine and lysine were detected in the recovered perfusate. In the cystinuric subject, though minimal quantities of free glycine were detected, lysine was found in higher concentrations. The source of this lysine is uncertain. It may have resulted from intraluminal hydrolysis of the dipeptide, free glycine being readily absorbed while lysine accumulated within the lumen. Alternatively, free lysine may have diffused back into the intestinal lumen after dipeptide absorption and intracellular hydrolysis.

We are grateful to Professor E. F. Scowen for allowing us to study patients under his care, to Mr. C. Thirumalai for technical help, and to our subjects for their co-operation.

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Medical Memoranda

Irradiation-induced Constrictive Pericarditis in Intestinal Lymphangiectasis

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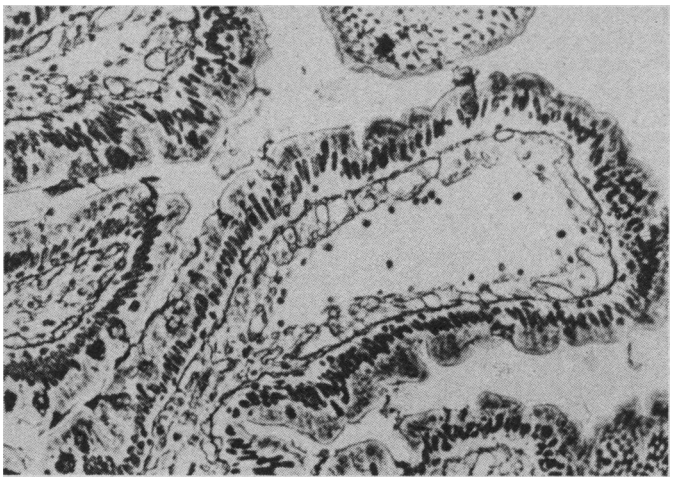
The following case report confirms earlier reports (Peterson and Hastrup, 1963; Wilkinson *et al.*, 1965) that the features of lymphangiectasis with abnormal intestinal protein leak may disappear after pericardiectomy. Constrictive pericarditis in the present case was irradiation-induced; this has never previously been reported in association with intestinal lymphangiectasis.

Case Report

The patient, a 40-year-old woman, had a scirrhous carcinoma locally excised from her left breast in 1959. Subsequently she received a course of radiotherapy. At no time has there been evidence of local recurrence or metastases. Within a year of treatment unusually severe radiation stigmata developed with considerable atrophy of the skin of the left chest, moderate lymphoedema of the left arm, and radiation fibrosis in the upper lobe of the left lung.

She remained well until 1964 when, after a mild chest infection, generalized oedema developed. Initially this responded to diuretics but recurred intermittently until 1966. Since then she has never been completely free from oedema.

Full investigation was refused until January 1967, when persis-



Preoperative villus with dilated lacteal containing macrophages. (Stained for reticulin.)

tent hypoalbuminaemia and a protein-losing enteropathy were found. Total serum proteins were 4·4 g./100 ml. (albumin 2·8 g., globulin 1·6 g.) and electrophoresis was normal. The ^{131}I polyvinylpyrrolidone test showed a 96-hour faecal recovery of 5·2% of the administered dose (normal range 0-1·5% (Gordon, 1959)). A jejunal biopsy specimen showed intestinal lymphangiectasis with a dilated lacteal in most villi, maintenance of epithelial integrity, and minimal disturbance of villous architecture (see Fig.). Routine investigations were all normal. There was no evidence of impaired hepatic protein synthesis, renal loss of albumin, or intestinal malabsorption. Symptomatic treatment with diuretics was continued.

In October she complained of increasing exertional dyspnoea and showed signs of cardiac failure. In addition to the dependent oedema there was a left-sided pleural effusion. The arterial pulse was regular, paradoxical, and of low volume (blood pressure 120/80). The jugular venous pressure was raised 8 cm. above the sternomanubrial junction with the patient resting at 45°. Kussmaul's sign was positive. The venous wave form comprised a prominent "a" wave and "y" descent. Chest *x*-ray films and cardiac screening showed possible right ventricular enlargement, no calcification, and normal pulsations. The E.C.G. showed low-volume complexes and generally depressed T waves with inversion in leads V2, V3, and V4.

The patient was still unwilling to submit to further investigation, so the clinical diagnosis of a constrictive cardiac disorder was not confirmed by catheter studies until October 1968. Pressures recorded then were: right atrium 20/15, right ventricle 30/15, pulmonary artery 30/15, and wedge pulmonary capillary 20/15. In the right ventricular pressure tracing there was an early diastolic dip followed by a sharp rise. Further investigation of intestinal function was carried out and malabsorption could still not be shown.

Pericardiectomy was performed in October. The thoracic duct was not visualized at operation. There was a distinct line of demarcation between fibrosed pericardium on the left and macroscopically normal pericardium on the right. The line coincided exactly with the sternal extremity of the area exposed to radiation in 1959. Some degree of myocardial fibrosis was noted. The pericardium was stripped uneventfully and she made a good postoperative recovery. Within a month peripheral oedema had disappeared, and distended neck veins emptied. Exercise tolerance was much improved and serum proteins were normal.

When finally assessed in January 1969 the patient was feeling well and receiving no specific treatment. The serum proteins were normal, faecal recovery of ^{131}I polyvinylpyrrolidone was 0·2% of the administered dose, and jejunal histological appearances had returned to normal.

Comment

Since 1960 the association between constrictive pericarditis and protein-losing enteropathy has been described in 11 patients (including the present one) in whom the results of pericardiectomy are available (Plauth *et al.*, 1964; Wilkinson *et al.*, 1965; Takashima and Takekoshi, 1968). A preoperative intestinal biopsy in one of those patients showed the histological features of intestinal lymphangiectasis; five weeks after pericardiectomy the histological appearance of the small intestine was normal (Wilkinson *et al.*, 1965).

The mechanism by which cardiac constriction produces intestinal lymphangiectasia is unknown. Less than 5% of patients develop heart disease after irradiation. Fibrotic lesions involving both pericardium and, less often, myocardium occur only in the minority of patients and usually follow the administration of very high doses of irradiation, often in repeated courses (Cohn *et al.*, 1967). The case reported here had macroscopic evidence of myocardial damage in addition to pericarditis, despite a moderate dose of irradiation.

This patient has latterly been under the care of Dr. H. P. Brody. The catheter studies were carried out by Dr. D. Verel and the staff of the Regional Cardiothoracic Centre, the Northern General Hospital, Sheffield. Mr. D. G. Taylor performed the pericardiectomy.

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Parachlorophenylalanine Treatment in Carcinoid Syndrome

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Classically the carcinoid syndrome produces chronic diarrhoea, cyanosis, flushes, respiratory distress, and valvular disease of the heart. Engelman *et al.* (1967) reported that parachlorophenylalanine, an inhibitor of tryptophan hydroxylase, is effective in depleting serotonin and relieved gastrointestinal symptoms in four of their five patients. The present case report on the effect of parachlorophenylalanine in another patient with the carcinoid syndrome confirms their observation. Emphasis is placed on study of the mental changes of our patient during treatment.

Case Report

A 67-year-old woman was admitted to hospital in September 1967 with a two-week history of fever and pains in the right upper quadrant of the abdomen. Diarrhoea was not present at the time of admission. Laparotomy showed a primary carcinoid tumour in the terminal ileum and caecum with extensive hepatic and peritoneal metastases. An ileotransversostomy bypass was performed. The patient excreted 150 mg. of 5-hydroxyindoleacetic acid in 24 hours.

After a three-month symptom-free period diarrhoea and oedema in the legs developed. She passed 20-30 stools a day, thus showing no response to even 100 drops of tincture of opium daily. She had lost 15 kg. in weight since the disease started. On admission to hospital in December 1967 she was emaciated, the liver was enlarged to 7 cm. below the costal margin, and pronounced pitting oedema of the ankles was noted. The heart was normal in size, and there was a grade II/IV apical systolic murmur. She excreted