with acquired aplastic anaemia. Since then three other adult patients apparently suffering from aplastic anaemia have developed P.N.H.: in two the P.N.H. defect became severe and dominated the picture, while the fourth patient had a mild P.N.H. defect and died while the aplastic phase was still dominant. These cases have not been included in the series analysed above, although in their initial presentation they were indistinguishable from acquired aplastic anaemia. They are recorded here to draw attention to the fact that the possibility of the development of P.N.H. should perhaps be considered when the prognosis in aplastic anaemia is assessed.

Summary

In a 12-year period 60 patients suffering from chronic acquired aplastic anaemia have been investigated. In some cases the disease has run an acute course with death in weeks. Half the patients died within 15 months of onset. Eighteen are still alive but only six are in full remission, while another three are in partial remission with normal haemoglobin, with or without neutropenia, but with persistence of thrombocytopenia. Invariably platelets have been the last component to return to normal, usually after a prolonged period.

Both sexes were equally affected, but the outlook may be more serious in patients over the age of 40; it was especially grave in a group of 16 patients who had profound neutropenia (fewer than 100/c.mm.) and severe thrombocytopenia (fewer than 20,000/c.mm.), but on the whole neutropenia did not materially affect prognosis to the same extent as did thrombo-

cytopenia; death was usually due to haemorrhage rather than infection. In 22 cases bone-marrow aspiration showed normal or hyperplastic foci, but prognosis was little affected by this.

Evaluation of treatment is difficult, as spontaneous remissions may occur, but testosterone and corticosteroids in moderate doses can induce remissions in children near puberty. In adults prognosis and median survival seemed little influenced. Fresh blood or platelet transfusions were valuable during haemorrhagic episodes. Splenectomy was carried out in four patients with equivocal results.

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REFERENCES

- Adams, E. B. (1951). *Lancet*, **1**, 657.
 Allen, D. M., and Diamond, L. K. (1961). *Amer. J. Dis. Child.*, **102**, 416.
 Bärkman, S. E. (1962). *Acta haemat. (Basel)*, **27**, 124.
 Block, M., Jacobson, L. O., and Bethard, W. F. (1953). *J. Amer. med. Ass.*, **152**, 1018.
 Bomford, R. R., and Rhoads, C. P. (1941). *Quart. J. Med.*, **10**, 235.
 Dacie, J. V., and Lewis, S. M. (1961). *Brit. J. Haemat.*, **7**, 442.
 Gardner, F. H., and Pringle, J. C., jun. (1961). *Arch. intern. Med.*, **107**, 846.
 Heaton, L. D., Crosby, W. H., and Cohen, A. (1957). *Ann. Surg.*, **146**, 637.
 Irsäels, M. C. G., and Wilkinson, J. F. (1961). *Lancet*, **1**, 63.
 Lewis, S. M. (1962). *Brit. J. Haemat.*, **8**, 322.
 Mohler, D. N., and Leavell, B. S. (1958). *Ann. intern. Med.*, **49**, 326.
 Scott, J. L., Cartwright, G. E., and Wintrobe, M. M. (1959). *Medicine (Baltimore)*, **38**, 119.
 Shahidi, N. T., and Diamond, L. K. (1961). *New Engl. J. Med.*, **264**, 953.

Value of Detection of Formiminoglutamic Acid in Urine for the Diagnosis of Malabsorption States

DAVID P. ROSE,* M.D.

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Increased amounts of formiminoglutamic acid (Figlu), an intermediate metabolite in the degradative conversion of histidine to glutamic acid (see Fig.), may appear in the urine of patients with folic-acid deficiency, vitamin-B₁₂ deficiency, and liver disease. Figlu is converted to glutamic acid by transfer of its formimino group to tetrahydropteroylglutamic acid. Folic-acid deficiency results in an accumulation of Figlu due to a lack of tetrahydropteroylglutamic acid, and consequently increased amounts of Figlu appear in the urine (Tabor and Wyngarden, 1958). The increased urinary excretion of Figlu in vitamin-B₁₂ deficiency also probably results from a reduction in available tetrahydropteroylglutamic acid (Herbert and Zalusky, 1962). In liver disease the enzymes concerned in the metabolic pathway of histidine degradation may be impaired, and reduced activity of one of these enzymes, Figlu transferase, may be responsible for the increased excretion of Figlu in liver disease without folic-acid deficiency (Merritt, Rucknagel, Silverman, and Gardiner, 1962).

Knowles (1962) has studied the urinary excretion of Figlu, using it as an index of folic-acid deficiency, in steatorrhoea and concluded that this provides a satisfactory screening test for idiopathic steatorrhoea.

In the present study the clinical value of determining the urinary excretion of Figlu has been assessed in malabsorption

states due to a variety of causes. Particular attention has been paid to the likelihood of causes of abnormal excretions other than folic-acid malabsorption resulting in an erroneous diagnosis of small-bowel disease.

The metabolic pathway by which histidine is converted to glutamic acid.

* Department of Chemical Pathology, United Sheffield Hospitals.

The results have been compared with those of the urinary xylose-excretion test, the value of which in the diagnosis of intestinal malabsorption is well established (Fourman, 1948; Gardner and Perez Santiago, 1956; Christiansen, Kirsner, and Ablaza, 1959).

Methods and Material

Urinary Excretion of Figlu.—The determination of Figlu in the urine was performed as described by Kohn, Mollin, and Rosenbach (1961), using electrophoresis on cellulose acetate strips. A 15-g. loading dose of L-histidine was given orally to the fasting patient. Urine was collected for five hours; the period of collection beginning three hours after the dose of histidine. When Figlu was detected in the urine electrophoresis was repeated, at the same time running a series of standards made from dilutions of a urine of known Figlu concentration. By comparing visually the intensity of the test Figlu spot with those of the standards an estimate was made of the amount of Figlu present. The urinary excretion of Figlu has been expressed as milligrams per hour for the five-hour period of urine collection.

Urinary D-Xylose Excretion Test.—The patients were fasted overnight. At the start of the test the bladder was emptied and the urine saved. An oral dose of D-xylose (25 g. dissolved in 250 ml. of water) was then given, and all the urine passed during the next five hours collected as a pooled specimen. One and two hours after the xylose further 250-ml. amounts of water were given. The urine obtained before giving the xylose was tested for the presence of glucose. The concentration of xylose in the pooled urine was estimated by the Technicon Auto-Analyzer method for glucose determination, but with xylose standards.

Faecal Fat Excretion.—The patients were taking a normal ward diet. The faeces were saved in 24-hour collections for a five-day period, unless otherwise stated. The daily output of fatty acid, as stearic acid, was estimated by the method of Frazer (1956). The results have been expressed as the average daily output of fatty acid. The upper limit of normal has been taken as 6 g./day.

Serum Folic-acid and Vitamin-B₁₂ Levels.—The fasting serum folic-acid activity was estimated by the *Lactobacillus casei* method (normal range 5 to 22 mμg./ml.), and the serum vitamin B₁₂ by the *Euglena gracilis* method (normal range 140 to 850 μμg./ml.).

Controls.—The composition of the control group is shown in Table I. None of the hospital patients gave a history of diarrhoea and all had normal blood-urea levels.

TABLE I.—Control Group: Urinary Xylose Excretion (g./hour)

	Sex	Age	Result	Diagnosis	Sex	Age	Result
Staff	M	26	4.0	Convalescent pneumonia	M	77	6.7
Staff	F	27	6.1	Haematemesis; duodenal			
Staff	M	26	4.0	ulcer	M	62	6.8
Staff	M	30	5.3	Deep vein thrombosis	M	61	6.5
Staff	M	23	9.7	Convalescent, myocardial			
Staff	M	31	7.7	infarction	M	67	4.9
Staff	F	30	5.9	Chronic bronchitis	M	62	4.9
Staff	F	30	8.3	Chronic bronchitis	M	72	5.8
Staff	F	34	7.3	Convalescent myocardial	M	65	4.3
				infarction			

Urinary Figlu excretions: Less than 2 mg./hour for the 11 subjects tested.

Patients

Thirty-five patients were studied. The diagnoses and the faecal fat and the urinary xylose excretion results are given in Table II.

In addition to the 13 cases of idiopathic steatorrhoea five patients are believed to have idiopathic malabsorption despite normal results for the faecal fat estimations. These have been grouped together as "idiopathic malabsorption without steatorrhoea."

Two of the five (Cases 14 and 15) had had diarrhoea for several years and had the features of intestinal malabsorption on barium follow-through examination. Case 14 had osteomalacia. Case 16 had never suffered from diarrhoea and the stools were normal in appearance. A jejunal biopsy, however, showed almost complete atrophy of the villi. The other two patients (Cases 17 and 18) without steatorrhoea had folic-acid deficiency for which there was no apparent cause. Their diets appeared adequate, they were not taking anticonvulsant drugs, and were not pregnant. Jejunal biopsy examinations were not carried out.

TABLE II.—Patients Studied: Faecal-fat and Xylose-excretion Results

Diagnostic Group	Case No.	Sex and Age	Faecal-fat Excretion (Average: g./day)	Urinary Xylose Excretion (g. in 5 hours)
Idiopathic steatorrhoea	1	F 71	12.7	1.6
	2	F 48	7.5	4.7
	3	F 47	60.0	1.3
	4	M 36	4.8* (3 days)	1.2
	5	F 60	6.7	3.3
	6	M 61	8.5	2.6
	7	M 47	21.0	2.3
	8	M 17	22.1	—
	9	M 47	34.1	2.4
	10	F 39	26.6	5.2
	11	M 63	18.1	2.9
	12	M 40	14.3	1.3
	13	F 34	29.8	1.3
Idiopathic malabsorption without steatorrhoea	14	F 66	3.9	0.3
	15	M 36	5.1	5.5
	16	F 26	5.4	2.6
	17	F 42	1.1	6.1
Regional enteritis: Terminal ileitis	18	F 43	2.2	2.4
	19	F 25	2.8	4.0
Terminal ileitis	20	F 14	1.8 (1 day)	6.3
Previous right hemicolectomy	21	M 67	—	—
Jejuno-ileitis	22	F 66	1.4	3.1
Regional enteritis—? blind loop	23	M 27	18.4	4.1
Steatorrhoea following gastric surgery:				
V. and G. J.	24	M 58	11.6	6.5
P. G. and D. J.	25	F 72	12.8	3.5
V. and G. J.	26	M 34	13.1	—
Polya P. G.	27	M 43	13.0	—
V. and G. J.	28	F 41	15.8	2.6
Malabsorption associated with other diseases:				
Carcinoma of common bile-duct	29	F 34	15.0	7.1
Scleroderma	30	M 55	3.9	1.2
Abdominal radiotherapy	31	F 66	9.7	0.4
Lymphosarcoma	32	M 50	2.8	2.2
Lymphosarcoma	33	M 47	13.0	2.1
Lymphosarcoma	34	M 52	8.6	3.2
Chronic lymphocytic leukaemia	35	F 49	7.8	3.8

* Abnormal result for radiotriolein absorption test.

G.J. = Gastrojejunostomy. V = Vagotomy. P.G. = Partial gastrectomy. D.J. = Duodenojejunostomy.

Four patients had the diagnosis of regional enteritis confirmed histologically. Case 23 was diagnosed on clinical grounds only. Case 25, with a blind-loop syndrome, had impaired absorption of vitamin B₁₂, as shown by a Schilling test. Jejunal biopsy was normal. The steatorrhoea was improved by tetracycline therapy.

Case 29 had a carcinoma of the common bile-duct with widespread invasions of the pancreas and liver. Case 31 had had deep x-ray therapy two years previously, after a hysterectomy for carcinoma of the uterus. A laparotomy performed after the investigation of small-bowel function revealed no evidence of recurrence of the neoplasm. Case 32 had lymphosarcoma with chylous ascites. Subsequent post-mortem examination showed many enlarged mesenteric glands and involvement of Peyer's patches. The other two patients with lymphosarcoma (Cases 33 and 34) had clinical evidence of widespread abdominal involvement, as did the patients with chronic lymphocytic leukaemia (Case 35).

Results

Control Group.—The urinary excretions of Figlu were less than 2 mg./hour for the 11 subjects tested. The results of

the xylose-excretion tests are shown in Table I (range 4.0 to 9.7 g.).

Patients

The results of the urinary Figlu-excretion estimations, the serum folic-acid and vitamin-B₁₂ levels, and the haematological data are given in Table III.

TABLE III.—Results of Urinary Figlu Excretion and Haematological Investigations

Case No.	Hb (g./100 ml.)	R.B.C. (mil./c.mm.)	Bone-marrow Appearance	Serum Vitamin B ₁₂ (μg./ml.)	Serum Folic Acid (mg./ml.)	Urinary Figlu Excretion (mg./hour)
I.S. 1	11.4	3.5	T.M.	164	—	20
2	7.7	4.0	—	190	—	20
3	13.0	—	—	300	—	26
4	5.3	1.4	M	132	1.2	47
5	10.9	3.0	M	276	—	16
6	10.2	2.5	M	52	2.9	39
7	12.4	4.1	N	168	27.0	<2
8	4.6	1.3	M	128	3.0	105
9	10.9	4.6	N + M	—	—	17
10	10.4	—	—	350	6.2	<2
11	12.9	4.2	T.M.	202	1.1	38
12	13.5	—	T.M.	536	1.0	17
13	16.4	—	—	—	Received folic acid	<2
I.M. 14	8.1	2.5	T.M.	172	—	25
15	9.8	—	—	510	3.0	6
16	9.3	2.7	M	—	0.8	18
17	4.0	1.1	M	152	1.7	67
18	12.9	—	Occasional T.M.	80*	1.0	10
R.E. 19	11.8	—	—	368	—	<2
20	11.3	—	—	254	—	<2
21	12.6	3.3	T.M.	222	2.5	<2
22	13.0	4.1	T.M.	296	1.5	11
23	16.0	5.2	—	194	4.4	2
PGS 24	15.4	—	—	—	—	<2
25	13.3	—	—	138	—	<2
26	14.6	—	—	290	—	<2
27	14.1	—	—	Receiving B ₁₂	—	<2
28	5.8	2.4	—	222	—	<2
O.D. 29	10.2	3.2	N	1,600	—	35
30	11.8	4.0	N	—	—	15
31	13.3	—	—	248	—	<2
32	9.4	—	N	676	—	11
33	8.7	—	T.M.	186	1.7	32
34	9.2	—	—	206	2.1	26
35	10.1	—	T.M.	—	2.0	42

* This vitamin-B₁₂ level was not that at the time of the other investigations. When these were carried out the patient had received vitamin B₁₂.

I.S. = Idiopathic steatorrhoea. I.M. = Idiopathic malabsorption without steatorrhoea. R.E. = Regional enteritis. PGS = Post-gastric surgery steatorrhoea. O.D. = Malabsorption associated with other diseases. M = Megaloblastic. T.M. = Transitional megaloblastic. N = Normoblastic.

The urinary excretions of Figlu were abnormal in all of the 10 patients with idiopathic steatorrhoea tested before starting folic-acid therapy, as they were in all of the five patients with idiopathic malabsorption without steatorrhoea. In all the cases in which the serum folic-acid level was estimated it was below the normal range when the urinary excretion of Figlu was increased.

Ten patients with idiopathic steatorrhoea excreted less than 4 g. of xylose in five hours, including one (Case 7) who had been taking folic acid for a year prior to investigation and another (Case 13) who had received a short course of folic acid six months before the present study. Two patients (Cases 2 and 10) with normal xylose excretions had been taking folic acid for several weeks before the tests. Three of the five patients with idiopathic malabsorption without steatorrhoea had abnormal results for the urinary xylose test.

Case 22, with jejuno-ileitis, had abnormal xylose and Figlu results despite a normal faecal-fat excretion, as did Case 30 (scleroderma) and Case 32 (lymphosarcoma) with evidence of disease throughout the small bowel. The other two cases of lymphosarcoma, and the patient with chronic lymphocytic leukaemia, had steatorrhoea, low xylose excretions, and raised Figlu excretions. As in the cases of idiopathic malabsorption, the serum folic-acid activity was found to be low in all those patients with raised Figlu excretions in whom it was estimated. One patient (Case 21), however, showed transitional megaloblasts in the bone-marrow and had a low serum folic-acid level,

but the urinary excretion of Figlu was normal. This is the only example in the series of a patient considered to be deficient of folic acid but having a normal Figlu test. Unfortunately results for the urinary xylose excretion and faecal fat estimation were not obtained.

The two patients (Cases 19 and 20) with regional enteritis limited to the terminal ileum had normal urinary Figlu and xylose results. The Figlu excretions were also normal in the group of patients with steatorrhoea following gastric surgery, but two (Cases 25 and 28) had urinary xylose excretions below the normal range.

Discussion

Impaired intestinal absorption of folic acid is virtually a constant feature of idiopathic steatorrhoea (Girdwood, 1953a; Chanarin, Anderson, and Mollin, 1958). In the present study all of the cases of untreated idiopathic steatorrhoea had increased urinary excretions of Figlu, and the results of the serum folic-acid assays indicate that these were associated with folic-acid deficiency. The results therefore support the finding of Knowles (1962) that an abnormal Figlu excretion is the rule in idiopathic steatorrhoea.

Abnormal excretions of Figlu occur in a proportion of patients with megaloblastic anaemia due purely to vitamin-B₁₂ deficiency (Zalusky and Herbert, 1961; Knowles and Pranker, 1962), and so the demonstration of an increased excretion of Figlu does not assist in the recognition of patients with megaloblastic anaemia resulting from occult intestinal malabsorption. The results of Knowles (1962) and of the present study indicate, however, that a normal Figlu test may be regarded as strong evidence against a diagnosis of idiopathic malabsorption.

The xylose-excretion test is often abnormal in those cases of intestinal malabsorption with disease of the jejunal mucosa. Its use has therefore been recommended for the diagnosis of idiopathic steatorrhoea (Christiansen *et al.*, 1959; Fowler and Cooke, 1960), tropical sprue (Gardner and Perez Santiago, 1956), and regional enteritis with jejunal involvement (Shiner, Vakil, and Wilcox, 1962).

Folic-acid deficiency resulting from intestinal malabsorption may be regarded as indicative of jejunal disease. The interpretation of an abnormal Figlu result in a patient with suspected small-bowel malabsorption is therefore assisted if considered together with the result of a xylose-excretion test. In the present series all of the untreated cases of idiopathic steatorrhoea had abnormal results for both these tests, as did three of the patients considered to have idiopathic malabsorption without steatorrhoea, and the cases of jejuno-ileitis due to Crohn's disease, intestinal scleroderma, and lymphomatous involvement of the small bowel.

The low xylose excretion in one of the patients (Case 28) with steatorrhoea following gastrojejunostomy and vagotomy was unexpected. This patient had severe iron-deficiency anaemia, and low xylose excretions have been reported in such cases (Wormsley, 1963). Jejunal biopsy was not performed and "latent" idiopathic steatorrhoea aggravated by gastric surgery, as described by Paulley, Fairweather, and Leeming (1957) and Joske and Blackwell (1959), cannot be excluded. The urinary Figlu excretion, however, was normal.

The group of patients with steatorrhoea following gastric surgery all had normal Figlu excretions. Vitamin-B₁₂ deficiency is not uncommon, however, after partial gastrectomy (Deller and Witts, 1962), and such cases may have abnormal Figlu excretions (Chanarin, Bennett, and Berry, 1962). An abnormal Figlu test in patients with steatorrhoea following gastric surgery cannot, therefore, be regarded as evidence of malabsorption of folic acid.

The patient (Case 29) with carcinoma of the common bile-duct and steatorrhoea had a high Figlu output but a normal urinary xylose-excretion result. The serum folic-acid level was

not determined, but there was no haematological evidence of folic-acid deficiency. Kershaw and Girdwood (1964) found two out of six patients with disseminated carcinoma to have low serum folic-acid levels and increased Figlu excretions, and Girdwood (1953b) has reported evidence of folic-acid deficiency in this condition. The most likely explanation for such cases is that there is an increased demand for folic acid due to the proliferation of malignant cells. Dymock (1964a) has estimated the urinary excretion of urocanic acid and Figlu in 28 patients with malignant disease, and in 24 the outputs were abnormal. He did not measure the serum folic-acid levels, and in 10 cases there was some evidence of liver dysfunction (Dymock, 1964b). It is possible, therefore, that in some cases of disseminated malignancy the abnormal Figlu excretion results from an impairment of hepatic Figlu transferase activity.

A rapid turnover of folic acid may have contributed to the folic-acid deficiency observed in the three patients with lymphosarcoma and the patient with chronic lymphocytic leukaemia. Abnormal Figlu excretions occur frequently in both acute and chronic leukaemias and reticuloses, and in such cases the serum folic-acid levels are often low (Rose, 1964).

Summary

The excretion of Figlu in the urine has been estimated in 35 patients with a variety of diseases accompanied by intestinal malabsorption. It is concluded that although the Figlu excretion test is of limited value for screening patients with suspected idiopathic steatorrhoea, such a diagnosis is unlikely if the Figlu excretion is normal.

It is suggested that the urinary Figlu excretion and the urinary xylose-excretion test used in combination provide a

simple means of assessing jejunal function in patients with small-bowel disease.

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REFERENCES

- Chanarin, I., Anderson, B. B., and Mollin, D. L. (1958). *Brit. J. Haemat.*, **4**, 156.
 ———, Bennett, M. C., and Berry, V. (1962). *J. clin. Path.*, **15**, 269.
 Christiansen, P. A., Kirsner, J. B., and Ablaza, J. (1959). *Amer. J. Med.*, **27**, 443.
 Deller, D. J., and Witts, L. J. (1962). *Quart. J. Med.*, **31**, 71.
 Dymock, I. W. (1964a). *Lancet*, **2**, 114.
 ——— (1964b). *Ibid.*, **2**, 475.
 Fourman, L. P. R. (1948). *Clin. Sci.*, **6**, 289.
 Fowler, D., and Cooke, W. T. (1960). *Gut*, **1**, 67.
 Frazer, A. C. (1956). Broadsheet 9 (new series) of the Association of Clinical Pathologists.
 Gardiner, F. H., and Perez Santiago, E. (1956). *Arch. intern. Med.*, **98**, 467.
 Girdwood, R. H. (1953a). *Lancet*, **2**, 53.
 ——— (1953b). *Brit. med. J.*, **2**, 741.
 Herbert, V., and Zalusky, R. (1962). *J. clin. Invest.*, **41**, 1263.
 Joske, R. A., and Blackwell, J. B. (1959). *Lancet*, **2**, 379.
 Kershaw, P. W., and Girdwood, R. H. (1964). *Scot. med. J.*, **9**, 201.
 Knowles, J. P. (1962). *Gut*, **3**, 42.
 ——— and Pranker, T. A. J. (1962). *Clin. Sci.*, **22**, 233.
 Kohn, J., Mollin, D. L., and Rosenbach, L. M. (1961). *J. clin. Path.*, **14**, 345.
 Merritt, A. D., Rucknagel, D. L., Silverman, M., and Gardiner, R. C. (1962). *J. clin. Invest.*, **41**, 1472.
 Paulley, J. W., Fairweather, F. A., and Leeming, A. (1957). *Lancet*, **1**, 406.
 Rose, D. P. (1964). *Ibid.*, **2**, 311.
 Shiner, M., Vakil, B. J., and Wilcox, P. B. (1962). *Gut*, **3**, 240.
 Tabor, H., and Wyngarden, L. (1958). *J. clin. Invest.*, **37**, 824.
 Wormsley, K. G. (1963). *Gut*, **4**, 261.
 Zalusky, R., and Herbert, V. (1961). *J. clin. Invest.*, **40**, 1091.

Myopathy in Metabolic Bone Disease

J. W. PRINEAS,* M.B., M.R.C.P., M.R.C.P.ED.; A. STUART MASON,† M.D., M.R.C.P.;
 R. A. HENSON,‡ M.D., F.R.C.P.

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Muscular weakness is often found in patients with metabolic bone disease (Albright and Reifenstein, 1948), but the symptom has attracted little attention in the literature. Indeed, weakness may be the outstanding symptom in primary hyperparathyroidism and osteomalacia, and the clinical picture then simulates progressive primary disease of muscle (Vicale, 1949; Dent, 1956; Murphy, ReMine, and Burbank, 1960; Shy, 1960). Diagnoses of myositis and Guillain-Barré syndrome were made initially in Vicale's two patients with primary hyperparathyroidism. Both showed symmetrical weakness and wasting of the proximal muscles of the limbs, a waddling gait, discomfort on movement, hypotonia, and brisk tendon reflexes, with resolution following parathyroidectomy. He also described an identical myopathic syndrome in a patient with osteomalacia.

It has been assumed that a disturbance of ionized calcium is directly responsible for the myopathy in both conditions (Murphy *et al.*, 1960; Shy, 1960; Adams, Denny-Brown, and Pearson, 1962). However, marked weakness has been recorded in osteomalacia in the presence of normal serum calcium (Albright and Reifenstein, 1948; Dent, 1963).

In the following report we describe two patients with long-standing proximal muscular weakness, associated in one case with a parathyroid adenoma and osteomalacia, and in the

other with osteomalacia and idiopathic steatorrhoea. Possible causes of the muscular disorder are discussed.

Case 1

A housewife aged 37 was admitted to Maida Vale Hospital in March 1962 complaining of increasing weakness of the arms and legs for eight months. Walking had been affected first, with particular difficulty in mounting stairs. Within two months she was confined to her home on account of the weakness; she could not lift her 3-year-old son from the floor, and required assistance to dress. She subsequently experienced discomfort and occasionally pain in the thighs on movement. She had lost 7 lb. (3,175 g.) in weight since the onset of weakness. For several years she had risen once nightly to micturate, but there had been no excessive thirst or polyuria. She had five normal children.

Examination showed her to be small and thin, but she looked well. Her gait was waddling, and she climbed up herself in rising from the floor. The muscles of the thighs and buttocks were wasted. There was generalized hypotonia. Hip flexion and extension, abduction of the shoulders, and extension of the elbows were markedly

* Senior Registrar, the London Hospital.

† Consultant Endocrinologist, the London Hospital.

‡ Consultant Neurologist, the London Hospital; Physician, the National Hospitals for Nervous Diseases (Maida Vale), London.