The order against *H. influenzae* and *Proteus* is also G>V>B, with considerable differences between G and the other two.

For the skilful and rapid execution of this work, and for devising the method used for resistant staphylococci, I am indebted to Miss Pamela M. Waterworth. I am also indebted to Beecham Research Laboratories Ltd. for a supply of "broxil," and to Dr. J. S. Murrell for many strains of staphylococci isolated during a current study of antibiotic resistance in septic lesions in out-patients.

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ANTERIOR PITUITARY DEFICIENCY IN DISORDERS ASSOCIATED WITH STEATORRHOEA

BY

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Intestinal absorption may be impaired by a variety of disorders which, despite their diversity, often evoke a pattern of symptoms and signs which conforms to a characteristic clinical picture. Furthermore, these patients have a number of features in common with those of Addison's disease (Salvesen, 1956; Cooke and French, 1958). Prominent among these similarities are asthenia, pigmentation, intermittent diarrhoea, disturbances of water and sugar metabolism, disordered gastric secretory function, and the occurrence of macrocytic anaemia.

It is the purpose of this paper to show that defective intestinal absorption may be associated with decreased anterior pituitary activity and to relate this state to certain metabolic abnormalities which may occur in patients with steatorrhoea.

Material

Seven female patients whose ages ranged from 16 to 64 years were studied; each had steatorrhoea with a 24-hour excretion of faecal fat which averaged 6 g. or more (Cooke, 1956). Two patients had idiopathic steatorrhoea, two had adult coeliac disease, one coeliac disease, one chronic relapsing pancreatitis, and one steatorrhoea following a partial gastrectomy (Table I).

All seven patients had clinical evidence, in varied degree, of endocrine deficiency; especially prominent were features reminiscent of Addison's disease. Investigations included estimation of the 24-hour urinary 17-ketosteroid excretion before and after corticotrophin administration, determination of the serum electrolyte and serum protein levels, examination of the peripheral blood and sternal marrow. With one exception (Case 2), routine urine tests for albumin and sugar were negative, and all had normal liver-function tests. Some patients were further investigated with water-loading and glucose-tolerance tests, a fractional test meal, and radioactive-iodine studies of thyroid function.

The influence of steroid therapy upon the water load and glucose-tolerance tests was studied in one patient (Case 1) over a period of five months. Water-loading tests were repeated four years later, when this patient reattended hospital, having ceased all therapy during the interval. In five patients the effect of treatment upon the blood-picture was also assessed.

Assessment of Endocrine Activity

Clinical Evidence

Pigmentation of the skin was present in five patients, three of whom had buccal pigmentation also. In one (Case 3) asthenia, abdominal discomfort, vomiting, and diarrhoea associated with extensive buccal pigmentation, and a low blood-pressure (100/50) would have justified a clinical diagnosis of Addison's disease.

A deficiency of both growth and gonadal stimulating hormones seemed probable in the youngest patient (Case 4), who had had coeliac disease since early childhood. She was physically retarded—height 53 in. (134.5 cm.), weight 65 lb. (29.5 kg.)—and lacked secondary sexual characteristics; her physical and bone age (assessed radiologically) were comparable with those of a girl aged 9, though her intelligence corresponded with her real age, 16 years.

The skin was smooth and atrophic in four patients; in one it had a semitranslucent appearance with an easily discernible vascular pattern. Some had fine "hair-lines" radiating from the angles of the mouth and eyes.

TABLE I.—*Patients with Intestinal Malabsorption*

Case No.	Age	Diagnosis	Associated Conditions	Fat Excreted in Faeces in 24 Hours (g.)	Anaemia (Hb g. per 100 ml.)	Fasting Blood Sugar (mg./100 ml.)	Blood Electrolytes (mEq/l.)				Blood Urea (mg./100 ml.)	Plasma Proteins (g./100 ml.)		
							Sodium	Potassium	Chlorides	Alkali Reserve		Total	Alb.	Glob.
1	47	Adult coeliac disease	Bronchiectasis	16	Normocytic (11·3)	30 57	147	4·4	102	36·0	32	6·5	3·4	3·1
2	54	Chronic pancreatitis	Chronic nephritis	6	Macrocytic (6·8)	—	144	5·9	112	—	77	6·5	4·2	2·3
3	26	Idiopathic steatorrhoea	—	6·5	Macrocytic (5·3)	95	140	5·1	100	—	45	6·8	4·4	2·4
4	16	Coeliac disease	—	14	Normocytic (9·3)	80	137	5·1	105	26·4	21	6·7	4·3	2·4
5	55	Adult coeliac disease	Pulmonary sarcoidosis	7·2	Normocytic (13·3)	—	140	5·0	103	28·3	—	6·9	4·3	2·6
6	64	Idiopathic steatorrhoea	Diverticulitis. Prolonged thyroid medication (20 years)	14	Macrocytic (12·0)	—	125	3·0	112	—	27	7·4	4·7	2·7
7	58	Partial gastrectomy (1952)	—	8·3	Normocytic (12·9)	83	130	4·9	102	30·0	30	6·7	4·9	1·8

TABLE II.—*Urinary 24-hour 17-ketosteroid Excretion (mg./day) Before and During Corticotrophin Administration in 7 Patients with Intestinal Malabsorption*

	Case 1					Case 2	Case 3				Case 4			Case 5	Case 6		Case 7
Before ..	<1	<1	<1	—	2·5†	1·5	<1	1·1	<1	1·0	2·2	<1	<1	3·9	2·3	2	4·4
During ..	—	—	3·2	4·6*	7·2†	4·4	—	—	—	9·5	—	3·8	2·9	10·8	—	—	11·1

Urinary 17-ketosteroid excretion was reassessed during the last 24 hours of a three-day course of intramuscular corticotrophin 40 units thrice daily.
* After 2 weeks' administration of intramuscular corticotrophin 60 units twice daily.
† Re-estimation after interval of four years without treatment.

In three patients the absence of axillary hair was associated with sparse pubic hair and fine thinned scalp hair, but one (Case 2) had a masculine distribution of body hair with facial and limb hirsuties and a male type of baldness.

Five patients were post-menopausal. In one (Case 1), oligomenorrhoea preceded by nine years the onset of symptoms which coincided with the menopause at the age of 42; another (Case 2) was 39 when the menopause occurred, antedating symptoms by eight years. Emotional shock caused sudden cessation of menstruation in both patients. Of the two pre-menopausal patients, one (Case 4) had not menstruated, and the other (Case 3) had missed only one period.

Investigations

Urinary 17-Ketosteroid Excretion.—The 24-hour urinary 17-ketosteroid excretion was measured (*a*) before treatment, (*b*) during the last 24 hours of a three-day course of intramuscular corticotrophin (Table II), and (*c*) after standard

TABLE III.—*Circulating Eosinophils Before and During Corticotrophin Administration*

Case No.	Circulating Eosinophils/c.mm.								
	Days Before Corticotrophin				During Corticotrophin				
	4	3	2	1	1	2	3	4	5
1	305	360	320	315	190	215	30	15	30
2	—	—	105	85	5	5	—	—	—

forms of treatment (Table IV). (*a*) All seven patients had subnormal steroid excretion levels and repeat estimations in four produced similar low values. (*b*) That these low steroid excretion levels were primarily due to anterior pituitary rather than adrenocortical deficiency was shown by the increased urinary steroid values during corticotrophin administration; one patient (Case 1) in whom corticotrophin therapy was continued had a further rise in 17-ketosteroid excretion after two weeks' treatment. Absolute eosinophil counts (Table III) before and during corticotrophin administration provided further evidence of adrenocortical responsiveness in two patients; a significant decrease in circulating eosinophils occurred, the response being immediate (within four hours) in Case 2 and delayed until the third day in Case 1. (*c*) Low steroid excretion levels persisted after two months' treatment with a gluten-free diet (Case 4), after administration of folic acid (Cases 2 and 4), and after vitamin B_{12} therapy (Cases 3 and 6); neither the degree of anaemia nor body weight influenced the steroid excretion (Table IV).

Serum Electrolytes.—Serum electrolyte values were normal in all except two patients (Table I). In Case 6 the subnormal sodium (125 mEq/l.) and potassium (3 mEq/l.) levels were associated with considerable muscular weakness and were attributed to profuse diarrhoea, which had recurred intermittently for five months. Diarrhoea and weakness were in turn relieved or induced by giving or withholding oral potassium chloride therapy. Case 7 had a subnormal serum sodium level (130 mEq/l.).

Diuretic Response to Oral Water-loading.—The first part of the Robinson-Power-Kepler test was used as a standard oral water-load investigation in Cases 1, 2, 3, 6, and 7.

> The patient was starved from 6 p.m., and all urine excreted between 10.30 p.m. and 7.30 a.m. was measured as the "night urine." After emptying the bladder at 8.30 a.m. the patient drank a quantity of water equivalent to 20 ml. per kg. body weight. At 9.30 a.m. and at hourly intervals until 12.30 p.m. the bladder was emptied; each hourly specimen was measured and the largest single hourly specimen noted as the "day urine."

In each of the five patients investigated the "day urine" failed to exceed in quantity the "night urine" (Table V). Case 2, however, had evidence of renal disease (albuminuria, and blood urea 77 mg./100 ml.), and in Case 6 the possibility of a renal tubular lesion could not be excluded owing to the presence of hypokalaemia (Cooke, 1957).

Glucose-tolerance Test.—Subnormal fasting blood-sugar levels were found in Case 1, but after oral glucose (50 g.) a satisfactory rise in blood sugar occurred (Table VI). Though normal blood-sugar curves were obtained in Cases 2, 3, and 4, the blood-sugar level failed to increase in Case 4 after oral glucose (Table VII).

Thyroid Function.—Radioactive iodine studies were made in two patients. They showed subnormal thyroid activity on two separate occasions in Case 1 and low normal activity in Case 2.

TABLE IV.—*Urinary 24-hour 17-ketosteroid Excretion in Relation to Age, Degree of Anaemia, Weight, Severity of Steatorrhoea, and Treatment*

Case No.	Age	Urinary 17-Ketosteroids (mg./Day)	Haemoglobin % (g./100 ml.)	Weight lb.	Weight kg.	Faecal Fat (g./24 Hours)	Therapy
1	47	<1	67 (11·3)	77	35·4	16	Initially
		<1	71 (10·5)	—	—	—	2nd week — No specific therapy
		<1	—	75	34·0	—	3rd ,,
	51	2·5	77 (11·4)	76	34·5	11	4 years later—no therapy during interval
2	54	1·5	70 (10·4)	158	71·7	6	After 16 months' treatment with folic acid
3	26	<1	44 (6·5)	96	43·5	—	3rd week
		<1·1	68 (10·1)	100	45·4	—	5th ,, — Vitamin B_{12}
		<1	89 (13·2)	103	46·7	6·5	6th ,, — therapy
		1·0	100 (14·8)	114	51·7	—	18th ,,
4	16	2·2	63 (9·3)	63	28·6	14	Initially — No specific therapy
		<1	72 (10·6)	65	29·5	—	4th week
		<1	95 (14·0)	64	29·0	—	After gluten-free diet for 2 months and folic acid therapy for 1 month
5	55	3·9	90 (13·3)	89	40·4	7·2	Initial estimation. No specific therapy
6	64	2·3	81 (12·0)	91	41·3	—	No specific therapy. After massive vitamin B_{12} therapy for 6 weeks
		2·0	68 (10·1)	98	44·5	14	
7	58	4·4	87 (12·9)	95	43·1	8·3	Initial estimation. No specific therapy

TABLE V.—*Patients with Steatorrhoea. Impaired Water Excretion Following Oral Water Loading*

Case No.	Volume "Day" Urine* (ml.)	Volume "Night" Urine (ml.)	Volume Ratio Night/Day Urine
1	170	670	3·94
2	320	565	1·77
3	275	995	3·44
6	170	681	4·01
7	220	235	1·07

* Largest single volume of urine voided at hourly intervals following oral water load of 20 ml. per kg. body weight.

TABLE VI.—*Case 1. Influence of Corticotrophin and Cortisone Therapy Upon Glucose-tolerance Test*

	Blood Sugar (mg./100 ml.)				
	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours
Before treatment	30	44	111	64	—
After 2 weeks' corticotrophin therapy	90	60	90	95	95
After 4 months' cortisone therapy	80	96	90	68	60

TABLE VII.—*Case 4. Influence of Corticotrophin Therapy and of a Gluten-free Diet Upon the Glucose-tolerance Test*

	Blood Sugar (mg./100 ml.)					
	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours	2½ Hours
Before treatment	80	80	65	80	80	80
After 3 days' corticotrophin therapy ..	80	80	100	100	110	—
After gluten-free diet for 6 months	100	—	95	100	100	100

Each patient in this series had features of deficient pituitary activity in varied degree. Adrenocortical insufficiency was universal, but increased urinary steroid excretion levels after corticotrophin administration indicated that the primary deficiency was pituitary in origin. That other adenohypophysial hormones were also involved was suggested by clinical evidence, though isotope studies in Case 1 indicated hypothyroidism and inferred thyrotrophic hormone deficiency. Normal serum electrolyte concentrations were to be expected since serum electrolyte levels are usually unaffected in anterior hypopituitarism, owing possibly to continued baseline aldosterone secretion independent of pituitary activity (Thorn *et al.*, 1957).

Implications of Anterior Pituitary Deficiency

Effects of Steroid Therapy

The existence of a state of adrenocortical deficiency in intestinal malabsorption would rationalize the beneficial effects of steroid drugs in patients with childhood and adult coeliac disease (Almy, 1951 ; Taylor *et al.*, 1952 ; Adlersberg *et al.*, 1953 ; Finlay and Wightman, 1956 ; Lepore, 1958). In these disorders cortisone therapy improves absorption of fat, increases appetite and weight, and arrests diarrhoea and abdominal distension. It improves the absorption curves of glucose, vitamin A, iron, and vitamin B_{12}, and also the capacity to excrete an oral water-load (Kelley *et al.*, 1955 ; Drenick *et al.*, 1955 ; Glass, 1956 ; Nabarro *et al.*, 1957) ; decreased serum calcium, protein, and prothrombin levels are corrected, anaemia improves, and radiologically the intestinal deficiency pattern disappears.

Hitherto these widespread effects of adrenal steroids have been attributed to a pharmacological action, particularly their ability to suppress inflammation and thereby reduce the mucosal damage described by Paulley (1954) and since substantiated by others (Shiner, 1956 ; Doniach and Shiner, 1957 ; Sakula and Shiner, 1957 ; Himes and Adlersberg, 1958). According to the results obtained in the present series, many of the beneficial effects of cortisone treatment could be attributed to correction of a steroid deficiency. Such replacement therapy is supported by the effectiveness of small (physiological) doses of corticosteroids for periods up to seven years, with relapse occurring within a few weeks of withdrawing treatment (Lepore, 1958).

The effects of steroid therapy were investigated in one patient (Case 1) who had evidence of decreased adrenocortical and thyroid activity, the consequence of anterior pituitary deficiency. Her serum protein and potassium levels were normal, and she had no evidence of renal, cardiac, or hepatic disease. Steroid therapy was given in hospital over a period of five months (intramuscular corticotrophin for one month, oral cortisone four months). After her discharge she failed to attend as an out-patient until four years later, when, all treatment having ceased during the interval, she was readmitted with a less severe recurrence of her original symptoms. Re-estimation of her urinary ketosteroid excretion before and after corticotrophin administration again revealed a state of secondary adrenocortical deficiency (Table II).

During her first admission cortisone treatment was associated with a steady improvement in her mental and physical state. Her attitude altered from reluctant

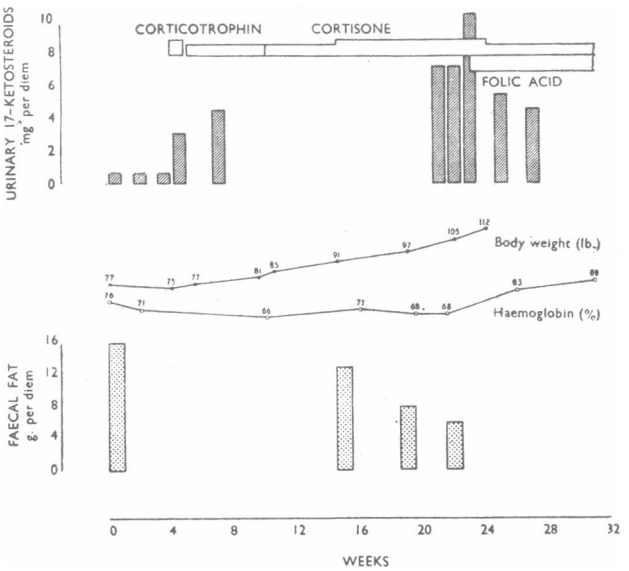

FIG. 1.—Case 1. 24-hour 17-ketosteroid excretion, body weight, haemoglobin, and faecal fat estimations, and their response to corticotrophin administration and cortisone therapy.

acquiescence to co-operation, mild depression was replaced by cheerfulness, appetite was increased, abdominal discomfort disappeared, and she gained 37 lb. (16.8 kg.) in weight in five months. While she was on a standard fat diet her average 24-hour excretion of faecal fat steadily decreased from its original level of 16 g. to 6 g. after 22 weeks' treatment (Fig. 1).

Relationship to Abnormal Water Metabolism

Two separate mechanisms have been implicated in the phenomenon of retarded water excretion in patients with steatorrhoea: (*a*) delayed absorption of water from the intestine (Reitemeier *et al.*, 1956 ; Higgins *et al.*, 1957), and (*b*) impaired renal excretion (Misk *et al.*,

1958), the latter mechanism being regarded as the more important by Misk and his colleagues. A similar impairment of water excretion is seen in patients with such diverse conditions as Addison's disease, cardiac, renal, or hepatic disease, and in those with malnutrition.

That abnormal water metabolism in these varied disorders may be due to a common mechanism is suggested by the work of Mickerson and Swale (1959), who demonstrated a state of anterior pituitary deficiency with secondary adrenocortical inactivity in patients with chronic cardiac failure. It was their opinion that adrenocortical deficiency associated with continued posterior pituitary activity had induced water retention in their patients, the normal antagonism between adrenocortical and antidiuretic hormones at the renal tubule (Talbot *et al.*, 1952) failing to occur. Since a similar deficiency of anterior pituitary function has been demonstrated in patients with malnutrition (Sydenham, 1946; Jacobs, 1948; Thorn *et al.*, 1950) and in those with steatorrhoea in this and other series (Hubble, 1952; Perloff *et al.*, 1954; Bloom, 1955; Krosnick and Kalser, 1956), a corresponding pituitary-adrenal mechanism might also contribute to impaired water excretion in these disorders. This hypothesis would similarly apply in Addison's disease, in which *primary* adrenocortical deficiency would permit unopposed antidiuretic hormone activity. In each of these varied conditions steroid replacement therapy, by countering antidiuretic activity, should encourage diuresis.

Variations in diuretic response to oral water-loading were assessed in Case 1 during her first admission by equating the volume of "day urine" to that of the "night urine" to obtain a volume ratio, decrease or increase of which reflected improvement or further impairment, respectively, in water diuresis. During treatment with corticotrophin the volume ratio decreased from a pretreatment value of 3.94 to 3.53 after three days and to 2.92 after two weeks (Table VIII). After

TABLE VIII.—*Case 1. Effects of Corticotrophin and Cortisone Therapy Upon the Ability to Excrete an Oral Water-load (20 ml./kg. Body Weight)*

Date	Volume "Day" Urine* (ml.)	Volume "Night" Urine (ml.)	Volume Ratio Night/Day Urine	Urinary 17-Keto-steroids (mg./diem)	Therapy
17/6/55	170	670	3·94	<1	
26/6/55	275	1,070	3·53	3·2	Intramuscular corticotrophin 60 units b.d.
9/7/55	250	730	2·92	4·6	
1/9/55	395	640	1·62	—	Cortisone 75 mg. daily
16/9/55	450	740	1·64	—	
6/10/55†	230	720	3·13	7·3	
21/11/55	380	663	1·75	4·7	Cortisone 50 mg. daily

* Volume of largest single hourly specimen following oral water-load.
† During severe bronchitis.

seven and nine weeks of cortisone therapy (75 mg. daily) the respective ratios were 1.62 and 1.64, but later the ratio increased to 3.13 during an attack of bronchitis. One month after recovery and with reduced cortisone dosage (50 mg. daily) the ratio was 1.75.

Though cortisone (and adrenal stimulation also) improved diuresis in this patient it did not restore a *normal* diuretic response to water-loading. This failure might be explained by an inability to correct impaired water absorption, the greater part of the improved water diuresis resulting from correction of its delayed renal excretion. In support of this view Reitemeier *et al.* (1956), using isotope tracers, were unable to increase the rate of intestinal water absorption in patients with steatorrhoea by cortisone administration. It is likely that intestinal mucosal damage accompanying steatorrhoea of long duration is permanent and incapable of being reversed by steroid therapy.

When this patient was readmitted four years later an attempt was made to estimate which of the two mechanisms, intestinal or renal, exerted the greater influence in delaying water excretion.

The diuretic response following oral and intravenous water-loading was determined before and during prednisolone therapy (15 mg. daily). Intravenous loading was assessed by substituting an intravenous infusion of 5% dextrose solution (15 ml./kg. body weight) for the oral water-load. Of the fluid administered orally only 33% was excreted within four hours, but 103% of the intravenous load was excreted over a similar period. During steroid therapy the corresponding percentage excretions were 61 and 162 (Fig. 2).

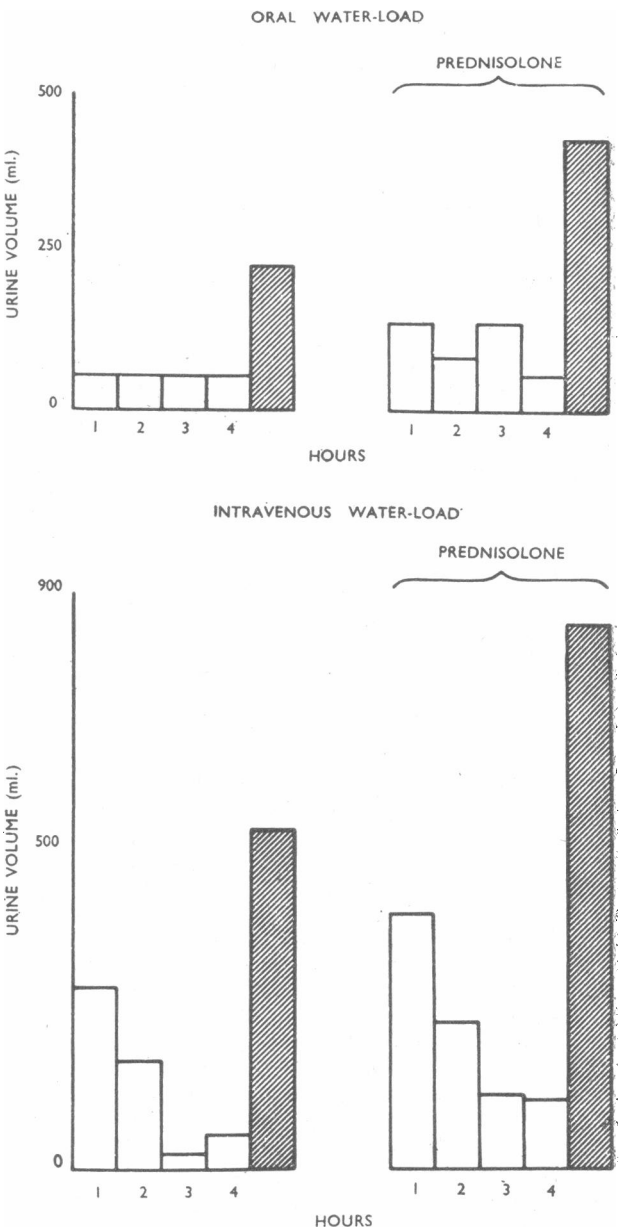

FIG. 2.—Case 1. The effects of prednisolone on the urinary excretion following oral (20 ml./kg. body weight) and intravenous (15 ml./kg. body weight) water loading.

These results indicate that, in this patient, an extra-renal (most probably impaired intestinal absorption) rather than a renal factor was mainly responsible for the delayed diuresis (see Addendum). Though the excretion of both oral and intravenous water-loads was enhanced during steroid therapy, it was not possible to determine the site of steroid activity.

Carbohydrate Metabolism

The association between adrenocortical deficiency and malabsorption states might also account for other metabolic abnormalities, since adrenocortical hormones are potent regulators of carbohydrate, protein, and fat metabolism. Thus could be explained low fasting blood-sugar values and flat glucose-tolerance curves in patients with steatorrhoea. The low initial fasting blood-sugar levels (30 and 57 mg./100 ml.) in Case 1 increased to normal values during steroid administration (Table VI), and in Case 4 a rise occurred in the glucose-tolerance curve after three days' treatment with corticotrophin, an improvement which was not matched by a gluten-free diet for six months (Table VII).

Gastric Secretory Function

The circumstances which have been postulated to explain abnormal water metabolism in patients with steatorrhoea might also explain the frequent occurrence of diminished gastric secretory activity in this disorder. That a state of adrenocortical deficiency might be incriminated is supported by the finding of depressed gastric secretion in hypopituitarism and Addison's disease and its restoration by cortisone therapy (Witts, 1958), and also by the suggestion of Kyle *et al.* (1956) that some correlation exists between gastric secretory activity and the urinary ketosteroid excretion. It is also possible that posterior pituitary activity might exert an influence, since inhibition of gastric secretion has been reported to follow pituitrin administration (Cutting *et al.*, 1937; Harries, 1956).

All five patients in this series (Cases 1, 2, 3, 5, and 6) in whom gastric secretion was investigated had an achlorhydria, and in Cases 2, 5, and 6 it was fast to histamine.

Blood Picture

Anaemia occurring in association with steatorrhoea may result from inadequate absorption of iron (Badenoch and Callender, 1954), folic acid (Cox *et al.*, 1958), or vitamin B_{12} (Oxenhorn *et al.*, 1957; Meynell *et al.*, 1957) alone or in combination.

Five patients in this series were anaemic (Table 1); two had a normocytic anaemia, and in the remainder it was macrocytic. All five were followed until their anaemia was corrected; in each instance it responded to folic acid, vitamin B_{12}, or cortisone therapy; none required iron supplements.

It has been shown that patients with regional ileitis and adult coeliac disease have a reduced absorption of vitamin B_{12} (Meynell *et al.*, 1957), and that this abnormality can be improved by steroid therapy. Though such inadequate absorption would account for the immediate response to intramuscular vitamin B_{12} and subsequent correction of anaemia in one patient (Case 3) whose peripheral blood and sternal-marrow pictures were characteristic of pernicious anaemia, similar treatment was ineffective in two others (Cases 2 and 6) with macrocytic anaemias which later responded to cortisone administration. Clearly, improvement in these two patients could not be attributed to enhanced absorption of vitamin B_{12}. Furthermore, the haemopoietic effect of cortisone therapy was not dependent upon improved absorption or utilization of folic acid (Cooke, 1958), since anaemia responded to folic acid therapy after earlier failure with cortisone in Case 1, while in Case 2 cortisone was effective after folic acid had failed to maintain its initial haemopoietic stimulus.

Discussion

The coexistence of a state of deficient adrenocortical activity found in patients with intestinal malabsorption in this series offers an explanation for certain features that are shared not only by patients with this disorder, irrespective of its cause, but also by those with Addison's disease.

It is not surprising that similar findings, previously recorded, have been attributed to malnutrition, since intestinal malabsorption is inextricably associated with a decreased calorie intake. That malnutrition should be assigned this important role is based upon a parallel with experimental animals (Gordan *et al.*, 1948; Li *et al.*, 1949; Samuels, 1950; D'Angelo, 1951) and human subjects, most of whom have been prisoners of war receiving grossly inadequate diets (McCullagh and Tupper, 1940; Sydenham, 1946; Jacobs, 1948; Thorn *et al.*, 1950). Under such circumstances "malnutrition" would imply impaired absorption to the extent of starvation, a conception which is difficult to accept in patients with steatorrhoea, however severe, since their intestinal absorption considerably exceeds that of subjects living under famine conditions. In this series decreased adenohypophysial activity could not be attributed to such dietary impoverishment. The body weight was greatly reduced in two patients (Cases 1 and 4), but one (Case 4) had the appearance of well-nourished underdevelopment rather than starvation; in every respect save that of mental ability, which was in keeping with her real age of 16, her development corresponded with that of a girl aged 9. A deficiency of dietary calories alone could not be incriminated in the remaining patients, one of whom (Case 2) was actually obese.

It is possible, however, that a qualitative dietary deficiency contributed to the development of anterior pituitary insufficiency. By virtue of its control over peripheral endocrine activity the pituitary maintains a nice equilibrium between anabolism and katabolism. Foremost in the conservation and replenishment of essential nutritional factors, the adrenocortical hormones, secreted in response to pituitary stimulation, exert considerable anabolic activity, and are potent regulators of carbohydrate, fat, protein, and electrolyte metabolism. Thus would the pituitary-adrenal mechanism be activated whenever minor deficiencies of these essential factors occur—a likely possibility with any gastro-intestinal lesion of sufficient severity to impair absorption. The longer the duration and more severe the intestinal lesion the greater will be the demand for adrenocorticoids.

Should the limit of pituitary responsiveness be surpassed by excessive or prolonged demands, anterior pituitary exhaustion will occur. In this manner the pituitary, having unsuccessfully attempted to correct the vital deficiency, allows peripheral endocrine activity to decrease, thereby reducing metabolism to a level

commensurate with nutritional supplies. Pituitary exhaustion would occur more readily when adrenocortical demands are extended by other coexistent factors—for example, infection, allergy, or hot climates (Conn *et al.*, 1948). The importance of superadded infection is well illustrated in Case 1, where the ability to excrete an oral water-load steadily improved during treatment with cortisone until respiratory infection created a demand for adrenocorticoids. The temporary deterioration in diuretic response (Table VIII) was attributed to deviation of administered steroids to the site of infection, and reduced activity at the renal tubule in consequence.

As a corollary of this hypothesis, anterior pituitary insufficiency, by inducing a state of decreased peripheral endocrine activity, particularly adrenocortical, would no longer resist the loss of essential nutritional factors via the intestine (indeed, they would not be required under such circumstances). A vicious circle would be established, with excessive loss of nutrient material in turn favouring continuation of the state of pituitary exhaustion. This circle would not be broken while the cause of pituitary exhaustion persisted, but continued steroid therapy would produce improvement by correcting adrenocortical deficiency and restoring opposition to the intestinal drain on nutrition.

Many patients with steatorrhoea may not seek advice until the state of pituitary exhaustion supervenes, by which time most of their symptoms would be due to pituitary-adrenal insufficiency *per se* or aggravation of their intestinal symptoms by such insufficiency, rather than to the primary intestinal lesion. At an earlier stage, during pituitary-adrenal stimulation, steatorrhoea may be symptomless and be discovered during routine investigation—for example, for unexplained macrocytic anaemia. During this phase symptoms and signs of corticoid deficiency would depend upon the residue of steroids available for vital activities elsewhere after a variable proportion has been utilized in attempting to correct defective absorption.

This hypothesis reinforces the statement by Cooke (1958), who emphasized that in patients with steatorrhoea the actual absorptive functions of the intestinal cell are relatively minor compared with the major metabolic functions that it performs.

Summary

Clinical and biochemical evidence is presented to indicate a state of anterior pituitary deficiency in seven patients with intestinal malabsorption.

A possible relationship is discussed between this state of decreased adenohypophysial activity and abnormal water and carbohydrate metabolism and also gastric secretory function in patients with steatorrhoea. This state is invoked to explain a number of features which are shared by patients with intestinal malabsorption, irrespective of the causal lesion, and which occur also in those with Addison's disease. The beneficial effects of steroid drugs in steatorrhoea are attributed to correction of the secondary adrenocortical deficiency by substitution therapy.

ADDENDUM.—Since this paper was completed an intestinal biopsy has been done on Case 1 by Dr. R. A. Parkins. Extensive mucosal atrophy was present.

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In their *Report for 1958–9*, the committee of the Museum of the History of Science in Oxford record the following gifts: a scarificator for vaccination, by "Weiss, London," nineteenth century, which belonged to Dr. Paulin Martin, Clock House, Abingdon; sterilized silk sutures, sealed in glass tubes, some with the label of S. Maw, Son and Sons, London, in two metal containers, *c.* 1914; and a pocket case of surgical instruments, which belonged to Dr. Henry Watson, nineteenth century. (*Oxford University Gazette*, January 5, 1960.)