

Hypophosphataemia in anorexia nervosa

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The prevalence, causes, and consequences of hypophosphataemia in the clinical treatment of various diseases are described in the literature, but are not so seriously regarded as a severe electrolytical disturbance.^{1–3} The clinical conditions when hypophosphataemia should be suspected are listed in fig 1. There is a triad of disturbances: hypokalaemia, hypomagnesaemia, and hypophosphataemia which often follows trauma, and glucose overload.⁴ In anorexia nervosa patients, hypokalaemia, hypochloraemia, and metabolic alkalosis are commonly seen.^{5–7}

A high prevalence of hypophosphataemia is seen among post-traumatic and/or critically ill patients undergoing intensive care.⁸ Infectious diseases are also associated with the risk of developing hypophosphataemia.⁹ Immunological disturbances can result from a deficiency of several nutrients, such as zinc.¹⁰ Hypophosphataemia was found in anorexia nervosa patients with respiratory distress and signs of pneumonia.^{11–13} Recently, it was reported that the main causes of death of patients with anorexia nervosa was electrolytic disturbance and infection.^{11–14}

The incidence of hypophosphataemia in a hospital population is usually associated with undernutrition followed by refeeding.^{15–18} Recent reports of hospital undernutrition should alert health and medical staff to the significance of low serum phosphate concentrations. For example, overambitious treatment of undernourished patients with high energy intake

can cause hypophosphataemia related paralysis and respiratory insufficiency.¹⁹

Hypophosphataemia with symptoms of phosphate depletion was first described in connection with starvation during wartime and in prisoners when refeeding was initiated after a period of phosphate loss.^{20–21} Milk (rich in phosphate) was a life saver.^{21–22} Protein energy undernutrition predisposes to hypophosphataemia.^{4–23} When a gradual breakdown of tissue takes place during starvation, total depletion of the body's phosphate stores may develop, even though the serum phosphate level most often remains normal.¹ Anorexia in adolescent girls occurs at a serum phosphate level of 0.8–1.0 mmol/l.²⁴ Reference values vary with age.

It has been stated that anorexia nervosa is a condition characterised by protein energy undernutrition, which may also explain other deficiencies said to exist in anorexia nervosa patients.²⁵ Most deficiencies have a protein source, for example zinc, selenium, potassium, phosphate and calcium, in addition to vitamin D deficiency, due to low fat intake.²⁶ These deficiencies may also contribute to loss of appetite.

Anorexia, well described symptom in phosphate depletion and/or hypophosphataemia, has frequently been documented before other disturbances in both experimental and clinical conditions.⁴ Eight out of 10 case reports on the sequelae of hypophosphataemia in anorexia nervosa have described female patients. In one study, only two of 65 adolescents with anorexia nervosa were boys.⁷ Causes and consequences are both related to gender, the consequences of phosphate depletion differing because of the smaller muscle mass of women than of men.²⁷ Progressive hypercalciuria and negative calcium balance developed in women but not men.²⁷ A smaller total phosphate pool in female rats has been found in experiments.²⁸ Fatigue and muscle weakness, often reported in anorexia nervosa patients, may be an early hypophosphataemic sign of phosphate depletion, as is loss of appetite.^{6–7–24}

The dangerous consequences of phosphate depletion emphasise the urgency of this discussion (box 1). The fatal condition is connected with disturbed oxidative phosphorylation and adenosine triphosphate (ATP) depletion in almost all vital functions. Loss of appetite can predispose to major complications, such as growth disturbances, neurological sequelae, and demineralisation of the skeleton. Hypophosphataemia has been reported in anorexia nervosa patients in connection with neurological complications and both respiratory and congestive heart failure. Several case reports of hypophosphataemia in anorexia nervosa, in addition to the most

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Hypophosphataemia in addition to:

- Malnutrition/undernutrition (semistarvation)
- Refeeding (syndrome)
- Alcoholism (withdrawal)
- Diabetic ketoacidosis
- Infectious disease
- Stress condition (surgery, burns, etc)
- Antacids and diuretics
- Accelerated growth (puberty)
- Catch-up growth in preterm infants
- Intensive care patients: parenteral nutrition
- Haemofiltration/dialysis
- Renal failure
- Post-renal transplantation
- Hyperparathyroidism

High risk in connection with:

- Anorexia nervosa
- Chronic infections
- Diabetic ketoacidosis
- PEM in children
- Crohn's disease
- Malignancies etc

Figure 1 Clinical conditions when hypophosphataemia should be suspected (PEM = protein energy malnutrition).

Box 1: Consequences of phosphate depletion and/or hypophosphataemia for different functions in anorexia nervosa

- Loss of appetite (anorexia).
- Neuromuscular.
- Cardiopulmonary.
- Haematological.
- Gastrointestinal.
- Renal.
- Endocrinological.
- Skeletal.

And

Life threatening due to ATP depletion and deranged composition of phospholipids in membranes of the nervous system, heart, red corpuscles.

And

Sudden death.

frequently cited reports from experimental studies, are referred to in the present paper.

The purpose of this review is to expand our knowledge of the role of phosphate, especially its depletion, a neglected condition in the clinical situation.

Underlying pathophysiology/ biochemistry

Reduced protein synthesis has been described in experimental studies as being associated with restricted eating.²⁹ It was concluded that an increased amount of phosphate is needed for ATP production which in turn is a prerequisite for protein synthesis (maintenance of the nitrogen balance) and appetite. This shows that phosphate depletion leads to anorexia by contributing to low protein synthesis.

Normal serum phosphate concentrations do not preclude pre-existing total body depletion of phosphate, with a low intracellular pool *vis-à-vis* nitrogen (lower phosphate/nitrogen ratio).³⁰ Starvation with weight loss results in a negative nitrogen balance affecting the skeleton, muscles and hormones, with changes in the protein nutritional status (low albumin concentrations). Low serum albumin is a late and severe manifestation of protein energy undernutrition, if there is a superimposed infection.

When anabolism is induced by high energy intake—and particularly carbohydrates—as the main source of energy, phosphate shifts from serum into cells, thus giving rise to hypophosphataemia.¹⁵ The priority of fat metabolism during starvation and semistarvation is superseded in the refeeding situation by carbohydrate priority and an increased need of phosphate for phosphorylation and protein synthesis.³¹ Intracellular trapping of phosphate is described when metabolism switches from lipolysis to glycolysis.³⁰ This concerns blockage of the intracellular utilisation of phosphate without any necessary change in the phosphate/nitrogen ratio. As phosphate is

involved in almost all cellular processes, the specific disturbances in different conditions are even more difficult to identify.

Low levels of ATP in red blood cells cause hypoxia and haemolysis while contractility is reduced in the myocardium and respiratory muscles.^{4 32} Experimentally induced phosphate depletion affects left ventricular energy generation, impairing myocardial contractile force.^{32 33} Red blood cells are dependent on a certain level of extracellular phosphate, as the means of membrane transport is passive diffusion. Low levels of both ATP and 2,3 diphosphoglycerate have been reported in hypophosphataemia in a patient with anorexia nervosa.³⁴ Low levels of ATP in leukocytes impaired immunofunction.⁴ An intracellular depletion of inorganic phosphate, which has been shown in experimental studies to be correlated to serum levels (concentrations are about 100:1), first affects the phosphorylation of creatine to creatinine phosphate, which is the primary donor of phosphate to adenosine diphosphate.^{1 4 32} Secondly, resynthesis of ATP is diminished. Electrolytic imbalance across cellular membranes, caused by a diminished adenosine triphosphatase activity, results in an intracellular accumulation of calcium, sodium, chloride, and water. This is probably the mechanism of oedema described in patients with anorexia nervosa and also in protein energy undernutrition.^{23 35}

Disturbances of the acid-base balance and electrolyte status have been reported in cases of anorexia nervosa and in phosphate depletion.^{5 11 30 36 37} Lactic acidosis and rhabdomyolysis can be caused by deranged phosphate metabolism.³⁰ A comparable condition has been described in an anorexia nervosa patient who had metabolic alkalosis and respiratory acidosis.⁶ Starvation, with severe nutrient deficiencies, may accelerate phosphate loss via the urine.^{24 38} Such loss is associated with increased acid excretion.³⁷

The ketone bodies produced by starvation, and/or the lactic acids produced by physical training, lead to an excess of hydrogen ions. The phosphate buffer, whose main source is bone, eliminates these ions. Bone, a dynamic store for calcium and phosphate, helps to regulate the composition of the extracellular fluid. An early sign of phosphate depletion in women is calcium loss via the urine, and increased risk of hypercalcaemia.²⁷ Significantly higher serum concentrations of calcium and lower serum phosphate were observed in patients with anorexia nervosa than in controls.³⁹ The hypercalcaemia is *per se* connected with morbidity and mortality risk.

Animals fed a low phosphate diet developed anorexia and increased bone resorption.^{40 41} A catabolic condition, such as starvation, mobilises phosphate from both skeletal muscle and bone. Resorption of the skeleton due to an acidic state may explain the low bone mineral content and is the result of acidosis (fig 2).⁴² Bone resorption supplies alkali to blood and urine.³⁰

Decomposition of the skeleton. The effect of altered pH in extracellular fluids, in addition to the effects of phosphate depletion on the pH, need to be observed

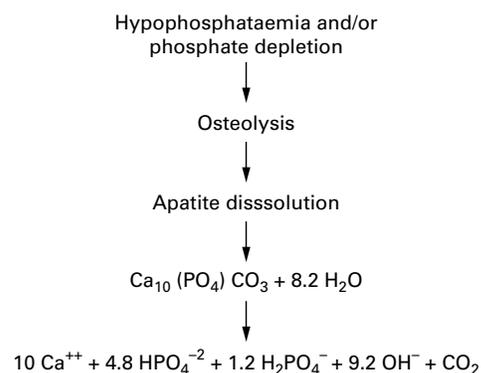


Figure 2 Decomposition of the skeleton.

It has been found that the resorption of phosphate in the kidney is reduced in metabolic acidosis.³⁸ High urinary phosphate excretion due to an extremely low threshold for phosphate resorption has also been described in a patient with anorexia nervosa.³⁴ By oral or intravenous phosphate supplementation, both phosphate and acid excretion via the urine can be made to increase. This acidotic correction produced by readjusting phosphate depletion results in weight gain.

Experimental studies in animals indicate that accelerated growth, despite an acceptable intake of phosphate, produces the symptoms of phosphate depletion.⁴³⁻⁴⁴ Phosphate depletion before or during puberty can affect the metabolism of chondrocytes in the growth plate—thus inhibiting growth of the long bones. Short stature was described in one patient with anorexia nervosa, who contracted the disease at the age of 11 years.⁴⁵ She had slightly raised serum phosphate values, probably the result of release from bone in connection with femoral head collapse.

Rickets may be caused by deficiency of calcium, vitamin D, and phosphate.⁴⁶ Repletion with phosphate, with increased collagen turnover, heals rickets.⁴⁷ It seems that an increased need of phosphate, in the catch-up growth, for example in premature infants, explains the development of the pathophysiology of rickets.⁴⁸ Premature closure of the epiphyseal growth plate is observed in stress induced disturbances, possibly resulting in disruption of the proliferation of chondrocytes in the epiphyseal cartilage. Since the metabolism of these cells is highly glycolytic (anaerobic), their growth depends on substrates penetrating the cells and the production of glycolytic ATP, which can hinder the proliferation and differentiation of the chondrocytes. Could it be that the reduced protein synthesis and growth retardation are an adaptation to the low energy intake? Phosphate depletion could be the signal for this state, as neither energy metabolism nor anabolism is maintained without the presence of phosphate. If phosphate depletion causes loss of appetite in order to maintain a balance between energy produced and metabolism, the

undernutrition *per se* needs to be analysed. Reduced DNA synthesis in growth plate cartilage has been attributed in experimental studies to undernutrition.⁴⁶

Clinical consequences

In patients with anorexia nervosa, starvation, vomiting, laxative abuse, and exercise all contribute to a negative phosphate balance. Loss of phosphate via stool and urine, in addition to low intake during periods of accelerated growth (puberty), can cause symptoms of phosphate depletion. The occurrence of hypophosphataemia in anorexia nervosa, concomitant with nutritional recovery, may reveal a phosphate deficiency. Avoidance of phosphate containing (protein rich) foods (milk, fish, meat, egg) when combined with low energy intake (protein energy undernutrition), depletes the body's pool of phosphate, leading to subnormal serum phosphate concentrations. Measurement of serum phosphate concentration yields little information regarding total phosphate body pool.

Protein energy undernutrition in a 12 year old girl and a 9 year old boy predisposed to refeeding hypophosphataemia.¹⁸ It is known that the level of serum phosphate is correlated to age and growth and that resorption of phosphate in the kidneys is higher in growing youngsters than in adults, and has also been described experimentally.⁴³⁻⁴⁹ This demonstrates the increased need of phosphate during growth.

It is obvious also from clinical studies that the level of phosphate intake is closely related to body growth and that the risk of phosphate depletion increases during periods when the growth rate is high.⁴³ Physical growth and the mineralisation of the long bones during puberty are associated with high serum phosphate levels.

In adults, hypophosphataemia causes osteomalacia, and rickets in children. Phosphate depletion and hypophosphataemic rickets in children stunts growth. In experimental studies, phosphate depletion restricted weight gain and caused growth disturbances.⁵⁰⁻⁵¹

Patients with anorexia nervosa have been found to have osteoporosis, with significantly reduced trabecular bone volume on biopsy.⁵²⁻⁵⁴ Undernutrition at the time of attaining peak bone mass could account for the low bone mass of anorexia nervosa patients.⁵⁵ Does the bone mass loss accompany weight loss? It is known that weight for height is correlated with bone mineral density in patients with anorexia nervosa as well as in controls.⁵⁶ Weight loss is correlated with debility due to phosphate depletion, while weight gain is dangerous unless enough phosphate is given in relation to energy requirements.⁵⁷ Restoration of body weight also improved bone mass before the oestrogen level was readjusted, indicating the importance of an overall delivery of nutrients to cause optimal accretion of tissue.⁵⁶

The high prevalence of scoliosis (24%) among ballet dancers with anorexia nervosa might also be attributable to a loss of phosphate caused by dieting and intensive

Table 1 Sequence of events after institution of total parenteral nutrition (TPN) in two cachectic patients (Weinsier and Krumdieck, 1981⁶¹)

	Case 1	Case 2
Within 48 hours of instituting TPN	Hypophosphataemia Hyperglycaemia Metabolic acidosis Hypomagnesaemia Chest pain Tachycardia Hypotension Cardiac arrhythmia Tachypnoea Adult respiratory distress syndrome Mechanical ventilation	Hypophosphataemia Hyperglycaemia Metabolic acidosis Hypokalaemia Lethargy Tachycardia Hypotension Apnoea Mechanical ventilation Adult respiratory distress syndrome Pulmonary infection
After correction of hypophosphataemia	Episode of gastrointestinal bleeding Pulmonary infection Sepsis Persistent cardiopulmonary irregularity Death	Episode of gastrointestinal bleeding Peritonitis Sepsis Persistent cardiopulmonary irregularity Death

training. Bergengren published an abstract presenting the hypothesis that anorexia nervosa and scoliosis develop due to phosphate depletion.⁴⁴ Hypophosphataemia and lumbar scoliosis in the spine and uncalcified osteoid were observed in the iliac crest of an anorexia nervosa patient.^{58 59} Phosphate depletion might also explain the femoral head collapse in another patient with anorexia nervosa.⁴⁵

Life threatening complications associated with refeeding in anorexia nervosa have been suggested as being caused by hypophosphataemia, with intracellular ATP depletion.⁶⁰ A low serum phosphate level is fatal and may account for sudden cardiac arrest in anorexia nervosa patients.¹³ Weinsier and Krumdieck described schematically the clinical situation in two cases during total parenteral nutrition (table 1).⁶¹ Electrocardiography measurements revealed QT prolongation. No discussion of the influence of serum phosphate was put forward. In one case report, heart failure had occurred secondary to severe hypophosphataemia despite oral phosphate supplementation.⁶² In another report, a variety of electrocardiographic abnormalities were found in 86% of patients with anorexia nervosa.⁶³ As death is sudden and unexpected in an unknown number of patients, the hypophosphataemia—but more probably phosphate depletion (due to undernutrition) despite normal serum phosphate levels—may be the causative factor. Schocken *et al* concluded that further clinical studies are needed to define better the full effects of anorexia nervosa and starvation on the heart and to determine the ideal method of nutritional rehabilitation.²⁵

Clinically, in anorexia nervosa, hypophosphataemia may be involved in the development of cardiac arrhythmia and explain the small heart size and reversible cardiomyopathy.^{60 64 65} Other symptoms from the heart, such as bradycardia due to atrophy of the myocardium and left ventricular dysarrhythmia, are described in case reports. Reduced stroke output and cardiomyopathy have been described in other patient populations in connection with hypophosphataemia.⁶⁶ Improvement of myocardial function is observed when hypophosphataemia is corrected.^{66 67}

Hypophosphataemia has been described in anorexia nervosa patients with neurological complications, acute renal and respiratory failure, congestive heart failure possibly due to a combination of reduced phosphate intake and increased loss via the urine, and precipitated by refeeding.^{6 12 24–26 34 39 60 68 69} Children with protein energy undernutrition subjected to refeeding may suffer from dysphagia in addition to hypophosphataemia.¹⁸ In a semistarved male, hypophosphataemia due to alcohol poisoning caused dysphagia.⁷⁰ Within 12 hours of a phosphate infusion, there was marked improvement in his dysphagia and dysarthria. Achalasia, a reduced oesophageal motility due to loss of neurological regulation has been described in anorexia nervosa.⁶⁰ The neurological disturbances caused by hypophosphataemia can be severe, causing delirium, paralysis, and even death.^{19 31 60 61 64 69 71} In patients with anorexia nervosa, peripheral sensory neuropathy was also present.¹¹ The prolonged starvation in some patients may have caused cerebral atrophy.⁶⁴

Treatment/prevention

Large quantities of nutrients can result in cardiac, pulmonary, haematological, and neuromuscular dysfunction and the amount of phosphate given should be calculated. This condition, described in both anorexia and infant undernutrition, is called the “refeeding syndrome”.¹⁷ Knowledge in the field of refeeding and how to reduce the risk of hypophosphataemia is mostly lacking in the clinical setting. Figure 3 gives a few guidelines, taken from cited references, which could be helpful. Two mg phosphate/kg body weight over six hours is proposed as a suitable dose in the initial phase and serum phosphate will be restored within 36 hours.⁷² Acute respiratory failure occurs in hypophosphataemic patients with anorexia nervosa.¹² The patient hypoventilates, in consequence of neuromuscular dysfunction. Rapid improvement after phosphate supplementation for one week, and a stabilised serum phosphate level (1.2–1.5 mmol/l), indicate the involvement of phosphate depletion.

Treatment		1 mmol of phosphate contains 31 mg of elemental phosphorus (0.032 mmol = 1 mg) 1 mmol of phosphate/l = 3.1 mg phosphorus/dl (0.323 mmol/l = 1 mg/dl)
IV	279 mg (9 mmol)	Vannatta <i>et al</i> , 1981 ⁷²
IV	0.32 mmol/kg/12 hours	Bugg and Jones, 1988 ⁷⁹
IV	10–15 mmol/4 hours (or 0.25–0.50 mmol/kg)	Kingston and Al-Siba, 1985 ⁸¹
IV	30 mmol/12 hours	Cariem <i>et al</i> , 1994 ¹¹
IV	115 mmol phosphate/4 days (2.8 mmol phosphate/kg)	Van Dissel <i>et al</i> , 1992 ³⁴
By mouth	30–90 mg phosphate/kg/24 hours (max 3000–4500 mg/24 hours)	Hall <i>et al</i> , 1994 ⁷¹
IV	15–45 mg phosphate/kg/24 hours (max 2000 mg/24 hours)	Hall <i>et al</i> , 1994 ⁷¹
By mouth	Skim milk (0.9 mg/ml–90 mg/dl)	Stoff <i>et al</i> , 1982 ²
IV	2.5–5.0 mg/kg/dose over 6 hours	Stoff <i>et al</i> , 1982 ²
IV	2.5 mg/kg/6 hours	Lentz <i>et al</i> , 1978 ³

- Slow refeeding
- Adequate phosphate intake
- Feeding by mouth or enteral (parenteral only in extreme situation)
- Avoiding side effects (for example, hypocalcaemia and hyperkalaemia)
- Close monitoring of serum phosphate
- Adjust infusion rate

Figure 3 Guidelines for refeeding.

Not only parenteral/intravenous nutrition but also enteral and oral nutrition causes hypophosphataemia if the amount of energy given is more than can be tolerated, and may occasionally (though not invariably) be connected with clinical disturbances.^{68 70 73 74} It is important to be aware of the deleterious effects of an excess of nutrients.^{70 74 75} Treatment with parenteral nutrition without phosphate supplementation is most probably the cause of hypophosphataemia.^{76 77}

It is essential to monitor serum phosphate concentrations in patients at risk, for example, all malnourished adolescents and anorexia nervosa patients.^{78 79} “Binge eating”, an extraordinarily high energy intake, causes hypophosphataemia in anorexia nervosa.⁸⁰ Thus, the amount of energy given should be calculated individually for each patient and supply all the nutrients that may be lacking and needed in increased quantity due to the suddenly induced anabolism. Phosphate supplementation may be necessary.^{57 79} With 6.8 mmol/l total parenteral nutrition (TPN), none become hyperphosphatemic.⁷⁶ TPN of 13.6 mmol/l reduces the risk of a decrease in serum phosphate while increasing the prevalence of hyperphosphataemia. Side effects and complications that may develop are listed in box 2.

It is important to realise that the consequences of hypophosphataemia in the condition of refeeding, for example, even when an adequate amount of phosphate is given, are far more serious than in chronic phosphate depletion.⁴ In the early phase, cardiac disturbance, high blood pressure, oedema, and neurological complications are all attributable to hypophosphataemia. In anorexia nervosa this condition is life threatening.^{31 60}

Box 2: Side effects and complications

- Hypocalcaemia and associated tetany (should also be corrected).
- Hyperkalaemia (if potassium phosphate salts).
- Hyperphosphataemia.
- Diarrhoea (with orally administered phosphate).
- Volume excess (if sodium phosphate).
- Hypotension.
- Renal failure.
- Electrocardiographic abnormalities.

Thus, the hypophosphataemia in susceptible conditions should be corrected. Prevention or prophylactic treatment would seem to be the best way to tackle and avoid the consequences of hypophosphataemia in patients with anorexia nervosa as well as in other conditions with increased risk of phosphate depletion.⁸¹ However, it was recommended that 1 g (32 mmol) per 24 hours at most should be given and that serum phosphate and the rate of rise in urinary phosphate be monitored closely.⁶⁷ Oral phosphate can be given in a dose up to 3 g (96 mmol)/day (~1 mg elemental phosphate/ml skim milk = 1g (32 mmol)/l).¹

Daily intake with diet may vary according to amount of protein and source of protein (availability differs). From 0.6–2.0 g (19.2–64 mmol/l) is often seen with a balanced diet. The increased demand for phosphate in anabolism needs to be satisfied and the amount given should be calculated according to energy available and the quantity of carbohydrates given. Energy requirement for optimal weight gain must be calculated carefully.^{10 75}

Daily monitoring of serum phosphate as well as adequate supplementation with phosphate should be considered. In some reviews advice on treatment and how to treat severe hypophosphataemia is given.^{3 78} More phosphate is needed in a condition with multiple causes of hypophosphataemia and, if it is protracted, compared with single causes and short term.³ Weight gain and the risk of symptoms of hypophosphataemia in the nutritional rehabilitation of patients with anorexia nervosa indicate the importance of more individualised dietary guidelines.

Conclusion

From these case reports and reviews of the consequences of hypophosphataemia, much should be learned and remembered. First, one must be aware of the imbalance in the presence of an unrecognised serum phosphate decline in metabolism with the possible fatal outcome. Secondly, undernutrition with weight loss, for example, all conditions with semistarvation and disease related cachexia, are high risk conditions for phosphate depletion. Third, nutritional rehabilitation is of importance and lifesaving if it is individualised and given in accordance with guidelines for phosphate administration.

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Medical Anniversary

Norman Rupert Barrett, 16 May 1903

Norman Rupert Barrett (1903-79) was born in Adelaide, Australia and educated at Eton, Trinity Cambridge, and St Thomas' Hospital where he qualified in 1928. He became consultant thoracic surgeon to St Thomas' and Brompton Chest hospitals and editor of the journal, *Thorax*. He is remembered now for his clear exposition of metaplasia of the lower oesophagus—Barrett's oesophagitis.—*D G James*