- 7 Seng C, Lessof L, McKee M. Who's on the fiddle? *Health Service Journal* 1993 January 7:16-7.
- 8 Edwards N, Werneke U. In the fast lane. *Health Service Journal* 1994 December 8:30-2.
- 9 Department of Health. *Hospital episode statistics. England: financial year 1990-91*. Vol 1. London: DoH, 1993.
- 10 Department of Health. *Hospital episode statistics. England: financial year 1992-93*. Vol 1. London: DoH, 1994.
- 11 House of Commons Health Committee. *Memorandum from the Department of Health on public expenditure on the health and personal social services. Session 1993-94*. London: HMSO, 1994. (HC 617.)
- 12 Written reply. *House of Commons Official Report (Hansard)*. 1995 January 26;253:1345.
- 13 Written reply. *House of Commons Official Report (Hansard)*. 1995 January 24;253:col 177.
- 14 Macfarlane AJ, Mugford M, Johnson A, Garcia J. *Counting the changes in childbirth: trends and gaps in national statistics*. Oxford: National Perinatal Epidemiology Unit, 1995.
- 15 Carr-Hill RA, Hardman G, Martin S, Peacock S, Sheldon TA, Smith P. *A formula for distributing NHS revenues based on small area use of hospital beds*. York: University of York, 1994.
- 16 Office of Population Censuses and Surveys. *General household survey 1992*. London: HMSO, 1994.
- 17 Appleby J, Little V. Health and efficiency. *Health Service Journal* 1993 May 6: 21-2.
- 18 Clarke A, McKee M, Appleby J, Sheldon T. Efficient purchasing. *BMJ* 1993;307:1436-7.
- 19 Department of Health. *Elective admissions and patients waiting: England at 30 September 1994. Statistical bulletin 1995-1*. London: DoH, 1995.
- 20 Written reply. *House of Commons Official Report (Hansard)*. 1995 January 23;253:cols 16-7.
- 21 Written reply. *House of Commons Official Report (Hansard)*. 1995 February 16;254:col 812.
- 22 Department of Health. *Waiting times for first outpatient appointments in England: quarter ended 30 September 1994. Statistical bulletin 1995/3*. London: DoH, 1995.
- 23 NHS Executive. *The patient's charter. Hospital and ambulances comparative performance guide*. London: DoH, 1994.
- 24 Written reply. *House of Commons Official Report (Hansard)*. 1993 December 9;234: col 333.
- 25 Smith P. Outcome-related performance indicators and organisational control in the public sector. *British Journal of Management* 1993;4:133-51.
- 26 Radical Statistics Health Group. *Sifting the figures. Health Service Journal* 1989 February 2: 142.
- 27 Dillner L. Scottish death rates published with health warning. *BMJ* 1994;309:1599-600.
- 28 Department of Health. *Health and personal social services statistics for England*. London: HMSO. Published annually.
- 29 McKie D. Will we pay for it all? Preview of British social attitudes survey. *Guardian Society* 1994 November 16:4-5.
- 30 Bruster B, Jarman B, Bosanquet N, Weston D, Erens R, Delbanco TL. National survey of hospital patients. *BMJ* 1944;309:1542-6.
- 31 Inpatient experiences. What do patients really think? *Health Service Journal* 1995 January 12:18-20.
- 32 Nicol D. *Purchasing for health: a framework for action*. Leeds: NHS Management Executive, 1993.

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Lesson of the Week

Vitamin A deficiency and xerophthalmia in the United Kingdom

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Vitamin A deficiency should be considered in all patients with recurrent conjunctival or corneal disorders associated with gastrointestinal or liver disease

Vitamin A was discovered at the turn of the century.¹ It is required for normal cellular growth and differentiation and has an important role in the visual process.² The effects on the eye of vitamin A deficiency are often seen in developing countries. It occurs primarily in children of school age and is usually seen in association with other nutritional deficits, such as multiple vitamin deficiencies and protein calorie malnutrition (marasmus). Over 124 million children worldwide are estimated to be deficient in vitamin A.³ This deficiency causes between one and two million deaths annually among children aged 1-4 years³ and is the commonest cause of childhood blindness in the world; over five million children develop xerophthalmia annually, a quarter of a million or more becoming blind.

Sporadic cases of dietary vitamin A deficiency are rare in the Western world,^{4,5} but patients with abnormal metabolism can manifest signs and symptoms of vitamin deficiency. These secondary deficiencies can occur with drugs and after small bowel bypass surgery, chronic alcoholic pancreatitis, and severe liver disease. In severe liver disease there is reduced production of retinol binding protein, reduced amounts of zinc, and reduced storage of vitamin A esters in the liver.

Case reports

CASE 1

A 53 year old man presented with a one month history of poor dark-light adaptation and "everything appearing orange in the morning." His nutritional problems developed after a complicated myocardial infarction had resulted in a superior mesenteric artery embolism. This necessitated extensive resection of the small bowel, leaving him with 46 cm of small bowel. This along with recurrent episodes of bacterial overgrowth resulted in nutritional deficiencies, for which he had received intravenous feeding (but no vitamin A supplement). On examination his visual acuities were 6/9 in both eyes. Funduscopy showed fine peripheral pigment granularity. Blood vitamin A concentrations were at the lower limit of normal

(β carotene concentration 1.9 $\mu\text{mol/l}$ (normal reference range 1.7-6.9 $\mu\text{mol/l}$)), and abnormal dark adaptation was found on electroretinography. After vitamin A supplementation his symptoms abated and his dark adaptation reverted to normal.

CASE 2

A 39 year old woman presented with a sore throat, for which she had been prescribed co-amoxiclav, and a skin rash. Her illness continued to progress, and features of toxic epidermal necrolysis developed. The skin lesions improved with prednisolone 60 mg and cyclosporin 5 mg/kg, but she continued to have erythema multiforme, which was confirmed by skin biopsy. In the acute phase she became toxic and deeply jaundiced. Liver biopsy specimens were difficult to interpret but suggested primary sclerosing cholangitis. Her condition subsequently stabilised and her liver problem improved. One year later she noted a gradual decrease in visual acuity. General examination suggested advanced liver disease, and her visual acuity was 6/24 in the right eye and 6/60 in the left. Severe ocular surface disease was characterised by superficial punctate epitheliopathy, a rapid tear film break up time (less than 10 s), keratinisation of the cornea, and mild meibomianitis (figure). Her drug regimen included Ketovite one tablet daily (vitamin A 2500 U, ergocalciferol 400 U, choline chloride 150 mg, cyanocobalamin 12.5 mg). Vitamin A deficiency was suspected and confirmed by conjunctival cytology and estimation of serum vitamin A concentration ($<0.3 \mu\text{mol/l}$). Her corneal disease rapidly progressed with ulcer formation. Topical and systemic vitamin A was given, leading to stabilisation of her corneas and re-epithelialisation of the ulcers.

CASE 3

A 78 year old woman presented with a connective tissue disorder that was initially diagnosed as polymyalgia rheumatica but subsequently suggested primary biliary cirrhosis. Her current treatment included prednisolone 15 mg, frusemide, modified

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Characteristic lustreless and dry conjunctiva and cornea of vitamin A deficiency in case 3

release potassium chloride, calcium, and vitamin D tablets. A previous attack of acute glaucoma had been treated surgically. She then started to complain of difficulty in reading at night and poor colour vision, together with grittiness and irritation of the eyes. Examination showed visual acuities of 6/12 in both eyes, marginal blepharitis and meibomianitis, and a quick tear film break up time. Funduscopy showed scattered multiple white spots in the retina. Conjunctival cytology did not show any goblet cells, and vitamin A was undetectable in plasma ($>0.3 \mu\text{mol/l}$). Vitamin A treatment was started, after which the symptoms abated and the fundus returned to normal.

Discussion

The natural dietary sources of vitamin A are animal tissues that are rich in retinyl esters, such as the liver, and leafy green vegetables, which contain precursors of β carotene. These water insoluble substances are first hydrolysed in the intestinal lumen to free retinol. Once it is absorbed the vitamin A is incorporated into chylomicrons. The chylomicrons are transported through the lymph and the general circulation, and are partially metabolised outside the liver. The chylomicron remnants, enriched in cholesterol and containing essentially all of the retinyl esters absorbed from the intestine, enter the liver, which is the main storage place for vitamin A in the body. Close to 95% of the vitamin is stored in cytoplasmic lipid droplets (as retinyl esters).⁶ The remainder is present either as the free alcohol or bound to cellular retinol binding protein.⁷ After secretion from the liver the complex of retinol and retinol binding protein is bound to plasma thyretin; in this form it circulates to target tissues such as the lacrimal gland and the retinal pigment epithelium. In the target cell the complex binds to specific receptors on the plasma membrane⁸ and then dissociates. The retinol enters the cell and the protein returns to the circulation.

Our three cases show some of the ways that end organ vitamin A deficiency may arise. These ways include reduced intake of vitamin A or carotenoids, fat malabsorption caused by pancreatic disease, reduced intestinal absorption after intestinal bypass or resection surgery, defects in usage or transport, and defective storage as in liver disease.

Vitamin A deficiency is difficult to diagnose in the early stages. Ocular symptoms are usually the earliest

manifestations (particularly night blindness).⁹ Clinical signs include a lustreless, wrinkled, red, and opaque conjunctiva,¹⁰ followed by conjunctival xerosis and keratinisation, blepharitis, and meibomianitis, and fundal changes.¹¹ Other features include hyperkeratosis of the skin, lengthening of the eyelashes, enhanced keratinisation and xerosis of other mucosal surfaces, increased intracranial pressure, and mental retardation.

Many patients with severe systemic diseases and malabsorption take dietary supplements, as were two of our patients. The quantities of vitamins in commercial supplements may be insufficient to rectify the tissue deficit¹² and may lead to normal blood concentrations in the presence of disease. After vitamin A supplementation blood retinol concentrations increase in five hours.¹³ Specimens for assessment of vitamin A concentrations should therefore be taken from a fasting patient. The normal range is $1.4\text{--}2.5 \mu\text{mol/l}$.¹⁴ In accordance with the criteria of the World Health Organisation patients with serum vitamin A concentrations below $0.35 \mu\text{mol/l}$ are considered to be deficient. Concentrations may, however, be noticeably above this range if the diet contains excessive vitamin A. The toxic effects of hypervitaminosis A was first noticed in 1596 in Arctic explorers who ate liver from the polar bear.

Histological examination of specimens taken from patients with vitamin A deficiency show squamous metaplasia of the conjunctival and corneal epithelia, with keratinisation of the surface and a reduced number of goblet cells. These changes, which after supplementation take weeks to respond,¹⁵ can be identified by cytology, which may more accurately assess the availability of vitamin A to target tissues.¹⁶ To avoid deficiency it may be prudent to measure vitamin A serum concentrations and conjunctival cytology, along with concentrations of other vitamins and trace elements in all patients considered at risk.

- 1 Brown M, ed. *Present knowledge in nutrition VI*. Washington, DC: International Life Science Institute Nutrition Foundation, 1990.
- 2 Ishihara S. On the etiology of night blindness in relation to conjunctival xerosis 1913 [classic article]. *Nutrition* 1991;7:81-91.
- 3 Humphrey JH, West KP, Sommer A. Vitamin A deficiency and attributable mortality among under-5 year olds. *Bull World Health Organ* 1992;70:225-32.
- 4 Rouland JF, Amzallag T, Bale F, Constantinides G. Xerophthalmia caused by self induced disease. *J Fr Ophthalmol* 1989;12:273-7.
- 5 Buchanan NM, Atta HR, Crean GP, McColl KEL. A case of eye disease due to dietary vitamin A deficiency in Glasgow. *Scott Med J* 1987;32:52-3.
- 6 Olson JA, Gunning D. The storage form of vitamin A in rat liver cells. *J Nutr* 1983;113:2184-91.
- 7 Kato M, Kayo K, Goodman DS. Immunocytochemical studies on the localisation of plasma and of cellular retinol-binding proteins and of transthyretin (prealbumin) in rat liver and kidney. *J Cell Biol* 1984;98:1696-704.
- 8 Bok D, Heller J. Transport of retinol from the blood to the retina: an autoradiographic study of the pigment epithelial cell surface receptor for plasma retinol-binding protein. *Exp Eye Res* 1976;22:395-402.
- 9 Periman I, Barsilia D, Haim T, Schrameck A. Night blindness in a case of vitamin A deficiency due to malabsorption. *Br J Ophthalmol* 1983;67:37-42.
- 10 Sommer A, Sugana T, Djunaed E, Green WR. Vitamin A responsive panocular xerophthalmia in a healthy adult. *Arch Ophthalmol* 1978;96:1630.
- 11 Teng KH. Further contributions to the fundus xerophthalmicus. *Ophthalmologica* 1965;150:219-38.
- 12 Jackson AA, Golden MHW. Severe malnutrition. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine Vol 1*. 2nd ed. Oxford: Oxford University Press, 1987:8.20-8.
- 13 Amedee-Manesme O, Mourey MS, Hanck A, Therasse J. Vitamin A relative dose response test: validation by intravenous injection in children with liver disease. *Am J Clin Nutr* 1987;46:286-9.
- 14 Arroyave G, Chichester CO, Flores H. *Biochemical methodology for the assessment of vitamin A status: a report of the International Vitamin A Consultative Group*. Washington, DC: Nutrition Foundation, 1982.
- 15 Wittpenn JR, Scheffer CG, Tseng MD, Sommer A. Detection of early xerophthalmia by impression cytology. *Arch Ophthalmol* 1986;104:237-9.
- 16 Resnikoff S, Filliard G, Carlier S, Luzeau R, Amedee-Manesme O. Assessment of vitamin A deficiency in the republic of Djibouti. *Eur J Clin Nutr* 1992;46:25-30.

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