Bone Disease in the Elderly

D. J. HOSKING, MD, MRCP (UK)
Senior Lecturer, Department of Medicine, General Hospital, Nottingham

Mineral metabolism, and calcium homeostasis in particular, is carefully controlled and safeguarded by a remarkable capacity to adapt to changing circumstances. Ageing may represent a considerable stress on the system at a time when many tissues are showing signs of degeneration, with a consequent loss of reserve capacity. Metabolic bone disease largely reflects the failure to adapt to such stress and it is not surprising that it should be a common affliction of the elderly.

Calcium Homeostasis in Ageing

Calcium absorption falls with age in both sexes, beginning at age 55 to 60 in women and about a decade later in men (Bullamore *et al.*, 1970). The explanation for this decline is not entirely known but an abnormality of vitamin D metabolism seems very likely. A consideration of the metabolic fate of vitamin D shows several potential sites where disruption could occur in the elderly. Poor dietary intake (Exton-Smith, 1971), malabsorption or reduced exposure to sunlight (Hodkinson *et al.*, 1973; Aaron *et al.*, 1974b; Lester *et al.*, 1977) could all lead to a deficiency of the parent vitamin. Impaired hepatic function or the effect of enzyme-inducing drugs could affect the conversion to 25-hydroxy vitamin D (Rushton, 1978). Although plasma levels of this metabolite are often low in the elderly (Corless *et al.*, 1975; Lester *et al.*, 1977) this is not an invariable finding, particularly in countries where fortification of foods with vitamin D is common (Lund *et al.*, 1975). Impaired renal hydroxylation to 1,25-dihydroxy vitamin D could also be involved (Nordin *et al.*, 1976; Gallagher *et al.*, 1976). This view is supported by the observation that while large doses of the parent vitamin (250-500 μg/day) may be required to correct the malabsorption of the elderly (Nordin *et al.*, 1976), much smaller doses (1 to 2μg) of the renal metabolite or its analogue, 1-alpha-hydroxycholecalciferol, are curative (Marshall and Nordin, 1977).

Loss of bone mineral seems to be a universal phenomenon of ageing (Garn *et al.*, 1967), as the two active processes of bone formation and resorption become dissociated in favour of net resorption. This decline begins a decade earlier in women than in men and is temporarily related to the onset of the menopause (Nordin *et al.*, 1975). Although bone loss affects the whole skeleton it shows marked variation between different sites and types of bone. Thus, the amount of trabecular bone in the vertebrae begins to decline in the third decade, whereas loss of cortical bone occurs much later. Controversy has surrounded the subject of age-related bone loss. Two alternatives have been proposed and, although the matter has not been completely resolved, neither view is necessarily exclusive of the other. One view holds that the skeletal mass at maturity is the dominant factor and that age-related bone loss is relatively constant (Newton-John and Morgan, 1968). It is implicit, therefore, that attempts at reducing this loss should be directed towards influencing either skeletal mass at maturity or the ageing process itself. The alternative view places emphasis upon an increased rate of bone loss in those who develop symptomatic osteoporosis (Garn *et al.*, 1967; Meema *et al.*, 1975). As a consequence, therapy should be directed at the control of factors causing this increased rate of loss.

Consequences of Altered Homeostasis

Age-related bone loss and calcium malabsorption may be linked in several ways. Some studies have shown that osteoporotic patients consume less calcium than control subjects (Nordin, 1960; Lutwak, 1964; Riggs *et al.*, 1967) but population studies of communities with widely differing levels of calcium intake have failed to substantiate such a connection (Smith and Frame, 1965; Garn *et al.*, 1967; Walker, 1972). Experience suggests that dietary intake may be a poor indicator of calcium deficiency since the critical factor is the ability of the intestine to increase fractional absorption at low calcium intakes (Nicolaysen *et al.*, 1953). However, the ability of the elderly to adapt to a low calcium diet is known to be impaired (Ireland and Fordtran, 1973) and calcium deficiency might therefore develop and produce osteoporosis (Nordin, 1960).

Conversely, it has been suggested that calcium malabsorption is the result rather than the cause of age-related changes in calcium homeostasis (Nordin *et al.*, 1976). From this viewpoint bone loss and the menopause are linked through a sensitising effect of oestrogen lack on parathyroid mediated bone resorption (Heaney, 1965; Jasani *et al.*, 1965). These views are not necessarily mutually exclusive. The likely roles of calcium deficiency and oestrogen lack are supported by reports that post-menopausal bone loss can be prevented or reduced by oestrogens (Lindsay *et al.*, 1976; Horsman, 1977; Recker *et al.*, 1977) and by 1-alpha-hydroxycholecalciferol (Marshall and Nordin, 1977; Sorensen *et al.*, 1977). Calcium supplements alone were less effective than oestrogens but better than no treatment (Horsman, 1977;

This article is based on a paper read at the College Regional Conference held at Nottingham in September 1978.

Recker *et al.*, 1977). Combination of 1-alpha-hydroxycholecalciferol and oestrogens appears particularly beneficial and considerably simplifies pre-treatment investigation (Marshall and Nordin, 1977).

Although malabsorption of calcium also occurs in osteomalacia, the pathognomonic feature is a failure of mineralisation of bone which affords distinction from osteoporosis. The earliest development is the loss of the calcification front (Bordier and Tun Chot, 1972), the granular zone between osteoid and bone where mineralisation is initiated. Although mineralisation is impaired, osteoblasts continue to lay down osteoid until the normal depth of the formation surface is achieved, usually about 120 microns in an adult (Jowsey, 1966). This process is then repeated at other sites so that the proportion of bone surfaces covered by osteoid increases. These changes must be distinguished from high turnover situations such as hyperparathyroidism or Paget's disease, where osteoid also accumulates. In these conditions the rate of mineralisation is normal, while that of osteoid production is increased. The usual delay between the completion of an osteoid seam and its mineralisation means that the surface covered by osteoid increases; the calcification front, however, is not reduced.

Clinical Manifestations

The risk of sustaining a Colles fracture is ten times greater in a 60-year-old woman than in her counterpart who is twenty years younger; men show similar but less striking increased risks. On the other hand, both sexes show an exponential increase in femoral neck fractures over the age of 60 years, the rate doubling every five years in women and every eight years in men (Knowlden *et al.*, 1964; Alffram, 1964). A similar pattern of response is seen in the trabecular bone of the vertebrae (Nordin, 1966). A link between the increased prevalence of structural failure and involutional osteopenia cannot necessarily be assumed just because of their simultaneous development.

First, if it is accepted that bone loss is a normal feature of ageing, we have, perhaps, more than a semantic difficulty in deciding at what stage disease becomes apparent. A practical extension of this dilemma is that if the presence of structural failure is taken as an end point, a diminished bone mass does not appear to be an inevitable accompaniment of fracture in the elderly. Thus, although some studies have shown that the incidence of long bone fracture is closely related to radiological bone density at these sites (Newton-John and Morgan, 1970; Foss and Byers, 1972), others have failed to find such a relationship (Smith *et al.*, 1975; Exton-Smith, 1976). Bone mass may not be the only factor controlling the propensity to fracture. Old bone is more fully mineralised than young, and less energy may be required to cause a fracture (Currey and Butler, 1975). Moreover, increasing infirmity, poor vision and the effects of barbiturate hypnotics (Macdonald and Macdonald, 1977) may all act to increase the risks of falling.

While the management of osteopenia developing around the menopause is prophylactic, that of the elderly is largely symptomatic. Such an approach is based upon the slow bone turnover in this age group (giving little scope for the development of a strongly positive calcium balance), the doubt about a simple relationship between bone mass and fracture incidence, and the lack of evidence demonstrating that current treatments decrease this incidence. Circumspection need not, however, be a *post hoc* rationalisation for therapeutic nihilism. Long bone fractures clearly require orthopaedic management, but back pain due to vertebral collapse often shows an episodic course with spontaneous remission of pain followed by relatively long periods with little disability (Dent and Watson, 1966; Rich *et al.*, 1966). The initial period of acute pain usually responds to 2 to 4 weeks' bed rest, after which mobilisation should start; longer periods of immobilisation are rarely indicated and accelerate bone loss. Mineralisation may be helped by an external spinal support, but some patients find these more uncomfortable than their back pain. It must not be forgotten that osteoporosis and osteomalacia may co-exist (Aaron *et al.*, 1974a; Faccini *et al.*, 1976) and that osteoporosis may be secondary to a variety of endocrine, metabolic or neoplastic diseases. Some of these will require treatment in their own right while others will be important in a prognostic sense.

Diagnosis is also an important prerequisite for the effective management of osteomalacia. Although elderly patients may present with a classical picture of osteomalacia, the disease is more commonly found in a subclinical form. Nevertheless, the defective mineralisation may contribute to the decreased tensile strength of the skeleton and significantly the prevalence of osteomalacia among fracture patients (Aaron *et al.*, 1974a) is five to ten times higher than in unselective hospital admissions of the elderly (Anderson *et al.*, 1966; Chalmers, 1968).

Routine biochemistry is of great value in the diagnosis of osteomalacia; serum calcium and phosphate is depressed while alkaline phosphatase is elevated. Some care is needed in interpreting the results. Most biochemistry laboratories measure total serum calcium and since about one-third is bound to serum albumin a correction to a reference value should be made. A convenient one is 0.02 mmol/litre for every 1 g/litre deviation from an albumin of 40 g/litre (*British Medical Journal,* 1977), additions to the total calcium being made for low values and subtractions for high values. Hypoalbuminaemia is common in the elderly and if this correction is omitted, hypocalcaemia will be over-diagnosed and patients needlessly investigated. The level of plasma phosphate is set by the renal tubule, itself influenced by many factors. Parathyroid hormone (PTH) is the most important in the present context since, as hypocalcaemia develops in osteomalacia, secretion is increased and phosphate reabsorption (and therefore the plasma level) falls. The fasting plasma phosphate is a useful measure of this secondary hyperparathyroidism but does not relate quantitatively to PTH levels (Walker *et al.*, 1977). However, plasma phosphate rises after food and as renal function deteriorates, these changes obscuring the hypophosphataemia of secondary hyperparathyroidism. In these circumstances, measurement of one of the indices of tubular reabsorption of phosphate is required; Tmp/GFR (Bijvoet, 1969) is one of the best and can be derived from simultaneous measurements of phosphate and creatinine in blood and urine using a nomogram (Walton and Bijvoet, 1975). Osteomalacia is not the only

cause of a raised alkaline phosphatase, but other forms of metabolic bone disease and liver disease causing such an elevation can usually be distinguished by history, examination and skeletal radiographs. Alkaline phosphatase also rises during fracture healing but since many elderly patients with femoral neck fractures also have osteomalacia (Aaron *et al.*, 1974a) it is important to distinguish these two effects. In uncomplicated femoral neck fractures the alkaline phosphatase does not begin to rise until the second week (Hosking, 1978) and measurements in the first week have the same diagnostic significance as those in non-fracture patients.

Management of patients with osteomalacia should include treatment of underlying nutritional, intestinal, hepatic and renal problems. Vitamin D should be given in conventional dosage (25 to 75 μg daily; 1000-3000 iu). Some elderly patients will require greater amounts (Dent and Stamp, 1977), but pharmacological doses or the newer hydroxylated derivatives (1-alpha-hydroxycholecalciferol or 1.25 DHCC) should not be used (because of the risk of intoxication) until it is clear that healing is not occurring despite regular medication. Hypocalcaemia in severe osteomalacia may not be corrected for several weeks and it is not an indication for heroic vitamin D therapy; an adequate calcium intake must be ensured. Serum phosphate and alkaline phosphatase show a more immediate response to treatment.

Other Skeletal Manifestations of Ageing

Paget's disease is the other common bone disease of the elderly but in contrast to osteoporosis and osteomalacia it is characterised by a greatly increased (and disordered) bone turnover and has a much less clear-cut relationship to ageing. Why it should show such a predilection for the elderly is uncertain but the recent descriptions of virus-like particles in Pagetic osteoclasts (Rebel *et al.*, 1976; Mills and Singer, 1976) may provide a clue. The intranuclear inclusions appear confined to Paget's disease and are seen as filamentous bodies hexagonally packed or occasionally lying as single strands. Nuclear degeneration may also develop, with release of microfilaments into the cell cytoplasm in a manner similar to that of viral infections. Morphologically there is a resemblance to measle virus and it may be significant that multinucleated cells are also found in this infection. Although osteoclasts are normally multinucleated, those seen in Paget's disease characteristically contain a greatly increased number. Furthermore, the ultrastructural changes are similar to those seen in subacute sclerosing panencephalitis, the clinical course of which is not unlike that of Paget's disease, as localised lesions may remain latent over many years.

Recent advances in treatment have provided further insight into the disease itself. Fluoride (Avioli and Berman, 1968), glucagon (Condon, 1971) and mithromycin (Ryan *et al.*, 1972) are all effective but only the calcitonins and the diphosphonates have proved to be of practical therapeutic value. Pain is the usual indication for treatment, there being as yet no evidence that deformity or fracture rate can be affected. Calcitonins and diphosphonates act by reducing bone turnover and it seems logical to restrict their use to patients who have active disease shown by raised levels of serum alkaline phosphate and hydroxyproline excretion. The presence of osteoarthritis adjacent to Pagetic involvement is not necessarily a bar to treatment but is likely to result in a poor therapeutic response.

Salmon calcitonin in a dose of 50 to 100 MRC units thrice weekly is no less effective than a daily regime (De Rose *et al.*, 1974) and is more convenient. Pain relief generally develops within the first two months of treatment and is maximal by three months (Kanis *et al.*, 1974). If no response has occurred by this time treatment should be discontinued since it is unlikely that an improved response will be obtained by a larger dose. Adverse effects may be troublesome and include nausea, flushing and malaise. They tend to decrease with time but can be mitigated by injecting the patient before he retires to bed, and giving promethazine. Clinical and biochemical responses to treatment are poorly correlated. Alkaline phosphatase and hydroxyproline excretion are usually reduced to about 50 per cent of pre-treatment values so that normal levels are achieved only in those whose disease is only moderately active. The explanation for the incomplete control of bone turnover is unknown but is not a reflection of inadequate dosage, secondary hyperparathyroidism or calcitonin antibodies (De Rose *et al.*, 1974).

Diphosphonates are not yet generally available but they appear to be very effective in controlling bone pain and turnover (Khairi *et al.*, 1974; De Vries and Bijvoet, 1974; Russell *et al.*, 1974). Although the number of osteoblasts and osteoclasts seen in bone histology are strikingly reduced, larger doses of diphosphonates appear to produce defective mineralisation (Smith *et al.*, 1973; De Vries and Bijvoet, 1974; Russell *et al.*, 1974). This may be associated with a recurrence of bone pain and an increased fracture rate (Khairi *et al.*, 1977; Canfield *et al.*, 1977). Lower doses may reduce this problem but biochemical control is also less complete. Some of these problems may be avoided by the newer diphosphonates (Bijvoet *et al.*, 1977) or by the use of calcitonin and diphosphonate in combination (Hosking *et al.*, 1975).

References

Aaron, J. E., Gallagher, J. C., Anderson, J., Stasiak, L., Longton, E. B., Nordin, B. E. C. and Nicholson, M. (1974a) *Lancet*, **1**, 229.

Aaron, J. E., Gallagher, J. C. and Nordin, B. E. C. (1974b) *Lancet*, **2**, 84.

Alffram, P. A. (1976) *Acta Orthopaedica Scandinavica*, **65**, (Suppl) 1.

Anderson, I., Campbell, A. E. R., Dunn, A. and Runciman, J. B. M. (1966) *Scottish Medical Journal*, **11**, 429.

Avioli, L. V. and Berman, M. (1968) *Journal of Clinical Endocrinology*, **28**, 700.

Bijvoet, O. L. M. (1969) *Clinical Science*, **37**, 23.

Bijvoet, O. L. M., Hosking, D. J., Lemkes, H. H. P. J., Reitsma, P. H. and Frijlink, W. B. (1977) In *Endocrinology of Calcium Metabolism. Proceedings of Sixth Parathyroid Conference*, p. 48. ICS No. 421. Amsterdam: Excerpta Medica.

Bordier, P. J. and Tun Chot, S. (1972) *Clinics in Endocrinology and Metabolism*, **1**, 197.

British Medical Journal (1977) **1**, 598.

Bullamore, J. R., Wilkinson, R., Gallagher, J. C., Nordin, B. E. C. and Marshall, D. H. (1970) *Lancet*, **2**, 535.

Canfield, R., Rosner, W., Skinner, J., McWhorter, J., Resnick, L., Feldman, F., Kammerman, S., Ryan, W., Kunigonis, M. and Bohne, W. (1977) *Journal of Clinical Endocrinology and Metabolism*, **44**, 96.

Chalmers, J. (1968) *Journal of the Royal College of Surgeons of Edinburgh*, **13**, 255.

Condon, J. R. (1971) *British Medical Journal*, **4**, 719.

Corless, D., Boucher, B. J., Beer, M., Gupta, S. P. and Cohen, R. D. (1975) *Lancet*, **1**, 1404.
Currey, J. D. and Butler, G. (1975) *Journal of Bone and Joint Surgery*, **57A**, 810.
Dent, C. E. and Watson, L. (1966) *Postgraduate Medical Journal*, **42**, (Suppl.) 583.
Dent, C. E. and Stamp, T. C. B. (1977) In *Metabolic Bone Disease*, Vol. 1, p. 237, (ed L. V. Avioli and S. M. Krene). New York: Academic Press.
De Rose, J., Singer, F. R., Avramides, A., Flores, A., Dziadiw, R., Baker, R. K. and Wallach, S. (1974) *American Journal of Medicine*, **56**, 858.
De Vries, H. R. and Bijvoet, O. L. M. (1974) *Netherlands Journal of Medicine*, **17**, 281.
Exton-Smith, A. N. (1971) *British Journal of Hospital Medicine*, **5**, 639.
Exton-Smith, A. N. (1976) *Modern Geriatrics*, **6**, 27.
Faccini, J. M., Exton-Smith, A. N. and Boyde, A. (1976) *Lancet*, **1**, 1089.
Foss, M. V. L. and Byers, P. D. (1972) *Annals of the Rheumatic Diseases*, **31**, 259.
Gallagher, J. C., Riggs, L., Eisman, J., Arnaud, A., Deluca, H. (1976) *Clinical Research*, **24**, 360A.
Garn, S. M., Rohmann, C. G. and Wagner, B. (1967) *Federation Proceedings*, **26**, 1729.
Heaney, R. P. (1965) *American Journal of Medicine*, **39**, 877.
Hodkinson, H. M., Stanton, B. R., Round, P. and Morgan, C. (1973) *Lancet*, **1**, 910.
Horsman, A. (1977) *British Medical Journal*, **2**, 789.
Hosking, D. J. (1978) *Journal of Bone and Joint Surgery*, **60B**, 61.
Hosking, D. J., Bijvoet, O. L. M., Van Aken, J. and Will, E. J. (1975) *Lancet*, **1**, 615.
Ireland, P. and Fordtran, J. S. (1973) *Journal of Clinical Investigation*, **52**, 2672.
Jasani, C., Nordin, B. E. C., Smith, D. A. and Swanson, I. (1965) *Proceedings of the Royal Society of Medicine*, **58**, 441.
Jowsey, J. (1966) *Journal of Anatomy*, **100**, 857.
Kanis, J. A., Horn, D. B., Scott, R. D. M. and Strong, J. A. (1974) *British Medical Journal*, **3**, 727.
Khairi, M. R. A., Johnston, C. C. Jr., Altman, R. D., Wellman, H. N., Serafini, A. N. and Sankey, R. R. (1974) *Journal of the American Medical Association*, **230**, 562.
Khairi, M. R. A., Altman, R. D., De Rosa, G. P., Zimmermann, J., Schenk, R. K. and Johnston, C. C. Jr. (1977) *Annals of Internal Medicine*, **87**, 656.
Knowlden, J., Buhr, A. J. and Dunbar, O. (1964) *British Journal of Preventive and Social Medicine*, **18**, 130.
Lester, E., Skinner, R. K. and Wills, M. R. (1977) *Lancet*, **1**, 979.
Lindsay, R., Hart, D. M., Aitken, J. M., MacDonald, E. B., Anderson, J. B. and Clark, A. C. (1976) *Lancet*, **1**, 1038.
Lund, B., Sorenson, O. H. and Christensen, A. B. (1975) *Lancet*, **2**, 300.
Lutwak, L. (1964) *Journal of the American Dietetic Association*, **44**, 173.
MacDonald, J. B. and MacDonald, E. T. (1977) *British Medical Journal*, **2**, 483.
Marshall, D. H. and Nordin, B. E. C. (1977) *Clinical Endocrinology*, **7**, 1595.
Meema, S., Bunker, M. L. and Meema, H. E. (1975) *Archives of Internal Medicine*, **135**, 1436.
Mills, B. G. and Singer, F. R. (1976) *Science*. **194**, 201.
Newton-John, H. F. and Morgan, D. B. (1968) *Lancet*, **1**, 232.
Newton-John, H. F. and Morgan, D. B. (1970) *Clinical Orthopaedics and related research*, **71**, 229.
Nicolaysen, R., Eeg-Larsen, N. and Malm, O. J. (1953) *Physiology Review*, **33**, 424.
Nordin, B. E. C. (1960) *Clinical Orthopaedics*, **17**, 235.
Nordin, B. E. C. (1966) In *Medicine in old age*, p. 5, (ed J. N. Agate). London: Pitman Medical.
Nordin, B. E. C., Gallagher, J. C., Aaron, J. E. and Horsman, A. (1975) In *Estrogens and the post-menopause. Frontiers of Hormone Research*, **3**, 131. Basel: Karger.
Nordin, B. E. C., Wilkinson, R., Marshall, D. H., Gallagher, J. C., Williams, A. C. and Peacock, M. (1976) *Calcified Tissue Research*, **21**, Suppl 442.
Rebel, A., Malkani, K., Basle, M. and Bregeon, C. (1976) *Calcified Tissue Research*, **20**, 187.
Recker, R. R., Saville, P. D. and Heaney, R. P. (1977) *Annals of Internal Medicine*, **87**, 649.
Rich, C., Bernstein, D. S., Gates, S., Heaney, R. P., Johnston, C. C. Jr., Rosenberg, C. A., Schnape, E., Tewkbury, R. B. and Williams, G. A. (1966) *Clinical Orthopaedics and Related Research*, **45**, 63.
Riggs, B. L., Kelly, P. J., Kinney, V. R., Scholz, D. A. and Bianco, A. J. Jr. (1967) *Journal of Bone and Joint Surgery*, **49A**, 915.
Rushton, C. (1978) *Age and Ageing*, **7**, 91.
Russell, R. G. G., Smith, R., Preston, C., Walton, R. J. and Woods, G. G. (1974) *Lancet*, **1**, 894.
Ryan, W. G., Schwartz, T. B. and Northrop, G. (1972) *Seminars in Drug Treatment*, **2**, 57.
Smith, D. M., Khairi, M. R. A. and Johnston, C. C. Jr. (1975) *Journal of Clinical Investigation*, **56**, 311.
Smith, R. W. and Frame, B.(1965) *New England Journal of Medicine*, **273**, 73.
Smith, R., Russell, R. G. G. and Bishop, M. (1973) *Quarterly Journal of Medicine*, **42**, 235.
Sorensen, O. H., Andersen, R. B., Christensen, M. S., Friis, T., Hjorth, L., Jorgensen, F. S., Lund, B., Melsen, F. and Mosekilde, L. (1977) *Clinical Endocrinology*, **7**, (Suppl.) 169.
Walker, A. R. P. (1972) *American Journal of Clinical Nutrition*, **25**, 518.
Walker, D. A., Davies, S. J., Siddle, K. and Woodhead, J. S. (1977) *Clinical Science and Molecular Medicine*, **53**, 431.
Walton, R. J. and Bijvoet, O. L. M. (1975) *Lancet*, **2**, 309.

The Scurvy

The word scurvy was used first in 1565 and accounts of later Elizabethan voyages commonly referred to it. That great sailor, Sir Richard Hawkins, described the salient features of scurvy and in 1590 had a clear idea of how to prevent it. He was all for keeping 'the company occupied in some bodily exercise of work, of agility, of pastimes, of dancing, of use of armes.' Difficult as this programme must have appeared to those on their tiny storm-tossed craft, it was easier to appreciate Hawkins' experience that 'sour oranges and lemons' were the cure for scurvy. 'This', he wrote, 'is a wonderful secret of the power and wisdom of God, that hath hidden so great and unknown vertue in this fruit to be a certain remedy for this infirmity.' But it was John Woodall, as Surgeon to the East India Company, who was the first doctor to have the right idea about the treatment of scurvy. In his book *The Surgeon's Mate*, published in 1617, he wrote: 'The Chirurgeon or his Mate must not fail to perswade the Governour or Purser in all places where they touch in the Indies and may have it, to provide themselves of juice of Oranges, limes or lemons, and at Banthame of tamarinds . . . And further experience teacheth that where a disease mostly raigneth, even there God hath appointed the best remedies for the same grief, if it be his will they should be discovered and used: and more for substance, the Lemmons, Limes, Tamarinds, Oranges, and other choice of good helps in the Indies which you shall finde there shall farre exceede any that can be carried thither from England, and yet there is a good quantitie of Juice of Lemmons sent in each ship out of England by the great care of the Marchants . . . The use of the juyce of Lemmons is a precious medicine and well tried, being sound and good; let it have the chief place, for it will deserve it.' Woodall recorded that a 'good quantitie of Juice of Lemmons' was provided on each ship by the 'great care of the Marchants.' It is surprising that James Lind, a century after Woodall, should usually be considered the first man to find the effective treatment of scurvy. It is thanks to Sir Geoffrey Keynes that Woodall's original contribution is now acknowledged.