Rickets

Don't ignore vitamin D

N Bishop

Perspective on the papers by Robinson *et al* (see page 564) and Das *et al* (see page 569)

Rickets has been cited as the commonest non-communicable disease of childhood worldwide. It is certainly a disease that has been well described over the last four centuries, initially by Glisson (1648), who differentiated it from infantile scurvy, Trousseau (p 38), who identified sunlight and cod liver oil as effective treatments, Mellanby (1919), who created an animal model of rickets that was cured by cod liver oil, and Hess and Unger (1921), who cured rickets in children by exposing them to sunlight on a rooftop in New York.

The epidemiology of rickets—lack of vitamin D from diet and/or the action of sunlight on exposed skin, or of the bone mineral substrates calcium and phosphate—is also well established. The contribution of such deficiencies to other human ill health problems is less clear. There is no doubt that vitamin D is important for function of the musculoskeletal and immune systems, neurological function, and possibly mental health. But how much vitamin D is necessary to support human health and should vitamin D supplementation be targeted or universal? How should vitamin D sufficiency be assessed? Are there critical periods during which attention should be concentrated? Two papers in this issue of *Archives* make useful contributions to the debate.

The first paper, by Robinson *et al*, examines the effects of vitamin D deficiency in infancy.¹ This is not new territory, but the message of increasing frequency of presentation over the period of a decade in a developed country makes salutary reading. The diagnosis of vitamin D deficiency in the paper by Robinson *et al* depended on clinical identification of ill health in the infants. Hypocalcaemia leading to convulsions (which may be accompanied by cardiac failure in severe cases), bone softening leading to deformity, metaphyseal swelling, proximal myopathy, and growth failure are all clear clinical indicators of deficiency. These immediate manifestations should be apparent to all practising paediatricians, and such signs should be actively sought in breast fed

non-white infants whatever the reason for their initial presentation.

Furthermore, children and young adults who had low intakes of vitamin D during infancy not necessarily resulting in such florid clinical manifestations may be at increased risk of problems later. In a retrospective study of a Finnish birth cohort from 1966, Hypponen *et al* found an eight-fold increase in the risk of diabetes in those who had not received the recommended 2000 IU/day of vitamin D during the first six months of life.²

The second paper in this issue, by Das *et al*, focuses on vitamin D deficiency in the adolescent period, when at least one third of the mass of the adult skeleton accrues.³ The authors show that vitamin D insufficiency is common in apparently healthy adolescent girls, with non-white girls not surprisingly more severely affected. Despite the low levels of vitamin D, however, there were no clear functional consequences with immediate impact. Nevertheless, the concern remains that failure to supply an essential nutrient during a period of rapid growth and development is likely to result in problems across the population as a whole. Severely deficient girls do develop alterations in pelvic shape that can lead to obstructed labour. Failure to accrue bone within the skeletal envelope, or to have a smaller envelope as a result of reduced skeletal growth, are factors that could predispose to osteoporotic fracture in later life. These girls are likely to have persistent deficiency of vitamin D unless their lifestyle or diet changes significantly. This may impact in turn on the future vitamin D status of any infants that they subsequently bear themselves.

The pressure to increase vitamin D intake is strong in some quarters; the references cited in Robinson and colleagues' paper to justify the use of serum 25-hydroxyvitamin D 50 nmol/l as a cut-off for deficiency come from the work of Holick,⁴ a vigorous pro-vitamin D and sunlight exposure campaigner. It is not entirely clear whether maintaining such a level is necessary to sustain health, however, at all ages. Using this cut-off, vitamin D insufficiency was found in 11/23 white adolescent girls in Maine during the period September

2000 to March 2003;⁵ no clinically relevant consequences appear to have been suffered. There has been no comparable work in infants until now. Previous work in the UK has taken the cut-off as being 25 nmol/l.⁶ In that study, while there was an average rate of 25% of insufficiency among children under age 2 years from South Asian ethnic backgrounds, the comparable rate in white young children was 1%. It would hardly be surprising if those numbers increased if the goalposts were moved. In fact, low levels of vitamin D in cord blood were reported as common in white Caucasians at the end of winter in Sheffield; in a study of 106 women (90% white Caucasian) and their infants, 70% of infants had serum 25-hydroxyvitamin D <20 nmol/l.⁷

How much vitamin D is needed to maintain human health? Robinson *et al* note the recent recommendation of the American Academy of Paediatrics that all should receive 200 IU vitamin D/day. In the Maine study, the average stated vitamin D intake was close to this value. It is interesting to note from Robinson's paper, however, that 31/106 had not been breast fed. If we assume that this means they received infant formula, is the vitamin D content of infant formula always adequate to maintain vitamin D sufficiency? Although not stated in the paper, it might be that infants born to vitamin D deficient mothers need more vitamin D to restore homeostasis.

In the UK, the Department of Health has made recommendations, based on the reports of COMA, for the vitamin D supplementation of breast fed infants and infants "at risk" of vitamin D deficiency, as well as for "at risk" pregnant mothers. These latter recommendations have been challenged by NICE who stated that "in the absence of evidence of benefit, vitamin D supplementation should not be routinely offered to pregnant women" (NICE, Compilation Issue 7, October 2003, p. 138). One might observe that absence of evidence for an effect is not evidence of absence; common sense would suggest that vitamin D deficiency, widely reported in the communities whose ethnic origins lie in sunnier climes, can affect pregnant as well as non-pregnant individuals. The high proportion of non-whites (96%) and the early presentation with hypocalcaemic seizures in one third in Robinson and colleagues' study clearly suggests that vitamin D deficiency should be actively sought in non-white pregnant women. Indeed, the advice offered in a recent edition of the CMO Update (Summer 2005, Issue 42, p. 6) is that supplements of 400 IU/day (10 µg/day) should be offered to pregnant women, and 280 IU/day (7 µg/day)

to children under the age of 5 from at-risk communities.

Taken together, the two papers published in this issue of *Archives* indicate a widespread insufficiency of vitamin D in children. Worryingly, from the perspective of current UK strategies to prevent vitamin D deficiency, virtually all of the vitamin D metabolite measured in the serum of the Manchester cohort was sunlight derived. Taken together with the earlier data from Sheffield, there may be a need to revise our current approaches to the prevention of vitamin D deficiency and insufficiency.

For now, however, we need to take simple, practical measures to reduce the burden of early bone disease and other later problems. These measures need to be part of our routine practice and recommendations, particularly in the at-risk groups of infants and young children from non-white backgrounds.

Education is a major part of this. Paediatricians, obstetricians, midwives, health visitors, and GPs all need to remind patients that there is virtually no vitamin D in breast milk, and that totally breast fed babies should be supplemented (irrespective of the colour of their skin) until receiving a full mixed diet. The other recommendations from the CMO are clear and simple and should now be applied universally in respect of infants and young children. We do still need to decide how best to meet the needs of older children and adolescents in a culture that covers up, either with clothing or with sunscreen. Perhaps more exercise outdoors would help deal with this problem.

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REFERENCES

- 1 Robinson PD, Höglér W, Craig ME, *et al*. The re-emerging burden of rickets: a decade of experience from Sydney. *Arch Dis Child* 2006;**91**:564–8.
- 2 Hyppönen E, Laara E, Reunanen A, *et al*. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;**358**:1500–3.
- 3 Das G, Crocombe S, McGrath M, *et al*. Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child* 2006;**91**:569–72.
- 4 Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. *Alternative Medicine Review* 2005;**10**:94–111.
- 5 Sullivan SS, Rosen CJ, Halteman WA, *et al*. Adolescent girls in Maine are at risk for vitamin D insufficiency. *J Am Diet Assoc* 2005;**106**:971–4.
- 6 Lawson M, Thomas M. Vitamin D concentrations in Asian children aged 2 years living in England: a population survey. *BMJ* 1999;**318**:28.
- 7 Pawley N, Bishop NJ. Prenatal and infant predictors of bone health: the influence of vitamin D. *Am J Clin Nutr* 2004;**80** (suppl 6):1748–51.

Children's medicines

Improving children's medicines

I Choonara

Perspective on the paper by McLay *et al* (see page 584)

It is reassuring that the majority of Scottish paediatricians are aware of the concept of off label prescribing (*p XXX*).¹ The term off label relates to the use of a medicine in a manner different from that recommended by the manufacturers in their product licence.² A formal classification system for the different types of off label and unlicensed drug use was described in 1997. In a period of a few years, several studies confirmed that off label drug prescribing was a significant problem in children in hospital,³ in neonates,⁴ and in primary care.⁵

The main reason for carrying out these epidemiological studies was to highlight the fact that medicines used in children have not been scientifically evaluated to the same extent as those used in adults.^{6,7} Groups such as the European Network for Drug Investigation in Children have highlighted that this is a problem in different European countries⁸ and subsequent studies have shown that it is a world-wide problem.⁹ Off label prescribing is associated with a greater risk of drug toxicity.¹⁰ This is to be expected as the

licensing process is carried out to ensure the efficacy and safety of medicines.

EUROPEAN LEGISLATION

The political response to the problem of off label prescribing in children has been discussed both nationally and at a European level. Legislation is currently being proposed that would hopefully improve the scientific study of medicines in children.¹¹ This proposed legislation will offer a financial incentive to the pharmaceutical industry as it is accepted that the cost of studying medicines in children is greater than in adults. Legislation in the USA has been successful in ensuring that more medicines are licensed for paediatric use.¹² Concerns have been raised, however, that the types of medicines studied are those that generate the greatest profits rather than address the clinical needs of children.¹³

The proposed European legislation recognises this point and suggests the establishment of a paediatric committee.¹¹ It is essential that the members of the paediatric committee are advocates of children and ensure that the

medicines studied are those that will improve patient care. The majority of Scottish paediatricians are prepared to participate in clinical trials.¹ A weakness of the Aberdeen study, however, is that it did not try to differentiate between clinical trials of medicines for conditions where treatment is currently unsatisfactory and clinical trials of "me-too" medicines.

A major weakness in the proposed European legislation is the lack of funding for Medicines Investigation for the Children of Europe (MICE). This was in the original proposal but was unfortunately dropped owing to differences over who should fund it. The creation of a fund to ensure research and development of off patent medicines would significantly benefit children.

DEVELOPMENTS IN THE UNITED KINGDOM

There have been three major developments within the UK over the last few years. The publication of the BNF for Children following on the success of Medicines for Children will hopefully result in safer prescribing of medicines. The establishment of a Medicines for Children Research Network should facilitate the performance of clinical trials. The UK is unique in that it now has a formally recognised training programme in paediatric clinical pharmacology.¹⁴ The first fully accredited trainee has recently completed her training. Paediatric clinical pharmacologists working alongside other paediatric health professionals have helped to