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LETTERS

VITAMIN D DEFICIENCY

Systems failure

A systems approach is needed to ensure proper treatment of vitamin D deficiency.[1] Many practical problems have arisen with diagnosis and management in practices, laboratories, hospitals, and populations. Some doctors are discouraged from measuring vitamin D because of perceived costs, or testing is not readily available. Midwives are not encouraged to test pregnant women, a highly vulnerable group.

Results come in different units from different laboratories, often with winter normal ranges, which reflect deficient populations, not normal or desirable concentrations. Could all laboratories use consistent ranges, given that values over 50 nmmol/l are found in healthy, sun exposed populations?

Could the Department of Health ensure that supplies of D3 are consistently available in preparations suitable for all ages and in high enough doses to treat deficiency?

Adherence to treatment can be poor. Many patients do not know that food contains little vitamin D, and thus do not complete treatment courses and stop maintenance treatment, leading to relapse.

Vitamin D status is often forgotten in hospitals in the work-up for tiredness, weakness, and diabetes, and even in rheumatological, musculoskeletal, and orthopaedic clinics. Paediatricians have inconsistent approaches, seeming not to realise that the children of vitamin D deficient mothers are at high risk and should routinely be given supplements.

Trusts and health authorities have not realised the public health importance of vitamin D. Routine testing and supplementation are not prioritised even for high risk patients, such as those in residential care or prison. The perception is that this is a minority problem affecting only certain ethnic groups. It is time to blow the whistle on this systems failure.

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Competing interests: None declared.

1 Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:b5664. (11 January.)

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Screen more widely?

Now that testing for vitamin D is easy, we are overwhelmed by evidence of deficiency.[1] In the past two years 10% (1085) of our practice patients have had vitamin D measured, of whom only a third were above treatment threshold. Most of those tested were young and middle aged adults, some with vague aches and pains, some just pregnant. Among the unrecordably low values are white male bankers, as well as those with darker skins and those who are covered up for religious reasons. Should we be screening more widely?

Meanwhile, vitamin D replacement has become a high expenditure item in the local drugs budget.

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What should we be doing?

Like general practitioners responding to the clinical review on the diagnosis and management of vitamin D deficiency,[1 2] we would appreciate guidance on whether a vitamin D assay is required in all patients considered at risk of deficiency, or only in selected cases.

Our laboratory received over 3900 requests for 25-OH vitamin D assay in 2009; demand for this test has increased ninefold over the past four years. The cost in 2009 was over £54 000, a large impost on the department's budget.

We see the same high prevalence of vitamin D deficiency (25-OH vitamin D concentration ‹50 nmol/l) as Hull and Boomla.[3] The conundrum posed by these data is this. Most patients for whom our doctors request vitamin D assay are deficient; thus if the doctor suspects vitamin D deficiency, he or she is probably correct, so could supplementation be started without biochemical confirmation? Any risk of toxicity would be low, given the available vitamin D supplements, periodic monitoring of serum calcium concentrations, and review of patient's symptoms. Note that this approach is not advocated in certain groups of patients, such as children, patients starting bisphosphonate treatment, and those with chronic kidney disease, for whom the need for 25-OH vitamin D measurement is more clearly defined.

Alternatively, if vitamin D treatment is to be directed only to those with basal 25-OH vitamin D concentrations that indicate supplementation, the funding of vitamin D assays needs to be reviewed by the relevant bodies so that laboratories can provide this service in an orderly and efficient manner.

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Competing interests: None declared.

1 Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:b5664. (11 January.)
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3 Hull S, Boomla K. New vitamin D preparations needed. *BMJ* 2010;340:c906.

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How can we treat it in the UK?

Management of vitamin D deficiency[1] is complicated by several factors:

- The only licensed oral, high dose vitamin D supplements (ergocalciferol tablets 10 000 IU and 50 000 IU) were discontinued by UCB Pharma in May 2009. There is currently no high dose vitamin D oral supplement licensed in the UK. In our experience, products containing vitamin D of around 400 IU tend not to replace vitamin D concentrations very well
- The injectable form of ergocalciferol (300 000 IU) was the only high dose vitamin D product available, and then only sporadically. It did not produce a clinical response (increase vitamin D values) in any patient in the general practices I support when administered regularly for up to 12 months

- A high dose, oral formulation of vitamin D (20 000 IU and 50 000 IU capsule) is unlicensed in the UK but can be imported from Europe. However, evidence is lacking that it improves clinical outcomes
- Two low dose oral vitamin D preparations that contain around 1000 IU can be prescribed on the NHS, but only one of these is vegetarian—a concern for some patients with dietary and religious requirements—and compliance is likely to be a challenge if a high dose is indicated.

Thus in the UK we have no licensed, evidence based treatment for vitamin D deficiency for all those who need it.

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New preparations needed

The call for a change in UK public health policy on vitamin D is welcome.[1] In 2009, our audit found that 80% of tests by general practitioners in Tower Hamlets in South Asian and black groups showed deficiency or insufficiency of vitamin D, as did over 50% of those in white people (table). Vitamin D supplements were prescribed to 58% of those with deficiency and 39% of those with insufficiency

This socially deprived, ethnically diverse inner city population has much higher insufficiency rates than the 50% UK average.[1 2] These populations already have a high prevalence of cardiovascular disease and diabetes—chronic disorders associated with vitamin D deficiency.

Treatment is problematic—adherence to oral medication is low because vitamin D combined with calcium is unpalatable,[3] and the availability of calcium-free preparations is poor. A range of oral preparations to suit all requirements (taste, diet, and religion) is needed. Parenteral administration must be avoided because of blood monitoring requirements, overmedicalisation, and workload implications for general practices.

The NHS needs a coherent public health response for this common and preventable condition that disproportionately affects inner urban deprived populations. This should include reintroduction of free vitamin drops for children and mothers, food supplementation, and production of suitable and palatable vitamin D preparations. What about a new 1000 IU ergocalciferol tablet without calcium, safe for daily use without blood monitoring? There is a large and growing market for such preparations, which should be commissioned from drug companies by the NHS.

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No to universal supplementation

We do not agree that the public health approach to vitamin D deficiency should be universal supplementation (as in pregnant women, children, and elderly people) or fortification of foods with vitamin D.[1] Apart from hospital based data and a few small scale studies, there are no national data showing that vitamin D deficiency is increasing to the point of being a public health priority. The evidence linking the different health problems and vitamin D as an independent risk factor is also inconclusive.

For example, the most recent systematic review published in August 2009 included 165 studies and 11 systematic reviews.[2] With acknowledgment of the challenges of synthesising a dose-response relation between intake and health outcomes from a heterogeneous body of literature, the review concluded that most of the findings for vitamin D or calcium, or both, on the different health outcomes were inconsistent. Studies were few or reported inconsistent findings on the association between either serum 25-OH vitamin D concentration or calcium intake and cancer (colorectal, pancreas, prostate, all-cause), hypertension or specific cardiovascular disease events, immunological disorders, and pregnancy related outcomes, including pre-eclampsia.[2]

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1 Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:b5664. (11 January.)
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Vitamin D values for 13 183 tests performed during 2009 in Tower Hamlets (population 250 692)

Variable	Number tested	% Deficient (<25 nmol/l)	% Insufficient (25-49 nmol/l)	% Adequate (50-75 nmol/l)	% Optimal (>75 nmol/l)
Ethnicity					
White	2630	17	35	28	20
Black	941	47	32	17	4
Asian	8361	42	40	14	3
Mixed	144	29	42	20	8
Other	299	24	39	27	10
Not stated	808	41	35	15	8
Total	13183	37	38	18	7
Age (years)					
<16	1084	45	35	14	7
16-64	10328	38	39	17	6
>64	1771	26	38	24	12
Total	13183	37	38	18	7

VENOUS THROMBOEMBOLISM

Let's not talk about sex . . .

In summarising the latest guidance from the National Institute for Health and Clinical Excellence (NICE) on reducing the risk of venous thromboembolism in hospital patients, Hill and Treasure do not say that oestrogen containing contraceptives should be stopped four weeks before elective surgery.[1] Even in the full guidance some aspects of contraception are discussed almost in layperson terms.[2]

Contraceptives containing oestrogen (combined hormonal contraception) are not just given orally. The transdermal patch and the vaginal ring are now licensed in the UK, and injectable forms are available in other countries.

NICE concludes on oral contraceptives: "If the decision to stop oral contraceptives is taken it is important that women are provided with advice on the use of contraceptives in the interim period."[2] But not all oral contraceptives contain oestrogen, and contraceptive pills containing only progestogen do not need to be stopped before surgery.

NICE seems not to include any recommendation about when combined hormonal contraception may be restarted, and this will vary. For example, a patient opting for condoms alone in the interim period may be keen to restart combined hormone contraception as soon as possible. But a single injection of the contraceptive depomedroxyprogesterone acetate would last 12 weeks (four weeks preoperatively and eight weeks postoperatively). The Faculty of Sexual and Reproductive Healthcare recommends discontinuing combined hormonal contraception until at least three weeks after major surgery.[3]

In the UK 75% of women aged 16-49 are using some form of contraception, with at least 16% using the combined contraceptive pill.[4] Why, even as professionals, do we seem to find it difficult to talk about contraception?

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Competing interests: None declared.

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. . . or drugs

In its guidelines on reducing the risk of venous thromboembolism in hospital patients the National Institute for Health and Clinical Excellence (NICE) has averted its gaze not only from sex but also from drugs.[1 2] It has not considered intravenous drug users, specifically those injecting into their femoral veins, a group at clinically significant risk of deep vein thrombosis.

In Glasgow injecting drug use was the commonest predisposing factor for a group of women presenting with deep vein thrombosis.[3] Experience in our practice for homeless people in Leeds is similar. This risk factor should not be forgotten when homeless patients are admitted for surgery.

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Competing interests: None declared.

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Cite this as: *BMJ* 2010;340:c919

DEPRESSION IN ADOLESCENTS

Collaboration to overcome barriers in primary care

Thapar and colleagues' review of managing and preventing depression in adolescents highlights primary care's role in detection and initial management and alludes to pragmatic psychosocial approaches.[1] However, attempts to increase the involvement of primary care are impeded by concerns about medicalising depression, which means that psychological problems are not explored even when they are perceived to be present.[2]

Our collaboration between child psychiatrists and general practitioners has developed, piloted,[3] and feasibility tested a programme to address this lack. The TIDY programme—therapeutic identification of depression in young people[4]—is a training package and tools to help general practitioners to engage in conversations about emotional wellbeing with adolescents who present mainly with physical complaints. Guidelines facilitate the differentiation of depression from normal moodiness, with intervention strategies that can be offered during the consultation for milder cases while identifying those requiring specialist referral.

Since adolescents attending primary care have increased rates of depression (usually unrecognised)[5] and primary care is the only medical setting to which they have ready access, we developed a single dose intervention that provides advice on self help and encourages adolescents to seek support from within their family and social environment. Preliminary analysis of the feasibility study suggests that selective, opportunistic use of TIDY is followed by a small but significant increase (from a low baseline) in the recognition of depression in attenders. Therapeutic components of TIDY are used selectively and are acceptable to adolescents. Further research is required to fully evaluate adolescent views, as well as clinical and cost effectiveness.

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Competing interests: None declared.

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INDUSTRY INFLUENCE

Big Pharma's long tentacles

The *BMJ* gives two more examples of penetration by the pharmaceutical industry into what, in a better world, would be protected places: Harvard Medical School[1] and the World Health Organization.[2]

In this atmosphere of hidden payments and conflict of interest, medical professionals still go with some confidence to journals such as the *BMJ*, and the general public to trusted media such as the *New York Times*. It is distressing therefore to come across an article in the *New York Times* calling into question the safety and effectiveness of generic medicines.[3] It has already met with warm approval on the internet, especially on pharmaceutical industry sponsored websites.

But before suspicion of generic drugs becomes received wisdom under the imprimatur of the *New York Times*, the subject deserves a closer look.

By introducing the subject as a problem of generic *v* brand products, the author plays into the hands of the pharmaceutical industry, which for decades has attempted to plant suspicion in the public's mind about generic medicines. The problem is, of course, one of bioavailability, not generic drugs per se. This is made clear in the body of the article.

Readers will be impressed with the statements of Dr James A Reiffel in favour of brand name products. After all, we are told that he is a "cardiologist and professor of clinical medicine at Columbia." But don't we also deserve to know that Dr Reiffel is also a paid consultant for GlaxoSmithKline, the manufacturer of two drugs (bupropion/Wellbutrin and lamotrigine/Lamictal) discussed favourably in the article? Or that Dr Kimford Meador of Emory University, another expert cited, has received financial support from GlaxoSmithKline and also from UCB Pharmaceuticals, the manufacturer of levetiracetam/Keppra, another product cited favourably?

The comments of Reiffel and Meador are balanced and reasonable. They do not directly promote any brand product by name. So, no problem? Perhaps the fact that these two experts have also received payments for various services from many other pharmaceutical companies means that there is no particular conflict of interest. Does conflict of interest get diluted out somehow? A five minute internet search of disclosed competing interests reveals that between them, Reiffel and Meador have additional financial ties with Pfizer, Boehringer Ingelheim, Merck, Bristol Myers-Squibb, Ciba-Geigy, Johnson and Johnson, Wyeth Pharmaceuticals, Abbott Laboratories, Procter and Gamble, Searle, Park-Davis, Solvay, Astellas Pharma, Cardiome, Pharmacia, Sanofi-Aventis US, CV Therapeutics, Reliant Pharmaceuticals, Novartis Pharmaceuticals, Ortho-McNeil Pharmaceutical, Shire US, AstraZeneca, Xention Discovery, and Elan Corporation.

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Competing interests: None declared.

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Cite this as: *BMJ* 2010;340:c941

DRUG FIRM CONFLICTING INTERESTS

If only WHI was done well

Barrington claims that the women's health initiative (WHI) trial had impeccable standards.[1] We recently highlighted some of its shortcomings relating to hormone replacement therapy (HRT).[2]

The data and safety monitoring board used a global index of health which was modified on three occasions, including once after formal monitoring had started. Although the oestrogen-progestogen arm of the studies was stopped after a designated safety boundary was breached, the oestrogen alone arm was stopped by staff of the National Heart, Lung and Blood Institute and not by the monitoring board. The primary outcome was coronary heart disease, with breast cancer being a secondary outcome but subjected to unadjusted analyses resulting in false indication of significance. The WHI analysis protocol stipulated that data would be analysed by baseline age, yet that was completely ignored in the initial publication.[3]

Subsequent publications of the analyses of more complete data from the WHI showed changes in outcomes from those widely publicised in the initial report.[2] Contrary to Barrington's letter, a post hoc change in the significance level occurred in the WHI publication of 2007,[4] thereby rendering non-significant (P=0.02) a trend for reduction in coronary heart disease in women starting HRT within 10 years of menopause. Other WHI publications dispensed with statistics completely.[2] For example, it was concluded that HRT treatment may increase the risk of ovarian cancer, despite the difference from placebo being non-significant (P=0.02).[5]

Thus, the WHI trial was far from impeccable and has introduced substantial biases into the literature, with the potential for consequent adverse effects on health. Barrington claims that Lawton "shoots himself in the foot" by using the WHI as an example of a non-industry funded study that deviates from good standards,[1] but in reply seems to have blown both his own legs off.[1]

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FEVER AS NATURE'S ENGINE

Some clinical data

We read with interest recent letters on the potential benefit of fever in infection.[1 2] In keeping with previously published data,[3] we recently found that hypothermia (‹36°C) on admission to hospital was significantly associated with 30 day mortality in patients with community acquired pneumonia classified as being non-severe by the CURB-65 criteria (CURB-65 score 0-2).[4] The table shows unadjusted data for the entire cohort (CURB-65 scores 0-5).

Association between temperature at hospital admission and mortality[4]

Temperature (°C)	% Mortality (n/N)
‹35	50 (2/4)
35-35.9	31 (13/42)
36-38	21 (62/300)
38.1-39.9	9 (11/124)
›40	0 (0/7)

This could be explained by sicker patients taking antipyretics just before admission, but the association was maintained when data were stratified by severity using the CURB-65 score. A similar association was seen in a separate cohort of 118 patients with clinically significant bloodstream infection[5]: mortality decreased from 50% (2/4) in patients with a temperature ‹36°C at the time of blood culture to 23% (11/48) in those with a temperature between 36°C and 38°C and 17% (11/66) in those with a temperature ›38°C.

Although these results could be the result of confounding, our clinical observations and Dixon and colleagues' in vitro data suggest that the association between temperature, antipyretics, and clinical outcomes in infection should be investigated.

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Competing interests: None declared.

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