

Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study

Rebecca J Stoltzfus, Jane D Kvalsvig, Hababu M Chwaya, Antonio Montresor, Marco Albonico, James M Tielsch, Lorenzo Savioli, Ernesto Pollitt



The full version of this article appears on bmj.com

Abstract

Objective To measure the effects of iron supplementation and anthelmintic treatment on iron status, anaemia, growth, morbidity, and development of children aged 6-59 months.

Design Double blind, placebo controlled randomised factorial trial of iron supplementation and anthelmintic treatment.

Setting Community in Pemba Island, Zanzibar.

Participants 614 preschool children aged 6-59 months.

Main outcome measures Development of language and motor skills assessed by parental interview before and after treatment in age appropriate subgroups.

Results Before intervention, anaemia was prevalent and severe, and geohelminth infections were prevalent and light—*Plasmodium falciparum* infection was nearly universal. Iron supplementation significantly improved iron status, but not haemoglobin status. Iron supplementation improved language development by 0.8 (95% confidence interval 0.2 to 1.4) points on the 20 point scale. Iron supplementation also improved motor development, but this effect was modified by baseline haemoglobin concentrations ($P = 0.015$ for interaction term) and was apparent only in children with baseline haemoglobin concentrations < 90 g/l. In children with a baseline haemoglobin concentration of 68 g/l (one standard deviation below the mean value), iron treatment increased scores by 1.1 (0.1 to 2.1) points on the 18 point motor scale. Mebendazole significantly reduced the number and severity of infections caused by *Ascaris lumbricoides* and *Trichuris trichiura*, but not by hookworms. Mebendazole increased development scores by 0.4 (−0.3 to 1.1) points on the motor scale and 0.3 (−0.3 to 0.9) points on the language scale.

Conclusions Iron supplementation improved motor and language development of preschool children in rural Africa. The effects of iron on motor development were limited to children with more severe anaemia (baseline haemoglobin concentration < 90 g/l). Mebendazole had a positive effect on motor

and language development, but this was not statistically significant.

Introduction

Iron deficiency anaemia is associated with comparatively poor performance in tests of mental and motor development in infants and toddlers and of intelligence and cognitive function in preschool and school children.¹⁻⁴ In young children aged 12-18 months, one randomised trial found that development improved in children treated for iron deficiency anaemia⁵; however, most quasi-experimental studies in children of a similar age have shown no such benefit.⁶ Prospective trials have also produced discrepant findings.^{7, 8}

Associations between geohelminth infection and mental performance in schoolchildren have been reported,⁹⁻¹³ but results from randomised trials have been inconclusive.¹⁴ We are not aware of published investigations of the relation between geohelminth infections and development in preschool children.

We report a trial designed to measure the effects of iron supplementation and anthelmintic treatment on iron status, anaemia, growth, morbidity, and development of children aged 6-59 months at the start of the trial.

Participants and methods

Location

The study was conducted in Kengeja village on the island of Pemba north of Zanzibar. The environment is rural, with fishing and farming as the main occupations. *P falciparum* is holoendemic and transmitted throughout the year, and *P malariae* is also present. A number of helminths are highly endemic in this population, including two hookworm species, *Ascaris lumbricoides*, *Trichuris trichiura*, and *Schistoma haematobium*.

Study sample and randomisation

We estimated that 640 children were needed for a 5 g/l difference in mean haemoglobin response in two age subgroups to be seen, with $\alpha = 0.05$ and $\beta = 0.10$.

During June and July 1996, a census was conducted in Kengeja and a database of all children whose age was reported by their parents as 3-56 months was cre-

Editorial by Saloojee and Pettifor

Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205-2179, USA
Rebecca J Stoltzfus
associate professor

Department of International Health, Bloomberg School of Public Health
James M Tielsch
professor

Child Development Programme, University of Natal, Congella 4013, South Africa
Jane D Kvalsvig
director

Ministry of Health, Zanzibar, Tanzania
Hababu M Chwaya
director of preventive services

Parasitic Diseases and Vector Control, World Health Organization, 1211 Geneva 27, Switzerland
Antonio Montresor
medical officer
Lorenzo Savioli
coordinator

Ivo de Carneri Foundation, 20129 Milan, Italy
Marco Albonico
scientific secretary

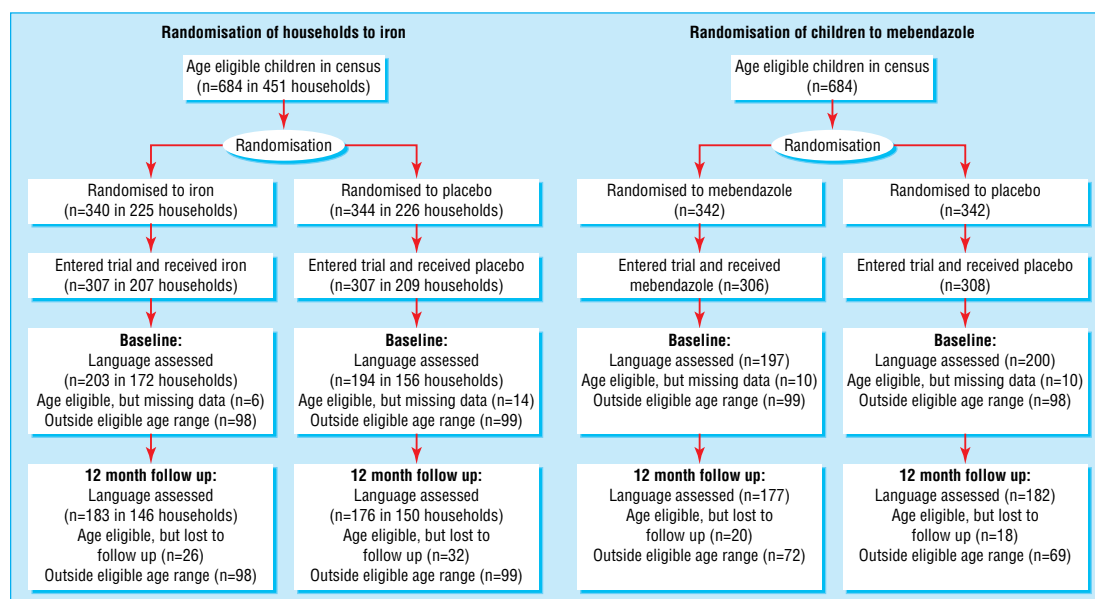
continued over

BMJ 2001;323:1389-93

Department of Pediatrics, School of Medicine, University of California, Davis, CA 95616, USA

Ernesto Pollitt
professor of human development and behaviour research

Correspondence to: R J Stoltzfus
rstoltzf@jhsph.edu



Randomisation of preschool children in Zanzibar to iron and mebendazole or placebo, and retention in trial

ated. The database contained 684 children from 451 households. Their parents were invited to enter their children in the trial.

Households, rather than children, were randomly allocated to receive iron or placebo, so that mothers of siblings would have to manage only one bottle of supplement. Of the 684 children identified in the census and randomised to treatment, 614 attended the baseline clinic at the local primary healthcare centre during September 1996. In total, 538 children completed the follow up period of 12 months, including the final clinical assessment during September 1997. The randomisation and retention of children in the trial is shown in the figure. The developmental scales were not appropriate to be used for the entire age range of the children in the study; language development is reported for children aged 12-48 months at baseline and motor development for children aged 12-36 months at baseline.

Interventions

Iron treatment—Iron treatment consisted of a ginger flavoured liquid supplement containing 20 mg/ml ferrous sulphate, or an identical placebo (both supplied by Alpharma USPD, Baltimore). At the baseline clinic, each mother was trained on how to give a 0.5 ml dose (equivalent to 10 mg iron) to her children, and she was instructed to give this dose daily for the next year. During the 12 month trial, study staff visited each mother weekly to ask how many days in the past week she had given the supplement to her child and to deal with any compliance problems.

Anthelmintic treatment—Anthelmintic treatment consisted of 500 mg mebendazole in an orange flavoured chewable tablet, or an identical placebo tablet (Pharmamed, Zejtun). After the baseline clinic, study staff made home visits to all children every three months to give the anthelmintic treatment.

Oral iron—Children with severe anaemia (haemoglobin concentrations <70 g/l) at the baseline clinic were treated with oral iron 60 mg/day for 30 days, but they were also given their randomly allocated iron. The total iron dosage for these severely anaemic children for

the first month of the study, therefore, was 60 mg/day or 70 mg/day. These children were also given mebendazole (500 mg) in place of their randomly allocated anthelmintic treatment, but they subsequently received their randomly allocated treatment at the baseline clinic. Parents of these children were informed that their child was severely anaemic and the treatments given were explained. These children were included in the subsequent analyses on an intention to treat basis.

Assessments

Clinical assessments—The numbers of helminth eggs in faecal samples were counted for 591 (96%) of 614 study children by the Kato-Katz method.¹⁵ Anthropometric measures were converted to z scores with Anthro version 3.0 (CDC, Atlanta). Stunting was defined as height for age z score < -2.0, wasting as weight for height z score < -2.0, and underweight as weight for age z score < -2.0. Blood samples (3 ml) were collected to determine haemoglobin concentration, erythrocyte protoporphyrin concentration, the numbers of malaria parasites, and serum ferritin concentrations.

Developmental assessments—Motor and language development were assessed by the parents reporting gross motor and language milestones—a method known to have considerable accuracy and sensitivity for identifying developmental delays.¹⁶⁻¹⁹

Analysis of treatment effects

Several characteristics (sex, breast feeding, stunting and developmental scores), were unbalanced between the groups (table 1). To adjust for baseline imbalances we included baseline developmental scores, age (months), sex, haemoglobin (g/l), anthropometric measures (z scores), and presence of ≥ 5000 malaria parasites/ μ l blood as in generalised linear models.²⁰⁻²¹ To look at variables that might modify the effects of treatment on developmental outcomes, we tested the interaction term of treatment (iron or mebendazole) with each variable.

Table 1 Characteristics of children in Zanzibar aged 12-48 months at baseline with complete developmental assessments at baseline and after treatment. Values are numbers (percentages) unless otherwise specified

	Iron		Mebendazole	
	Placebo	Treatment	Placebo	Treatment
General characteristics:				
Mean (SD) age (months)	29.4 (11.1)	29.6 (10)	29.4 (10.8)	29.7 (11)
Female sex	85/176 (48)	82/183 (45)	86/182 (47)	81/177 (46)
Breast fed in the past 24 hours	56/176 (32)	45/183 (25)	53/182 (29)	48/177 (27)
Stunted	58/171 (34)	76/179 (43)	66/179 (37)	68/171 (40)
Wasted	10/171 (6)	9/180 (5)	10/179 (6)	9/172 (5)
Underweight	58/171 (34)	63/180 (35)	64/179 (36)	57/172 (33)
Malaria positive blood film	149/176 (85)	153/183 (84)	154/182 (85)	148/177 (84)
Anaemia and iron deficiency:				
Mean (SD) haemoglobin (g/l)	86 (15)	86 (15)	86 (15)	85 (15)
Mean erythrocyte protoporphyrin ($\mu\text{mol/mol}$)*	153	162	155	160
Mean serum ferritin ($\mu\text{g/l}$)	29.2	32.5	30.9	30.8
Helminth infections:				
Hookworm	74/170 (44)	88/181 (49)	86/180 (48)	76/171 (44)
<i>Trichuris trichiura</i>	115/170 (68)	125/181 (69)	125/180 (69)	115/171 (67)
<i>Ascaris lumbricoides</i>	73/170 (43)	74/181 (41)	79/180 (44)	68/171 (40)
Developmental scores:				
Language scale (mean (SD) score)	9.6 (5.8)	10.4 (5.8)	10.0 (5.8)	10.0 (5.8)
Motor scale (mean (SD) score)†	11.5 (6.2) (n=123)	12.0 (6.2) (n=132)	11.7 (6.3) (n=128)	11.8 (6.0) (n=127)

Differences in denominators result from missing data on anthropometry and helminth egg counts.

*Geometric mean. †Children 12-36 months old at baseline.

Results

The characteristics of children in the language scale cohort are shown in table 1. In total, 101/358 (28%) of participants aged 12-48 months were breastfed at the time of the study. Breast feeding was common in children aged 12-23 months (96/121, 79%) and rare in children ≥ 2 years (5/237, 2%). Stunted growth was common, while wasting was relatively uncommon. *P falciparum* malarial infection was nearly universal. Most characteristics were similar among the treatment groups, but more children who received iron than those who received the iron placebo had stunted growth at baseline (76/179, 43% v 58/171, 34).

At baseline, anaemia was prevalent and severe. In total, 347 of 359 (97%) children were anaemic by international standards (haemoglobin < 110 g/l) and 54/305 (18%) were severely anaemic (haemoglobin < 70 g/l). Haemoglobin concentration was strongly and positively associated with age at baseline.²² An overall increase in haemoglobin was seen in all treatment groups; this was mostly attributable to the increased age of the children at follow up. Erythrocyte protoporphyrin concentrations were high, and they were strongly associated with haemoglobin concentrations,²² suggesting that iron deficiency was prevalent. Serum ferritin values were higher than expected given the prevalence of anaemia and the raised erythrocyte protoporphyrin concentrations; this probably reflects the prevalence of malaria and other subclinical infections.²² Iron supplementation significantly increased serum ferritin and erythrocyte protoporphyrin concentrations, but it had little impact on haemoglobin concentrations (table 2). The effect of iron treatment on haemoglobin concentration was greater (but still not statistically significant) in children who were more anaemic at the start: 0.2 (–4.8 to 5.2) g/l in children with baseline haemoglobin concentrations ≥ 80 g/l compared with 5.4 (–2.7 to 13.1) g/l in those with initial haemoglobin < 80 g/l. Mebendazole had no impact on indicators of iron status, except to

decrease the average concentrations of serum ferritin (perhaps by reducing the gut inflammatory response secondary to helminth infection).

Helminth infections were prevalent (table 1), but of light intensity (number of eggs/g faeces; table 3). Regular treatment with mebendazole was highly efficient in reducing the prevalence and intensity of *A lumbricoides* infection (table 3). It was less efficacious against *T trichiura*, although the intensity of this infection was still greatly reduced in the participants who received mebendazole. The effect of mebendazole on hookworm prevalence and intensity three months after treatment was not statistically significant.

The adjusted main effects of iron and mebendazole treatments on motor scores were positive, but they were not statistically significant. However, there was a significant interaction between baseline haemoglobin concentration and iron treatment ($P=0.015$). Iron

Table 2 Anaemia and iron status before and after treatment in preschool children. Values are numbers (percentages) unless otherwise specified

	Iron		Mebendazole	
	Placebo (n=176)	Treatment (n=183)	Placebo (n=182)	Treatment (n=177)
Mean (SD) haemoglobin (g/l):				
Baseline	86 (15)	86 (15)	86 (15)	85 (15)
12 months	97 (16)	99 (15)	99 (15)	98 (16)
Haemoglobin < 110 g/l:				
Baseline	169 (96)	178 (97)	174 (96)	173 (98)
12 months	142 (81)	144 (79)	147 (81)	139 (79)
Haemoglobin < 70 g/l:				
Baseline	26 (15)	28 (15)	21 (12)	33 (19)
12 months	8 (5)	5 (3)	6 (3)	7 (4)
Mean erythrocyte protoporphyrin ($\mu\text{mol/mol}$):				
Baseline*	153	162	155	160
12 months	86	72†	76	80
Mean serum ferritin ($\mu\text{g/l}$):				
Baseline*	29.2	32.5	30.9	30.8
12 months	45.8	60.8‡	58.1	47.9§

*Geometric mean. †Iron v placebo, $P=0.032$.

‡Iron v placebo, $P=0.002$. §Mebendazole v placebo, $P=0.037$.

Table 3 Helminth infections before and after treatment in preschool children. Values are numbers (percentages) unless otherwise specified

Infection	Iron		Mebendazole	
	Placebo	Treatment	Placebo	Treatment
Children*				
Baseline	170	181	180	177
12 months	159	168	166	161
Tested positive for hookworms				
Baseline	74 (44)	88 (49)	86 (48)	76 (44)
12 months	103 (65)	103 (61)	109 (66)	97 (60)
Hookworms (eggs/g faeces)†				
Baseline	11.4	16.4	14.7	12.8
12 months	181.6	125.1	187.9	118.9
Tested positive for <i>Trichuris trichiura</i>				
Baseline	115 (68)	125 (69)	125 (69)	115 (67.3)
12 months	109 (69)	108 (64)	124 (75)	93 (57.8)‡
<i>T trichiura</i> (eggs/g faeces)†				
Baseline	53.2	60.9	52.4	61.8
12 months	260.9	179.3	511.3	88.1 ‡
Tested positive for <i>Ascaris lumbricoides</i>				
Baseline	73 (43)	74 (41)	79 (44)	68 (39.8)
12 months	62 (39)	62 (37)	82 (49.4)	42 (27.1)‡
<i>A lumbricoides</i> (eggs/g faeces)†				
Baseline	29.3	23.5	29.5	23.1
12 months	47.6	31.8	126.3	11.8†

*Differences between numbers at baseline and 12 months due to missing faecal samples.

†Geometric mean of all children; values of 0 set to 1 before taking logarithm.

‡Mebendazole treatment effect, $P < 0.001$.

treatment was associated with higher post-treatment motor scores only in children with low baseline haemoglobin. There was a benefit from iron treatment in children with baseline haemoglobin concentrations < 90 g/l, and this was statistically significant at concentrations < 80 g/l. In children with baseline haemoglobin of 68 g/l (one standard deviation below the mean value), the iron treatment effect was 1.1 (0.1 to 2.1) points on the 18 point motor scale. The adjusted effect of mebendazole treatment on motor scores in this final model was 0.44 (-0.22 to 1.10); this was not significantly modified by the concentration of haemoglobin at baseline or by iron treatment.

The adjusted main effects of iron and mebendazole treatments on language scores were positive, but only the effect of iron was statistically significant. The effect of mebendazole was a mean change in score of 0.3 (-0.3 to 0.9), and the effect of iron treatment was a mean change in score of 0.8 (0.2 to 1.4; $P = 0.011$). Although children who received iron and mebendazole treatments had the highest final language scores, the iron-mebendazole interaction term did not approach significance ($P = 0.48$). The effect of iron treatment was similar for all children within the wide range of haemoglobin concentrations and other measured characteristics in the study sample.

Discussion

Effects of iron and anaemia on motor and language development

Our results shed partial light on the contributions of anaemia and iron deficiency as causes of developmental delays. At baseline, motor scores were more strongly related to haemoglobin concentrations than to erythrocyte protoporphyrin concentrations (an indicator quite specific to iron deficiency in this population).²² Iron supplementation improved motor development

only in children with very low baseline haemoglobin concentrations. A similar plateau in the association of haemoglobin with motor development was recently found in children in the United Kingdom.²³ It is possible that the aetiology of anaemia changes with its severity, with more severe anaemia being more strongly related to iron deficiency. There is some evidence for this in our data, as the effect of iron treatment was lower in children with baseline haemoglobin concentrations ≥ 80 g/l than < 80 g/l, suggesting that the effect of iron on motor development was mediated through improved haemoglobin concentrations. Alternatively, the younger age of children with more severe anaemia may have been an important determinant of their increased response to iron.

In contrast, language scores at baseline were strongly related to haemoglobin and erythrocyte protoporphyrin concentrations. Iron supplementation improved language development across a wide range of baseline haemoglobin concentrations, despite the small effect of iron treatment on haemoglobin in all but the most severely anaemic children. This suggests that the effect of iron on language development was mediated through mechanisms that are independent of haemoglobin concentration.

Effects of anthelmintic treatment on motor and language development

We are not aware of previous reports on the effect of anthelmintic treatment on motor and language development of children in this young age range. In this study, children who received mebendazole had slightly better developmental scores, but the size of the effect was small and did not approach statistical significance. The power of our study to detect a statistically significant difference was $< 80\%$ for effect sizes smaller than 1 unit on our scales. During the 12 month study period, the most rapid increases in motor and language development scores were in the children aged 12-24 months. This group had low prevalences of the target parasite species, making it less likely that we would detect the effects of mebendazole treatment. At baseline, only 6% of the children aged 12-24 months were infected with all three helminth species compared with 39% of the children aged 37-48 months.

The lack of effect of mebendazole on motor and language development might be explained by the drug's relatively low cure rates for two of the species—different species having different effects on development—or by a causal relation too small to be detected with our methods or not present at all. The potential public health benefits of treating young children for worms include immunological and nutritional outcomes as well as motor and language development, and additional research is needed.

Summary

Our results highlight that in African communities in which malaria is endemic there are severely anaemic children who are not detected by the current healthcare system and who seem to be at considerable risk of poor development. Identifying the optimal treatment and follow up regimen for severely anaemic children is a high priority and, although the best dose and duration needs to be clarified, long term treatment with oral iron may be an important component.

Contributors: See bmj.com

Funding: Thrasher Research Fund, Cooperative Agreement #HRN-A-00-97-00015-00 between the Johns Hopkins University and the United States Agency for International Development, and Alpha USAID, Baltimore, MD.

Competing interests: None declared.

- Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, et al. Iron deficiency anemia and iron therapy effects on infant developmental test performance. *Pediatrics* 1987;79:981-95. [Published erratum appears in *Pediatrics* 1988;81:683.]
- Walter T. Infancy: mental and motor development. *Am J Clin Nutr* 1989;50:655-66.
- Oski FA, Honig AS, Helu B, Howanitz P. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. *Pediatrics* 1983;71:877-80.
- Watkins WE, Pollitt E. Iron deficiency and cognition among school-age children. In: *Nutrition, health, and child development: Research advances and policy recommendations*. Washington, DC: Pan American Health Organization, The World Bank and Tropical Medicine Research Unit, 1997:179-97.
- Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *Lancet* 1993;341:1-4.
- Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;105:E51.
- Williams J, Wolff A, Daly A, MacDonald A, Aukett A, Booth IW. Iron supplemented formula milk related to reduction in psychomotor decline in infants from inner city areas: randomised study. *BMJ* 1999;318:693-7.
- Morley R, Abbott R, Fairweather-Tait S, MacFadyen U, Stephenson T, Lucas A. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial. *Arch Dis Child* 1999;81:247-52.
- Kvalsvig JD, Cooppan RM, Connolly KJ. The effects of parasite infections on cognitive processes in children. *Ann Trop Med Parasitol* 1991;85:551-68.
- Sakti H, Nokes C, Hertanto WS, Hendratno S, Hall A, Bundy DA, et al. Evidence for an association between hookworm infection and cognitive function in Indonesian school children. *Trop Med Int Health* 1999;4:322-34.
- Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Robinson BA, Bundy DA. Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. *Parasitology* 1992;104:539-47.
- Simeon DT, Grantham-McGregor SM, Wong MS. *Trichuris trichiura* infection and cognition in children: results of a randomized clinical trial. *Parasitology* 1995;110:457-64.
- Hutchinson SE, Powell CA, Walker SP, Chang SM, Grantham-McGregor SM. Nutrition, anaemia, geohelminth infection and school achievement in rural Jamaican primary school children. *Eur J Clin Nutr* 1997;51:729-35.
- Dickson R, Awasthi S, Williamson P, Demelweck C, Garner P. Effects of treatment for intestinal helminth infection on growth and cognitive performance in children: systematic review of randomised trials. *BMJ* 2000;320:1697-701.
- Ash LR, Orihel TC, Savioli L. *Bench aids for the diagnosis of intestinal parasites*. Geneva: World Health Organization, 1994.
- Glascow FP, Sandler H. Value of parents' estimates of children's developmental ages. *J Pediatr* 1995;127:831-5.

What is already known on this topic

Iron is needed for development and functioning of the human brain

Anaemic children show developmental delays, but it is not yet clear whether iron deficiency causes these deficits or whether iron supplementation can reverse them

Helminth infections in schoolchildren are associated with cognitive deficits, but few studies have been made of helminth infection and early child development

What this study adds

Low doses of oral iron supplementation given daily improved language development in children aged 1-4 years in Zanzibar

Iron supplementation improved motor development, but only in children with initial haemoglobin concentrations below 90 g/l

The effects of routine anthelmintic treatment on motor and language milestones were positive, but non-significant, with our sample size

- Ireton H, Glascoe FP. Assessing children's development using parents' reports. The Child Development Inventory. *Clin Pediatr (Phila)* 1995;34:248-55.
- Cowen EL, Work WC, Wyman PA, Jarrell DD. Relationships between retrospective parent reports of developmental milestones and school adjustment at ages 10 to 12 years. *J Am Acad Child Adolesc Psychiatry* 1994;33:400-6.
- Knobloch H, Stevens F, Malone A, Ellison P, Risemberg H. The validity of parental reporting of infant development. *Pediatrics* 1979;63:872-8.
- Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988;44:1049-60.
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
- Stoltzfus RJ, Chwaya HM, Montresor A, Albonico M, Savioli L, Tielisch J. Malaria, hookworms and recent fever are related to anemia and iron status indicators in 0- to 5-y old Zanzibari children and these relationships change with age. *J Nutr* 2000;130:1724-33.
- Sherriff A, Emond A, Bell JC, Golding J. Should infants be screened for anaemia? A prospective study investigating the relation between haemoglobin at 8, 12, and 18 months and development at 18 months. *Arch Dis Child* 2001;84:480-5.

(Accepted 12 July 2001)

A memorable teacher

Asking the right questions

I was listening to the news during one of many times of tension in Israel. Most people spoke about "Hebron," but some of the Israeli settlers said "Hevron." It was like smelling a long forgotten odour. I was taken back to 1944 and to French lessons with Mr Hudson-Davies, a tall, rotund, bespectacled man whose passion for etymological connections often led him to stray outside the curriculum. I could see and hear him emphatically booming "P, B, V, and F are the same letter."

I realised that this was the only occasion from all my schooldays when I could recall the teacher, the location, and the specific fact imparted. I can recall the flavour of many other excellent teachers and their classes but none of their teaching. Equally, from my clinical student days I can recall only one episode where the memory of the setting, the teacher, and the teaching has endured.

The scene was in a ward at Paddington Green Children's Hospital, long since closed. The teacher was a paediatric registrar, Gordon Hesling, later a consultant at Preston. What he said, in a teaching round, of which I can remember nothing else, was: "In medicine the important thing is not so much knowing the answers as asking yourself the right questions." I am not sure why this idea fixed itself so firmly but experience has borne it out time and again.

Questioning yourself is, after all, a basic element in problem solving, from crosswords to clinical diagnosis. If, as a radiologist looking at lung shadowing, I do not ask myself, "Could it be tuberculosis?" I may never make the right diagnosis in a particular case. Going through a differential diagnosis is asking whether the cause of an illness could be infective, traumatic, neoplastic, endocrine, and so forth. A structured clinical history and examination can be a way of making sure appropriate questions are asked. A routine inquiry about medication is, or should be, like saying, "Could these symptoms be due to any drugs the patient is taking?" A routine palpation of the femoral pulses in a hypertensive patient is asking, "Could this be coarctation?"

Asking yourself questions is the antidote to working on autopilot, and doctors who do not regularly say to themselves, "What else could this be?" or "What else could I do?" may be failing their patients. Like all virtues, self questioning of this sort can be hard work, and the best of doctors will sometimes fall short of the ideal. Shooting from the hip is less demanding. But if you have anything that is less than straightforward, try to be seen by a doctor who asks himself or herself questions.

Hugh Saxton *retired radiologist, Stockbridge, Hampshire*