PN-ACC-764

98081

The Effects of Iron Deficiency and Anemia on Mental and Motor Performance, Educational Achievement, and Behavior in Children: An Annotated Bibliography

Catherine Nokes

Claire van den Bosch

Donald A.P. Bundy

a

USAID

pcd

ILSI

International Life Sciences INSTITUTE

JSI

OMNI Opportunities for Micronutrient Interventions

The publication of this report is made possible by support from Opportunities for Micronutrient Interventions (OMNI), a project of the Office of Health and Nutrition Bureau for Global Programs Field Support and Research, U S Agency for International Development under Contract HRN 5122 C 00 3025 00, Project 936 5122 and Partnership for Child Development The contribution of the Partnership for Child Development was made possible by a grant from the James S McDonnell Foundation

For additional information contact International Nutritional Anemia Consultative Group (INACG), c/o ILSI Human Nutrition Institute 1126 Sixteenth Street NW Washington DC 20036 4810 USA Phone 202 659 0789 Fax 202 659 3617 Email omni@ilsi org

INACG publications are available free of charge to developing countries and for $3 50 (U S) to developed countries Copies can be ordered from the INACG Secretariat

This report is the summary of the presentations and discussions that took place at the consultative meeting at the University of Oxford, on September 16–17 1996 and does not necessarily reflect the scientific recommendations or views of INACG USAID, or the International Life Sciences Institute

Printed April 1998 in the United States of America

CONTENTS

ALPHABETICAL LIST OF INCLUDED STUDIES

Aukett MA, Parks YA, Scott PH, Wharton BA (1986) Treatment with iron increases weight gain and psychomotor development Arch Dis Child 61 849-857 Reference 12

Bruner AB, Joffe A, Duggan AK, et al (1996) Randomised study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls Lancet 348 992-996 Reference 42

Cantwell RJ (1974) The long term neurological sequelae of anemia in infancy Pediatr Res 8 342 Reference 26

Deinard AS, Gilbert A, Dodds M, Egeland B (1981) Iron deficiency anemia and behavioural deficits Pediatrics 68 828-833 Reference 1

Deinard AS, List A, Lindgren B, et al (1986) Cognitive deficits in iron deficient and iron deficient anemic children J Pediatr 108 681-689 Reference 29

Grindulis H, Scott PH, Belton NR, Wharton BA (1986) Combined deficiency of iron and vitamin D in Asian toddlers Arch Dis Child 61 843-848 Reference 3

Groner JA, Holtzman NA, Charney E, Mellitts E (1986) A randomized trial of oral iron on tests of short term memory and attention span in young pregnant women J Adolesc Health Care 7 44-48 Reference 37

Heywood A, Oppenheimer S, Heywood P, Jolley D (1989) Behavioral effects of iron supplementation in infants in Mandung, Papua New Guinea Am J Clin Nutr 50 630-640 Reference 17

Hurtado EK (1995) Cross linking a third data set long term effects of iron deficiency during infancy and early childhood [abstract] Biennial meeting of the Society for Research in Child Development, Indianapolis, March-April 1995, 217 Reference 22

Idjradinata P, Pollitt E (1993) Reversal of developmental delays in iron-deficient anemic infants treated with iron Lancet 341 1-4 Reference 15

Johnson DL, McGowan RJ (1983) Anemia and infant behavior Nutr Behav 1 185-192 Reference 2

Kayshap P, Gopaldas T (1987) Impact of hemanitic supplementation on cognitive function in underprivileged school girls (8-15 years of age) Nutr Res 7 1117-1126 Reference 38

Lozoff B, Brittenham GM, Viteri FE, Urrutia JJ (1982a) Behavioural abnormalities in infants with iron deficiency anemia In Pollitt EL (ed), Brain biochemistry and behaviour Raven Press, New York, pp 183-195 Reference 8

Lozoff B, Brittenham GM, Viteri FE, et al (1982b) Developmental deficits in iron deficient infants effects of age and severity of iron lack J Pediatr 101 948-952 Reference 7

Lozoff B, Brittenham GM, Viteri FE, et al (1982c) The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants J Pediatr 100 351-357 Reference 6

Lozoff B, Wolf AW, Urrutia JJ, Viteri FE (1985) Abnormal behavior and low developmental test scores in iron-deficient anemic infants J Dev Behav Pediatr 6 69-75 Reference 11

Lozoff B, Klein NK, Prabucki KM (1986) Iron-deficient anemic infants at play J Dev Behav Pediatr 7 152-158 Reference 4

Lozoff B, Brittenham GM, Wolf AW, et al (1987) Iron deficiency anemia and iron therapy effects on infant developmental test performance Pediatrics 79 981-995 Reference 13

Lozoff B, Jiminez E, Wolf AW (1991) Long-term developmental outcome of infants with iron deficiency N Engl J Med 325 6876-6894 Reference 25

Lozoff B, De Andraca L, Walter T, Pino P (1996a)

Does preventing iron-deficiency anemia (IDA) improve developmental test scores? [personal communication] Reference 19

Lozoff B, Wolf AW, Jimenez E (1996b) Iron deficiency anemia and infant development effects of extended oral iron therapy J Pediatr 129 382–389 Reference 16

Moffatt MEK, Longstaffe S, Besant J, Dureski C (1994) Prevention of iron deficiency and psychomotor decline in high risk infants through use of iron-fortified infant formula a randomized clinical trial J Pediatr 125 527-534 Reference 18

Oski TE, Honig AS (1978) The effects of short term therapy on the developmental scores of iron deficient infants Pediatrics 92 21-25 Reference 5

Oski FA, Honig AS, Helu B, Howanitz P (1983) Effect of iron therapy on behaviour performance in non-anemic iron deficient infants Pediatrics 71 877-880 Reference 10

Palti H, Pevsner B, Adler B (1983) Does anemia in infancy affect achievement on developmental and intelligence tests? Hum Biol 55 189-194 Reference 23

Palti H, Meijer A, Adler B (1985) Learning achievement and behavior at school of anemic and non-anemic infants Early Hum Dev 10 217-233 Reference 20

Pollitt E, Greenfield D, Leibel R (1978) Behavioural effects of iron deficiency among pre-school children inCambridge, Mass Fed Proc 37 487 Reference 27

Pollitt E, Leibel RL, Greenfield D (1983) Iron deficiency and cognitive test performance in preschool children Nutr Behav 1 137-146 Reference 28

Pollitt E, Yunis F, Salem S, Scrimshaw NS (1985) Reported in Pollitt E, Soemantri AG, Yunis F, Scrimshaw NS, Cognitive effects of iron deficiency anemia Lancet 19 158 Reference 35

Pollitt E, Saco-Pollitt C, Leibel RL, Viteri FE (1986) Iron deficiency and behavioral development in infants and pre-school children Am J Clin Nutr 43 555-565 Reference 30

Pollitt E, Hathirat P, Kotchabhakdi NJ, et al (1989) Iron deficiency and educational achievement in Thailand Am J Clin Nutr 50 687-697 Reference 41

Seshadri S, Hirode K, Naik P, Malhotra S (1982) Behavioural responses of young anemic Indian children to iron-folic acid supplements Br J Nutr 48 233-240 Reference 34

Seshadri S, Gopaldas T (1989) Impact of iron supplementation on cognitive functions in preschool and school aged children the Indian experience Am J Clin Nutr 50 675-686 Reference 39

Soemantri AG, Pollitt E, Kim I (1985) Iron deficiency anemia and educational achievement Am J Clin Nutr 42 1221-1228 Reference 36

Soemantri AG (1989) Preliminary findings on iron supplementation and learning achievement of rural Indonesian children Am J Clin Nutr 50 698-702 Reference 40

Soewondo S, Husaini MA, Pollitt E (1989) Effects of iron deficiency on attention and learning processes in pre-school children Bandung, Indonesia Am J Clin Nutr 50 667-674 Reference 31

Walter T, Kovalskys J, Stekel A (1983) Effect of mild iron deficiency on infant mental development scores Pediatrics 102 519-522 Reference 9

Walter T, De Andraca I, Chadud P, Perales CG (1989) Iron deficiency anemia adverse effects on infant psychomotor development Pediatrics 84 7-17 Reference 14

Walter T, de Andraca I, Castillo M, et al (1990) Cognitive effect at five years of age in infants who were anemic at 12 months a longitudinal study [abstract] Pediatr Res 28 295 Reference 24

Wasserman G, Graziano JH, Factor-Litvak P, et al (1992) Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years J Pediatr 121 695-703 Reference 21

Webb TE, Oski F (1973a) Iron deficiency anemia and scholastic achievement in young adolescents J Pediatr 82 827-830 Reference 32

Webb TE, Oski FA (1973b) The effect of iron deficiency anemia on scholastic achievement behavioural stability and perceptual sensitivity [abstract] Pediatr Res 28 294 Reference 33

INTRODUCTION

Iron deficiency (ID) is a major public health problem affecting more than 2000 million persons worldwide. Iron is an essential nutrient not only for the normal growth, health, and survival of children, but also for their normal mental and motor development and cognitive functioning. Iron deficiency with anemia (IDA) is associated with significantly poorer performance on psychomotor and mental development scales and behavioral ratings in infants, lower scores on cognitive function tests in preschool children, and lower scores on cognitive function tests and educational achievement tests in school-age children.

A large number of studies have been conducted to examine the effects of ID and IDA on mental outcomes, yet the evidence is not always complete nor conclusive. A need was identified, therefore, to catalog each of the studies so that they could be easily accessed and consulted, allowing researchers to review the available data, draw their own conclusions from the available evidence, and verify any data reviewed or summarized elsewhere.

This bibliography is intended to be used in conjunction with and as a supplement to the *Oxford Brief Child Development and Iron Deficiency* (by Alizon Draper, ILSI Press, May, 1997).

Studies Included in the Bibliography

Included in this bibliography are studies that have looked directly at the relationship between iron status and some mental or developmental outcome in humans. Because this is the main focus of the bibliography, as far as possible all of the papers published in this area have been included and individually described and summarized. All reviews on this topic are listed in the Reading List section.

At the end of the bibliography, a description of selected papers on related topics (Satellite Issues) is included such as studies investigating the relationship between iron status and mental and motor development in animals. Papers were selected if they were considered to have used a strong experimental design, were a good or representative example of the type of research in the area, and gave a comprehensive review of the subject.

Structure of the Bibliography

The bibliography consists of 5 parts:

1. Detailed description of each experimental study
2. Detailed tabulation/summary of each study
3. Brief tabulated summary of studies
4. A list of reviews given in the reading list
5. A summary of studies on related/satellite issues

The following description of the structure of the bibliography refers only to those papers that have directly examined the relationship between iron status in humans and its effect on mental function and development.

The bibliography has been structured to focus on the age of subjects studied, the experimental design, and the date of publication. Specific details on each of these descriptors are given below.

Age The papers are described and catalogued first according to the three main age groups being studied. A discussion and overview of the results for each age group is given at the beginning of each section. The age groups are as follows:

- Infants and young children. Subjects studied were children between ages 6 and 24 months, the outcome measures were mental and motor development and behavior.
- Preschool children. Subjects studied were children ages 2 to 5 years, the outcome measure was cognitive function.
- School-age children and adolescents. Subjects studied were children between ages 5 and 16 years, the outcome measures were cognitive function and educational achievement.

Age is emphasized because it seems to determine the observed level and type of developmental or cognitive response to iron treatment The age of children who may require preventative or supplementary iron treatment also has important public health implications because children in different age groups are accessible through different channels, thus, age also determines the most appropriate delivery system

Experimental Design Within each age group, studies are further classified under subheadings according to experimental design Because of the complex range of intervention trials that have been undertaken (particularly in studies with infants), studies have been grouped according to the following subcategories

- Observational
- Intervention These are further divided into studies assessing short-term or long-term effects Short-term studies looked for an improvement in mental or motor outcomes from 1 week to 8 months after iron supplementation Iron supplementation in these short-term studies was either brief or extended (with or without a placebo group) With brief supplementation, children were supplemented with iron for 5 to 10 days only, with extended supplementation, children were supplemented with iron for more than 2 months Long-term studies looked at the effects of ID and IDA or the benefits of iron supplementation more than 2 years later These studies also include prospective studies (no treatment given)
- Preventative

An understanding of the experimental design is important for interpreting the results from each study and for drawing valid conclusions Thus, a brief description of the advantages and disadvantages of each experimental design is given below

In observational, cross-sectional, or case-control studies, iron and psychometric or developmental measurements are taken from experimental groups at one time point only These types of studies can show that one condition (developmental status) is associated with another (iron status) but they cannot determine the causality of the relationship For example, other factors associated with iron status (such as socioeconomic conditions, maternal education, and other nutritional deficits) could be responsible for the observed developmental level of children

In intervention studies, the groups with ID and IDA are given iron supplements after the initial baseline developmental or psychometric assessment and then the developmental and psychometric assessments are repeated to determine the degree of improvement Intervention studies may be double-blind, randomized, and treatment or placebo-controlled, but those that include all of these features will have the strongest experimental design and the best ability to infer causality between the putative cause (iron status) and the outcome (cognition or development) This is because each feature is designed to ensure equality among the groups in all respects (for example, in socioeconomic status (SES), maternal education, and nutritional status) other than the treatment they were given so that any confounding variables are equally distributed between the control and experimental groups If this is ensured, the experimental groups can be directly compared and the unique effect of iron treatment on children's development determined

In a double-blind trial, both the subjects and the person who assesses the response are unaware of which group the child has been assigned to and what treatment has been given This means that both groups will be dealt with by the experimenters in the same way and also that one group of children will not feel more or less privileged than another

In a randomized trial, children are assigned randomly to the treatment groups (treatment and no treatment or treatment and placebo) Random assignment should ensure that all the characteristics of the two groups are similar so that any differences among individuals, for example, differences in SES, are equally distributed between the two groups

In a placebo-controlled trial, an effective control is provided by the placebo, an inert preparation formulated to appear indistinguishable from the iron supplement It is important to give a placebo to the control group because it accounts for unspecific differences in developmental or cognitive responses that arise simply from the children being given something rather than nothing Without a placebo group it is not possible to determine whether improvement in development or cognition observed after iron supplementation is due to improvement in iron status or to something related to iron but not iron itself, such as low birth weight, lack of breast-feeding, or environmental disadvantage

The inclusion of a nonanemic, iron-sufficient control group (which may or may not be matched with the ID or IDA group), although not essential to a treatment- or placebo-controlled trial, is important for two reasons First, the inclusion of an iron-sufficient group can help determine whether there is any initial deficit in developmental or cognitive outcome between the children with ID or IDA and the iron-sufficient children If no deficit exists at baseline, an improvement following treatment would not be expected Second, an iron-sufficient group can help determine whether the adverse effects of ID or IDA on performance are fully or only partially reversible following treatment, that is, whether the improvement in performance of children with ID or IDA who received iron treatment is large enough for them to catch up to the iron-sufficient control group by the end of the study

In conditions in which benefits from treatment have not been commonly observed, it is difficult to determine whether this is because there are no direct effects of IDA on performance or whether there are effects of IDA that are not correctable with treatment If the latter is considered the case, this could be studied in a preventative trial in which children who are supplemented (by receiving iron-fortified milk formula, for example) and protected from becoming iron deficient with anemia are compared with children who are not supplemented Although preventative trials have not been commonly undertaken in this area of research, they are considered to have a strong experimental design

Date Studies are presented within each of the subsections (e g , under observational studies, intervention trials, or preventative trials) according to the year in which they were published The date of publication is considered important for putting the studies into a historical perspective and for observing how the research methods and questions progressed over time

Other Features of the Studies Highlighted in the Bibliography

Certain key features of each paper presented have been emphasized in the text and in the tabulated summary (Appendix A) because they are considered important for interpreting results and for comparing results across studies These characteristics include the location of the study, the iron status of children at baseline, the length of treatment, and the developmental, cognitive, or educational outcome measures used

Location of Study It is conceivable that baseline differences and responses to iron therapy could vary according to the environment in which the child has grown up For example, some environments may put children at increased risk of anemia or ID whereas others may provide children with psychological buffers that prevent such hematologic impairment impeding development

Iron Status of Children Whether children recruited to the study have ID or IDA is clearly specified because evidence suggests that the effects of these conditions on development or psychometric function may differ Usually, only IDA is associated with lower developmental or cognitive scores, but this is not exclusively so and it is not easy to differentiate whether the effect on development or cognition is due to the severity of the deficiency in iron, the age of onset of deficiency, or the duration of the deficiency

A distinction has also been made between severe, moderate, and mild IDA Where possible, the authors' definitions have been used, otherwise, the mean hematologic values within each group as specified in the paper are used This is because, while there are international criteria for defining IDA, (Hb 110g/L for children between 6 months and 6 years of age (WHO, 1972), the studies have not applied these criteria consistently For example, according to Lozoff et al (1987), a hemoglobin concentration less than 10 0 g/dL (or 100 g/L, to convert conventional values in g/dL to SI values in g/L, multiply by 10) signifies moderate anemia and greater than or equal to 10 0 g/dL and less than 11 0 g/dL signifies mild anemia On the other hand, according to Deinard et al (1981), values of hemoglobin greater than 11 0 g/dL and a serum ferritin less than or equal to 9 ng/mL (or 9 g/L, to convert conventional values in ng/mL to SI values in g/L, multiply by 1) signify severe ID, and values for hemoglobin greater than 11 0 g/dL and serum ferritin between 10 and 19 ng/mL signify mild ID When a study includes subjects from more than one category of severity, it is classified according to the most severely iron-deficient group

Length of Treatment The length of treatment has been specified because it is important for determining the degree of improvement in iron status and the replenishment of iron stores It is supposed that very-short-term therapy of less than or equal to 10 days (termed "brief supplementation") will not result in any significant rise in hemoglobin levels but will reduce the level of ID Longer-term iron supplementation of 2 to 8 months (termed "extended supplementation") will result in a rise in hemoglobin and should therefore correct anemia if present

Developmental, Cognitive, or Educational Outcome Measures Used The tests used need to be sensitive to changes in iron status, culturally acceptable, reliable, and valid for the study population Meeting all these criteria may be extremely difficult, which may account for the failure of some studies to show improvement in the outcomes measured after iron supplementation

The outcomes used to measure the effects of ID and IDA must vary according to the age of the children being studied Most studies with infants looked at differences on the Bayley Scale of Infant Development (BSID), which provides indicators of mental development, motor development, and, indirectly, behavior By being a global measure of development, BSID is often criticized as being insensitive in the context of ID because of its inability to isolate effects on specific functions and its low test-retest reliability in children younger than age 18 months However, in the absence of good alternative tests of development, BSID is the most commonly used outcome measure in infants Thus, its wide usage facilitates comparison of results across studies Indeed, when drawing comparisons across studies, the term "patterning" has been used to describe situations in which a group consistently fails certain items or subtasks of a developmental measure Studies with preschool children have tended to focus on trying to isolate the specific cognitive functions which are affected by ID and IDA In practice, however, the range of functions which can be measured in any one study is limited and the cultural validity of the tests themselves may be questionable

Studies with school-age children have tended to measure educational and/or cognitive function While educational achievement is an important outcome because effects on school performance have potential to influence policy, it is a global measure and children's performance will be heavily influenced by environmental and socio-emotional conditions at home and at school For example, improvements in educational achievement following iron treatment may be difficult to measure if children are not attending school regularly or if the classroom is not condusive to learning

How to Use the Bibliography to Find Specific References: The Numbering System

A numbering system has been used so that the papers described in detail in the main body of the text can be easily located Each reference has been assigned a number, which is given each time the reference is listed Examples of how to use the numbering system to find a reference are as follows If the name of the first author is known, look in the section Alphabetical List of Included Studies (on pages i and ii) and find the reference number of the paper (given at the end of the citation) A written summary of the paper can be found within the text, in which papers are discussed in numerical order

Alternatively, to find, for example, all the observational studies conducted with infants several options are available

(a) for a detailed description, look in the Infants and Young Children (6–24 months) section of the text under the subheadings Short-term Effects Observational Studies (page 8), and Long-term Effects Observational Studies (page 19),

(b) for a list, Table 1 in the Infants column and the Observational studies row (page 6), or in Appendix A in both the Age and Study design columns (page 39)

(c) for a detailed tabulation, studies are listed in Appendix B according to the age of the subjects and, for infants and young children, according to whether the studies looked at short-term or long-term effects (page 59)

Glossary of Terms and Key to Abbreviations

Each citation in the text is annotated at the beginning according to its importance, experimental design, baseline results, post-intervention and follow-up results, and conclusions The other subsection includes details of any noteworthy features of the paper (e g , if the paper usefully discusses biological mechanisms or the role of potentially confounding variables)

A complementary key word section is included with each annotation Studies reporting a baseline positive association between hematologic impairment and low developmental test scores are indicated by an asterisk (*) Studies reporting an association between iron treatment and developmental improvement are indicated by a dagger (†) A value of $p <$ 0 05 is considered a statistically significant result

Several terms and abbreviations are used throughout These are defined as follows

Hematology	**Developmental Measures**	**Study design**
Hb = hemoglobin	BSID = Bayley Scale of Infant Development	Difference—used when reporting results, refers to a statistically significant difference (at least $p <$ 0 05)
ID = iron deficiency without anemia	IBR = Infant Behavior Record (subscale of BSID)	Intervention—the IDA and ID groups are given iron supplementation, usually after baseline assessment
IDA = iron deficiency with anemia	MDI = Mental Development Index (subscale of BSID)	Nonanemic control—a nonanemic group is included, usually matched to the IDA or ID group by age as a minimum, and given the same developmental assessments, in these studies the nonanemic group is often given the same iron or placebo interventions as the IDA and ID children
	PDI = Psychomotor Development Index (subscale of BSID)	Observational—only baseline hematologic and developmental measurements are taken from groups to be compared
	WISC = Wechsler Intelligence Scale for Children	Placebo control—a subgroup of the IDA and ID children are given a placebo according to the same procedure as the administration of the iron supplement
		Preventative—anemia in subjects from an at-risk population is prevented early in life with prophylactic supplementation, and development of this group is compared with the development of subjects from the same group not given supplements
		Randomized—subjects are randomly assigned to treatment and placebo groups
		* Studies that report a baseline positive association between hematologic impairment and low developmental test scores
		† Studies that report an association between iron treatment and developmental improvement

Appendix C gives a summary of the all the psychometric, development and educational tests which have been used in studies of ID and IDA

Table 1 Summary of experimental designs by studies examining the effects of iron deficiency with (IDA) or without (ID) anemia on development or cognition

	Infants	Preschool	School age
Observational studies performance of IDA/ID compared with IS, cross-sectional design	Deinard et al, 1981 (1) Johnson and McGowan, 1983 (2) Grindulis et al, 1986 (3) Lozoff et al, 1986 (4)		Webb and Oski, 1973 (31,32)
Short-term effects of treatment for ID/IDA on performance			
Treatment, no placebo in IDA group brief supplementation (5–10 days)	Walter et al, 1983 (9) Oski et al, 1983 (10)		
Extended supplementation (2–8 month)	Lozoff et al, 1987 (13) Lozoff et al, (1996a) (16)	Pollitt et al, 1978 (27) Pollitt et al, 1983 (28) Deinard et al, 1986 (29) Pollitt et al, 1986 (30)	Seshadri and Gopaldas, 1989 (Study 1) (34, 39)
Treatment and placebo, brief supplementation (5–10 days)	Oski and Honig, 1978 (5) Lozoff et al, 1982 (6-8) Lozoff et al, 1985 (11) Lozoff et al, 1987 (13) Walter et al, 1989 (14)		
Extended supplementation (2–8 month)	Aukett et al, 1986 (12) Idjradinata and Pollitt, 1993 (15)	Soewondo et al, 1989 (31)	Soemantri et al, 1985 (34) Pollitt et al, 1985 (35) Groner et al, 1986 (37) Soemantri, 1989 (40) Seshadri and Gopaldas, 1989 (Studies 2,3,4) (34,39) Pollitt et al, 1989 (41) Bruner et al, 1996 (42) Kayshap and Gopaldas, 1987 (38)
Long-term effects of ID/IDA on performance			
>2 years follow-up after treatment	Palti et al, 1983 (23) Palti et al, 1985 (20) Walter et al, 1990 (24) Lozoff et al, 1991 (25) Hurtado, 1995 (22)		
Prospective studies (no treatment or supplementation)	Wasserman et al, 1992 (21)		
Effects on performance of preventing IDA and ID Preventative trials (iron supplementation)	Cantwell, 1974 (26) Heywood et al, 1989 (17) Moffatt et al, 1994 (18) Lozoff et al, personal communication, 1996 (19)		

IS, iron sufficient Reference number of each study given in parentheses

INFANTS AND YOUNG CHILDREN (6-24 MONTHS)

Summary of Findings

There is good evidence that IDA is associated with poorer performance on developmental ratings of infants, but the data are inconclusive as to the causal nature of these effects This is because most evidence comes from observations of baseline differences between infants with IDA and nonanemic infants Despite efforts to carefully control for confounding factors during recruitment and in subsequent statistical analyses, these studies cannot remove the possibility that another factor related to ID is responsible for the differences observed

What is certain from the evidence is that lower developmental test scores are most likely seen in infants and young children with anemia rather than ID alone, furthermore, although precise cutoffs cannot be specified, the general observation is that the more severe the anemia, the more pronounced the effect on test scores Where low developmental test scores have been found in children who are iron deficient without anemia, a small amount of evidence suggests that it is severe deficiency that results in poorer performance

Infants and young children with IDA often show difficulty with language, poor motor coordination and balance, and perhaps most evident, poorer ratings on attention, responsiveness, and mood assessments In some studies, assessments of poorer attention and responsiveness and lower motor test scores were found in the absence of lower mental development test scores It has been postulated, therefore, that poorer attention, poorer performance on motor tasks, or both may mediate lower scores on tests of mental development

Most intervention studies in which oral or intramuscular iron treatment was administered for less than 2 weeks used a double-blind, randomized treatment, placebo-control design The causal nature of the association between a change in iron status (without correcting the anemia) and poorer performance on developmental tests was determined However, in none of these studies was a significant improvement in mental or motor development found that could be attributed to iron Only in the study by Oski and Honig (1978) [Ref 5], was a benefit of treatment on behaviour observed

Studies with infants that looked at the effects on development of extended iron supplementation have also mostly found no significant improvement The best evidence in support of a causal link between IDA and development comes from Idjradinata and Pollitt (1993) [Ref 15], who found a reversal of poor mental and motor developmental test scores after 4 months of therapy There may be many reasons why most studies have not found an improvement in development after treatment of iron-deficient or anemic infants the anemia may not have been particularly severe or chronic, the treatment period was not long enough to correct the anemia, the developmental tests were not sensitive enough, parental stimulation or an improved socioeconomic environment may be required in addition to any treatment for children's development to progress, the association was not causal, because some other factor associated with iron but not iron itself may have led to the developmental deficits observed at baseline, or because the effects of IDA on development are not reversible with treatment

Although these reasons are all plausible, it has generally been supposed that the failure to find a significant beneficial treatment effect is because the effects of anemia on development in infants and young children are not reversible One way to test this hypothesis is to conduct a preventative trial that is double-blind and placebo- controlled If low developmental test scores are the result of some other factor in the infant's environment and not a result of IDA, then preventing anemia from an early age should not prevent infants from scoring lower than their nonanemic counterparts on tests of development Three preventative trials have been conducted and different results were obtained (Heywood et al 1989 [Ref 17], Moffatt et al 1994 [Ref 18], Lozoff et al 1996 [Ref 19]) It is therefore difficult to draw any conclusion, however, the evidence seems to suggest that IDA in infants does affect mental and motor development directly but only under certain underprivileged conditions - such as in poor homes or communities, where the prevalence of anemia is high, among low birth weights babies or where breastfeeding is uncommon (Moffatt et al 1994 [Ref 18]) If this is the case, then under these conditions prevention rather than treatment of IDA in infants may offer the greatest benefit Further evidence from preventative studies with infants with IDA is needed to clarify this issue

Investigations of the long-term effects of anemia in infancy have generally shown there to be a significant adverse effect on development or cognition and educational achievement in later life This relationship appears to exist even in those children who, after receiving iron treatment in infancy, scored similarly on tests of development to nonanemic control children The long-term effects on development are seen on tests of motor and mental development and behaviour Although infant assessment scales such as BSID may not predict later intelligence quotients (IQs), evidence suggests that the same children performing less well on these scales during a period of infant anemia show poorer IQs at age 5 years and older In one study, care was taken to assess the extent to which the long-term poorer test performance was attributable to confounding variables, such as maternal education, rather than hematologic status earlier in development (Palti et al 1983) [Ref 23] The authors found that at age 5 years, the contribution of anemia in earlier childhood to lower developmental scores was significant even after confounding variables such as maternal education and socioeconomic status were controlled for

There are two excellent reviews of the effects of ID and IDA on infants and children The first by Lansdown and Wharton (1995) includes all age groups and is notable for its clear tabulation of studies cited, its comprehensive reference list, and its systematic discussion of methodology and issues of theoretical importance The second review by Lozoff (1990) deals exclusively with studies concerning infants and young children, and starts by clarifying whether any association can be concluded from the available evidence before moving on to discuss whether such an association has been shown to be causal Both reviews discuss the problem of confounding and cofactors and highlight areas of the field yet to be studied

Short-term Effects: Observational Studies

1 Deinard et al (1981) Key Words USA, age 15 months, ID of various severities, cross-sectional comparison only, BSID, an habituation measure, and the Uzgiris and Hunt Ordinal Scales of Psychological Development, design observational

Importance This study sought to investigate the effects of ID on development It is of particular interest given its assessment of independent effects as a function of the specific ID level A specific habituation measure is used, as well as the more global BSID

Design An observational design was used to compare the various ID groups with one another and an nonanemic control group

Baseline There was no difference in the overall scores on any of the measures in any of the iron-deficient groups and the nonanemic group However, isolated and patterned differences were found in the severely iron-deficient group on items in the Infant Behaviour Record (IBR, a subscale of BSID) These children were rated as more fearful, less auditorily and visually attentive, and more vocal This patterning is similar to that reported in other studies (see Oski and Honig 1978 [Ref 5], Lozoff et al 1982a [Ref 8], Walter et al 1983 [Ref 9], Lozoff et al 1985 [Ref 11], Walter et al 1989 [Ref 14])

Conclusions A number of difficulties with this paper have been raised, notably the fact that the hematologic measures used were unreliable, thus making it possible that some of the children described as iron-deficient may actually have been anemic The observational design of the study means that a causal relation between iron deficiency and assessments of poorer behavior cannot be inferred, although it should be noted that the paper showed a baseline association of ID with lower developmental test scores that was restricted to the most severely iron-deficient children However, the use of the unreliable hematocrit measure to determine absence of anemia means that the behavioral effects may still result specifically from anemia rather than more generally from iron deficiency

Other There is a good discussion of the possible methodological and theoretical reasons for their overall nonsignificant finding and a comment on the involvement of environmental risk.

---

2 Johnson and McGowan (1983) Study 1 Key Words USA, 12 months, IDA, mother-child interaction tests of activity, reactivity, emotional tone, and attention span, design observational

---

Importance This study was conducted for two reasons, first, the authors wanted to continue to test the association between anemia and the behavior of infants, given that "based on previous research, it was hypothesized that anemic babies would show disturbed activity levels, be more irritable, less attentive and less responsive to their mothers" Second, the authors wanted to compare in Study 1 these behaviours under "low-demand" conditions with relatively high-demand conditions in study 2 (below) The authors made a particular effort to determine the role of potentially intervening variables Under low demand conditions, children's behavior was observed during normal play activity with their mothers

Design This was an observational comparison of IDA children with nonanemic control children

Baseline Under these low-demand test conditions, there were no significant differences between the groups on any of the behavioral measures, even when the authors compared only the most severely anemic infants with the most clearly nonanemic Interestingly, this lack of difference between the groups may be explained by the fact that these infants were also not different in maternal education, family income, birth order, language preference, or scores on the Home Observation for Measurement of the Environment (HOME) inventory

Conclusions The hypothesis of baseline association between anemia and behavioral disturbance is not supported, perhaps because, as with the Deinard et al (1986) [Ref 29] differences in development between ID/IDA and nonanemic children are a result of intergroup differences on intervening variables with which anemia frequently co-occurs Alternatively, the so-called low-demand situation may have been such that "latent" differences between the groups were not manifested

---

2 Johnson and McGowan (1983) Study 2 Key Words USA, 12 months, IDA, BSID (including IBR), design observational, double blind

---

Importance In contrast to Study 1, children's development and behavior were measured in a relatively high demand situation in which the BSID was given to children formally to replicate the test conditions under which they are usually assessed

Design An observational study comparing IDA infants with nonanemic control infants Assessment was conducted blind to the infants' iron status

Baseline Under the high demand conditions, no differences between groups were found on MDI, PDI, or IBR Also, no differences were found between groups for maternal education, family income, birth order, language preference, or scores on the HOME inventory

Conclusions The demand of the environment cannot be invoked as an explanation for the lack of intergroup differences observed in the first of these two studies, in this second observational study, the hypothesis of association of anemia with behavioral disturbance still receives no support

Other There is good comparison of this with similar studies

---

3 Grindulis et al (1986) Key Words UK, age 22 months, IDA, Sheridan developmental sequences for psychomotor development, design observational, double blind*

Importance This study, primarily aimed to investigate the relation between IDA and vitamin D deficiency, also assessed the children's psychomotor development

Design The authors used a double-blind, observational design

Baseline Although no association was noted between lower psychomotor test scores and vitamin D deficiency, children who were anemic showed significantly poorer performance on fine motor and social development items

Conclusions No conclusions can be drawn regarding the nature of the association between IDA and psychomotor development, given the observational design There were baseline differences between the IDA children and the other groups for SES and maternal education, however, no statistical analysis was conducted to assess the contribution of these intervening variables to the between-group differences found The Sheridan Test has not been used elsewhere

---

4 Lozoff et al (1986) Key Words Guatemala, age 6–24 months, IDA, behavior rating on BSID, design observational, double blind*

Importance This report on the Guatemala study described below (Lozoff et al 1982a,b,c) [Refs 6, 7, 8], assessed the behavior of infants and their mothers as a function of the infant's iron status It aimed to determine the extent to which behavioral differences are manifested in free play (behavior rating of BSID) rather than in more stressful structured developmental testing environments The study can be compared with that of Johnson and McGowan (1983) [Ref 2], which found no differences in mother-child interaction during play between IDA and nonanemic matched control groups

Design A double-blind, observational comparison of infants with mild to moderate IDA and nonanemic control infants and their mothers No behavioral analysis was conducted after iron treatment Subjects were recruited from a socially homogenous, impoverished area of Guatemala

Baseline The infants were not more irritable, distractible or apathetic than the nonanemic control infants They were, however, more likely to seek body contact with their mother The mothers did not differ in the extent to which they initiated contact with and responded to contact from their children The mothers of IDA infants spent less time beyond arm's length of their children and were less likely to break close contact When infants moved away from their mothers, the mothers of the IDA infants were more likely to reinitiate the contact

To determine whether these differences were attributable to intergroup differences other than iron status, several other confounding variables were measured The infants did not differ in terms of parental age, education, or occupation or in terms of anthropometry The IDA infants came from larger families and had lower scores on the MDI but not the PDI (differences on the PDI in the larger sample (Lozoff et al 1982 a,b,c) were found) The lack of difference between IDA and nonanemic control infants on the PDI is attributed to the smaller size of the sample (fewer videotapes of infants were suitable for analysis) Play behavior remained significantly different between groups after controlling for differences in their baseline characteristics

Conclusions The authors concluded that infants respond to iron deficiency, as to many other insults, with an increase in proximity seeking and that this is both a manifestation of affective and activity disturbance and an effective compensatory and protective mechanism In the long term, increased attachment may interfere with infant development because of reduced exploratory behavior, which may mediate the acquisition of fundamental cognitive skills such as depth perception Although the study recruited infants from a socioeconomically, homogenous population and statistically controlled for other variables, the assessment of SES and other variables may have been too crude to detect critical between-group differences This possibility cannot be rejected without comparing play behavior after a placebo-controlled iron treatment

Other There is good discussion of attachment theory (the perspective on which the hypotheses of the study were formulated)

Short-term Effects: Intervention Trials

---

*5 Oski and Honig (1978) * H Key Words USA, IDA, age 9–26 months, 1 week of intramuscular (IM) therapy, BSID brief intervention, randomized, double blind with placebo control*

Importance This was a pioneering study that motivated many other researchers to investigate the associations between iron and cognition

Design The study was a double-blind, randomized, placebo-controlled intervention study looking at the effects of anemia on cognitive development in infants and young children A nonanemic control group was not included IDA infants and children were randomly assigned to receive either intramuscular treatment or placebo, which they received for 5–8 days

Baseline At baseline, there were no significant differences on either the MDI or the PDI between the treatment groups All anemic children demonstrated lower scores in fine and gross motor coordination and on IBR The IBR patterning reported agrees with that seen in a number of other studies, with poorer ratings in attention and reactivity (see summary of Deinard et al 1981 [Ref 1], for list of studies showing similar behavioral patterning)

Follow-up A significant beneficial effect of iron treatment on MDI scores, motor skills, and responsiveness (an IBR item) was reported after only 1 week but the benefit in the treatment group was only significantly greater than in the placebo group in the IBR rating It is noteworthy that a positive correlation was found between initial absolute hemoglobin (Hb) status and extent of MDI improvement, consistent with other studies reporting differential baseline poorer performance and differential developmental improvement as a function of severity of hematologic impairment (see Lozoff et al 1987 [Ref 13])

Because other studies have failed to find a treatment effect at 1 week, it has been suggested elsewhere that the treatment effect here is due to the treatment having been intramuscular rather than oral This suggestion is contradicted by Lozoff et al's 1987 study [Ref 13], described below

Conclusions Because no nonanemic control group was included, the study cannot confirm that lower developmental test scores at baseline are to be found in anemic children Furthermore, despite the significant MDI score improvement for iron-treated children, the unique effect of iron therapy on cognition cannot be concluded Oski and Honig state that although there was a significant improvement in the MDI scores of the iron-treated IDA children, this improvement was not statistically greater than the improvement in the placebo-treated group The improvement in scores in the treatment group can be attributed to the effect of repeating the same test within a short time The study confirms the baseline association of IDA with lower PDI scores and poorer IBR assessments but provides no evidence that the IDA infants' performance was poorer than that of nonanemic infants The study offers no confirmation of the contention that iron supplementation is beneficial to performance on the measures used

Other There is very good discussion of biochemical theories of the effects of iron deficiency on cognition and also of possible mechanisms associated with IBR and PDI measures that may mediate poor cognitive performance

---

6 Lozoff et al (1982c) Key Words Guatemala, age 6–24 months, IDA, 1 week of therapy, BSID, design brief intervention, randomized, double blind with placebo and nonanemic controls*

Importance The authors aims were to assess the effects of IDA on development, using a controlled and randomized placebo controlled design to enable firmer conclusions to be drawn than were previously possible

Design A double-blind, randomized, placebo-controlled intervention was used in IDA and nonanemic control children Although the authors describe the IDA subjects as mildly anemic, at least some of them had Hb levels below 10 0 g/dL, in the Lozoff et al 1987 paper [Ref 13], children with Hb below 10 0 g/dL were classified as moderately anemic

Baseline At baseline, the IDA children scored significantly lower than the nonanemic control children on MDI and nonsignificantly lower on PDI

Follow-up After treatment, Hb levels in the treated IDA children improved significantly, but the developmental scores of these children showed no effect of treatment All groups showed an improvement in MDI score, and the IDA group's scores remained significantly lower than those of the nonanemic control group

Possible explanations for this failure of developmental measures to improve are discussed extensively It is also suggested that, given the range of Hb levels within the anemic group, the anemia of the less severely anemic children had more reversible effects and that their response to therapy was concealed in these data The reality of this suggestion cannot be assessed

Conclusions Thus again the baseline association of IDA with lower cognitive test scores is confirmed, but there is no evidence of a causal association, given the failure of therapy to improve performance If the association is causal, then either longer treatment is needed or the effects are irreversible In support of a causal hypothesis, the authors did go to some trouble to assess the involvement of potentially confounding variables and found that the experimental groups were not different in birth history, SES, or general nutritional status Maternal education was not assessed

Other There is reference to animal studies and how these may help to explain a failure to improve development after therapy

---

7 Lozoff et al (1982b) Key Words Guatemala, age 6–24 months, IDA, 1 week of therapy, BSID, design brief intervention, randomized, double blind with placebo and nonanemic controls*

Importance This second report of the Lozoff et al 1982c [Ref 6] study described above is important in that it details analysis performed to determine whether lower developmental test scores and therapy responses are the same across age subgroups within their original sample, which spanned a large age range

Baseline At baseline, lower PDI scores were present and the same across all age subgroups, however, the poorer performance on MDI only emerged in the 19–24 months group (the oldest subgroup) Furthermore, and very importantly, the authors observed that within this subgroup the more severe the anemia, the poorer the performance on the developmental tests

Further analysis revealed patterning on the developmental scales the anemic infants had disproportionate difficulty with language items, a trend observed by Walter et al 1989 [Ref 14], and the 19–24 month-old children consistently failed 11 of the 12 items taken to predict later IQ

Follow-up No treatment effect, specific to an age subgroup, was found within PDI All infants with lower scores failed to improve after one week of treatment The iron-treated infants with lower scores at baseline on MDI also did not improve after treatment

Conclusions There are two interesting implications of this study First, the results agree with the observation by Lozoff et al 1987 [Ref 13] in that PDI scores will suffer with less severe anemia An interesting implication is that poorer motor performance may mediate poorer cognitive performance, having occurred earlier during the less severe stages of anemia Second, either the absolute timing of the hematologic deficit or the duration and severity of the anemia seem to be crucial factors in determining whether children will show lower cognitive test scores The older IDA children showed signs of being undernourished, suggesting that their anemia may have lasted longer Comparing this study with the Lozoff et al 1987 [Ref 13] study, where all the subjects were of an age similar to the differentially lower-scoring subgroup described here and only the moderately anemic children showed poorer performance on MDI, the suggestion seems to be that it is the nature of the anemia rather than the absolute age of the child that is important

---

8 Lozoff at al (1982a) Key Words Guatemala, age 6–24 months, IDA, 1 week of therapy, BSID, design brief intervention, randomized, double blind with placebo and nonanemic controls*

Importance This is the third report of the Lozoff et al 1982c study [Ref 6] The report deserves particular attention because the IBR ratings of the subjects are discussed

Baseline The IDA subjects were more fearful, showed increased body tension and decreased gross body movement, were less responsive to the examiner, were less reactive to ordinary stimuli, and tended to be less persistent These patterns were primarily in the 19–24 month age group, and they are very similar to the behavioral effects reported elsewhere (see the review by Deinard et al 1981 [Ref 1])

Follow-up These behavioral differences disappeared after treatment except for the elevated fearfulness The change could not be attributed to treatment, however, because iron- and placebo-treated infants showed the same reversal

Conclusions The study demonstrated an adverse effect of IDA on infant behaviour, but in contrast to the study by Oski and Honig (1978) [Ref 5] where parenteral iron was given, the effect was not reversible after short-term oral iron treatment At this time, they suggest the different results might be because the response times to oral and parenteral iron therapy differ The possibility that the observed differences in behaviour at baseline were due not to iron deficiency but to some other intervening variable is rejected because there were no characteristics which differed between the groups which could explain the results

Other The authors offer a short, clear discussion of the possibly mediating relation between behavioral effects and poorer performance on test of development

---

*9 Walter et al (1983) * † Key Words Chile, age 15 months, IDA and ID, 10 days of therapy, BSID, design brief intervention, double blind, with nonanemic control*

Importance This study is important in its direct comparison of the effects of IDA with those of ID

Design A double-blind iron-treatment-only intervention was used in IDA, ID, and nonanemic control children

Baseline The IDA children scored significantly lower on MDI and were rated as more unhappy than the nonanemic control group, the IDA children did not score lower on PDI Although the authors classify the anemia in the IDA children as mild, this classification is possibly incorrect because at least some of the children had Hb levels below 10 0 g/dL There were no significant differences in MDI or PDI at baseline between children with ID and non anemic controls

Follow-up After 10 days of iron treatment, IDA infants improved significantly on MDI, and this improvement coincided with an improvement in cooperativeness and attention span No similar improvement was found in the nonanemic group, and improvement was only seen in IDA children with two or more abnormal biochemical measures of hematology at baseline None of the groups showed improvement on PDI

Conclusions This study confirms the baseline association of impaired hematology and lower developmental scores and suggests that IDA, but not ID, will result in detectably lower developmental scores This contradicts the findings of Deinard et al (1981) [Ref 1] It may be suggested that ID was shown to be associated with poorer performance on tests of development, because infants with two or more abnormal biochemical measures improved in developmental measures even though they did not show relatively lower scores at baseline

If these data are valid, the implications of the score changes, after only 1 week of treatment, are that the lower scores are attributable to iron deficiency rather than specifically to anemia and that the locus of the effect is probably at least attentional or behavioral This latter suggestion receives support from the coincident behavioral effects and the behavioral response to therapy (see the review by Deinard et al (1981) [Ref 1]) for a list of papers reporting similar IBR patterning)

No placebo group was included in the study design The short-term improvement observed may be attributed to a practice effect rather than a therapeutic effect The lack of improvement in the control group may be due to a ceiling effect Because no follow-up assessment of hematology was performed, it is impossible to conclude that iron intervention and subsequent hematologic correction was responsible for the developmental improvements

Therefore, although a baseline association between IDA and lower developmental test scores (and possibly between ID and developmental test scores) is confirmed, the unique effect of iron treatment is not shown

---

10 Oski et al (1983) † Key Words USA, age 9–12 months, ID, 7 days of therapy, BSID, design brief intervention, double blind, with nonanemic control

---

Importance Because of Oski and Honig's 1978 study [Ref 5], which demonstrated a causal relation between IDA and lower cognitive test scores, the authors conducted this study to assess the extent to which ID is also associated with these lower scores The results should be compared with those of Deinard et al (1981) [Ref 29] and those of Walter et al (1983) [Ref 9], who directly compared the effects of IDA and ID

Design The study was a double-blind intervention, with iron-depleted and nonanemic ID subjects, matched for color and sex, and who received IM treatment for only 7 days There was no placebo control

Baseline At baseline, there were no significant differences between the groups, suggesting that neither iron depletion nor ID is sufficient to cause infants to score lower on developmental tests than nonanemic control subjects This contradicts Walter et al 's (1983) [Ref 9] findings of a baseline association but agrees with Walter et al 's negative finding for ID children

Follow-up After 7 days of treatment, however, MDI scores for ID children improved significantly and suggested, that this group had been performing suboptimally at baseline Because no placebo group was included, it is possible that this improvement was due to a practice effect

The authors note that their findings regarding the short-term effects of iron treatment disagree with similar studies by Lozoff et al (1982b,c) [Refs 7,6] in Guatemala They suggest that their positive treatment effect after only 1 week may have been attributable to the use of parenteral iron administration As discussed above, this possibility was subsequently rejected by Lozoff et al (1987) [Ref 13] In the Lozoff et al (1982) [Refs 6-8] studies, the children were ID rather than IDA

Conclusions The implication of this study is that treatment of ID may lead to improved performance on MDI

Other There is a good discussion of biochemical mechanisms

---

*11 Lozoff et al (1985) * Key Words Guatemala, 6–24 months, IDA, IBR of BSID (focusing on Test Affect and Task Orientation factors), design brief intervention, double blind, randomized, with placebo and nonanemic controls*

Importance This is a fifth report on the study conducted in Guatemala by Lozoff and collaborators This report explores the association between poor developmental test scores and abnormal behaviors documented in children with IDA Specifically, the authors investigated whether poor developmental test performance in infants with IDA may be mediated by disturbances in affective behavior

Design This study was a double-blind, intervention trial comparing IDA infants with nonanemic control infants recruited from a socioeconomically homogenous, impoverished area of Guatemala The infants in this study were randomly assigned to receive treatment or placebo, although the analysis documented in this report focused mainly on baseline data Infants were assessed on the mental and motor scales of the BSID as well as the IBR, and the extent to which individuals manifesting abnormal behaviors, with lower MDI or PDI scores, was determined

Baseline A greater proportion of anemic than nonanemic infants showed abnormal affective responses to testing, they were more fearful, tense, restless, withdrawn from the examiner, and unhappy The infants demonstrating abnormal affective behaviors were also the infants with profoundly lowered MDI scores, anemic infants who did not rate abnormally on the IBR did not show significantly lower MDI scores

Despite the age effect described by Lozoff et al (1982b) [Ref 7] for these infants, affectively abnormal infants in all age groups tended to receive low MDI scores Lozoff et al describe a severity effect such that the greater the number of abnormal affective behaviors demonstrated by the infant, the lower the MDI score

Lower PDI scores were found in IDA infants demonstrating abnormal affect, but this was completely accounted for by the infants who also demonstrated abnormal task orientation Interestingly, although Hb level was directly related to the extent of behavioral disturbance, it was not similarly directly related to MDI score

Follow-up Because of the small number of infants with abnormal behavior who also received iron treatment, a conclusion cannot be drawn from this study regarding the effects of short-term oral iron therapy on behavior The indication is that there is no treatment effect after 1 week and that repetition of testing leads to improved behavior in the affectively disturbed IDA infants and a greater improvement than found in the affectively disturbed nonanemic control subjects Also interesting is that the infants who improved their IBR ratings also improved their MDI scores No such improvement was found in PDI scores

Conclusion This study provides strong evidence that IDA is associated with IBR abnormalities and lower developmental test scores Furthermore, the close covariation els, and the differential MDI improvements after 1 week of treatment indicate that behavioral disturbances may mediate poor developmental performance Although statistical investigation revealed no involvement of potentially intervening variables, without finding a treatment effect it cannot be concluded that abnormal behavior is caused by anemia

Other There is good discussion of the similarities between the findings of this study and of others (principally those studies listed in the review of Deinard et al (1981) [Ref 1])

---

12 Aukett et al (1986) † Key Words UK, age 17–19 months, IDA, 2 months of therapy, Denver developmental screening test for psychomotor development, design extended intervention, randomized, double blind, with placebo control*

Importance The study assessed whether the well-replicated baseline association of IDA with lower developmental test scores was causal

Design A double-blind intervention design with placebo control was used IDA children were treated for 2 months

Baseline No nonanemic control group was included and baseline scores on the Denver Developmental Test are not reported so this study cannot confirm the hypothesis that IDA infants show poorer test performance than do their nonanemic counterparts

Follow-up After 2 months of treatment, 58% of the children with hematologic improvement of greater than 2 g/dL did not increase their developmental score by the expected amount However, more of the children who showed hematologic improvement increased their scores by the expected amount than did children who did not show such hematologic improvement

Conclusions Although the study provides some evidence that the association between IDA and cognitive development is causal, the evidence is not conclusive because neither the developmental test nor the use of a 2 g/dL response as a criterion for effective treatment has been used in any other study

Other This study also considers weight velocity as an outcome measure, and there is a very useful table included that compares this study with previous studies

---

13 Lozoff et al (1987) † Key Words Costa Rica, age 12–23 months, IDA, ID, and iron depletion, 1 week and 3 months of therapy, BSID, design brief and extended period intervention, randomized, double blind, partially placebo controlled, with nonanemic control*

Importance This is an important study because it investigates how much the severity of anemia alters the developmental outcome In particular, the results should be compared with those of Walter et al (1989) [Ref 14], who also investigated the existence of a differential developmental effect as a function of the specific level of anemia Other studies described above have also compared anemia with ID and with various severities of anemia (e g , see Deinard et al (1981) [Ref 1] and Walter et al (1983) [Ref 9]) This paper is also important for two other reasons First, it compares IM with oral iron therapy Oski et al (1983) [Ref 10] found a treatment effect after 1 week with IM therapy, in comparison with studies such as that by Lozoff et al (1982c) [Ref 6] where no oral iron effect was found after the same amount of time Oski et al (1983) [Ref 10] suggested that this difference may have been due to differing methods of iron administration Second, the authors undertook to assess the role of coexisting variables, such as low SES, in the etiology of the lower developmental test scores associated with IDA

Design The study was a double-blind intervention, with IDA, ID, iron depletion, and nonanemic control children randomly assigned to receive treatment or placebo for the first week, with some children assigned to IM treatment and others to oral treatment After the first week, all previously IM-treated children and all nonanemic control children were given a placebo for 12 weeks All previously iron-deficient children given oral iron were continued on oral iron, with no placebo-control, for the same time

Baseline At baseline, only the IDA children demonstrated poorer developmental test performance Within this group, lower PDI scores were found in the entire group (Hb 10 5 g/dL), regardless of the severity of the anemia However, lower MDI scores were only to be found in the moderately anemic children (Hb 10 0 g/dL)

There was patterning on the MDI and PDI scales comparable with that found by Walter et al (1989) [Ref 14] IDA children consistently failed the showing-shoes item, in the 12–14-month age group, the IDA children had particular difficulty walking alone, standing from sitting or being supine, and standing on left foot

Follow-up After 1 week of treatment, there were no differences between the orally and parenterally treated children, in contrast to Oski et al (1983) [Ref 10] After 1 week, all children improved on MDI scores regardless of their iron status or whether they received iron or placebo

After 12 weeks of therapy, the Hb level of most of the moderately anemic children was not corrected, and these children did not improve on either MDI or PDI The children whose Hb level was corrected (primarily the mildly anemic children) had no MDI improvement, but there was a PDI improvement

Conclusions The study provides evidence that compared to nonanemic controls, children with mild anemia (Hb 10 5 g/dl) will perform poorly on tests of psychomotor development whereas more severe or longer-term anemia (Hb 10 0 g/dl) is required before effects on mental functioning will be seen This may point to a mediating role of psychomotor disturbances in cognitive development, IM iron does not differ from oral iron treatment in its effects after 1 week, improvements after 1 week are probably attributable to a practice effect, whereas a beneficial hematologic and developmental effect of longer therapy relies on the initial anemia being mild, when anemia is moderate, mental functioning as well as psychomotor functioning is affected and does not seem to be reversible

Unfortunately, because of the lack of an appropriate placebo control, after the first week, for comparisons of the performance of the IDA orally treated infants and because no intergroup comparisons are reported, the unique effect of iron treatment still cannot be concluded from this study

Other The paper offers a good discussion of the related findings of other authors

---

*14 Walter et al (1989) * Key Words Chile, ages 12 and 15 months, IDA and ID, 3 months of therapy, BSID, design brief and extended intervention, double blind, with partial placebo control and nonanemic controls*

Importance This study is to be compared with those of Lozoff et al (1987 and 1982b) [Refs 13 & 7] because it investigates the existence of a differential effect on development as a function of the specific severity or duration of anemia Furthermore, certain specific areas of difficulty on MDI and PDI reported elsewhere are replicated and, again, there is clear evidence of IBR patterning

Design IDA, ID, and nonanemic control children were assigned to receive treatment or placebo for the first 10 days, after which time all children received iron treatment for 3 months Hematologic assessment was at ages 9 and 12 months and the first developmental assessment was at 12 months Treatment then recommenced for 3 months and the final developmental assessment was at 15 months All developmental assessments were reviewed as a function of hematology at 9 months, thus it was possible to distinguish children who had been anemic for at least 3 months from those who had become anemic in the last 3 months

Baseline At the first developmental assessment, IDA children had lower MDI and PDI scores than did the nonanemic control children, with no similar lowering of scores evident in the ID children Specifically, infants had difficulty on items requiring language comprehension (as in Lozoff et al (1982b) [Ref 7]), vocalization of bisyllabic words, showing shoes, clothing, or own toy, sitting from standing, standing and walking alone, standing from sitting, and standing on the left foot (similar to Lozoff et al (1987) [Ref 13]) The IDA infants also differed from the others on responsiveness to examiner, other people, and mother, general emotional tone, test affect and task orientation, goal directedness, attention span, activity, vocalization, and body motion This patterning was similar to that found in the studies listed in the review by Deinard et al (1981)

Importantly, the authors found that MDI and PDI scores were lower for all children with Hb less than 10 9 g/dL, and that the children with the lowest Hb values also had the lowest MDI scores, which were also lower than those of other less anemic children Children who had been anemic for at least 3 months were generally more severely anemic and were also the children whose test scores were affected the most The hemoglobin level at which effects on mental development are observed are remarkably similar between this study (Hb 10 5 to 10 9 g/dL for MDI and PDI g/dL) and that of Lozoff et al (1987) [Ref 13] where effects on MDI and PDI were observed in children whose Hb was less than 10 0 g/dL and 10 5 g/dL, respectively

Follow-up As in the Lozoff et al (1987) study [Ref 13] and others, after only 10 days of treatment, all groups had improved their MDI and PDI scores After 3 months of treatment, there were no changes in any of the children's BSID scores (including IBR), with IDA children still scoring low on the language and psychomotor items listed above

Conclusions The baseline association of iron and development was again confirmed, with further support for the view that the size of the difference in test scores between IDA and nonanemic control children reflects the duration or severity of the anemia However, the causal hypothesis receives no support from this study perhaps because the association between IDA and development is not causal, or because 3 months of therapy is not long enough, or because the effect is irreversible

---

*15 Idjradinata and Pollitt (1993) * † Key Words Indonesia, age 12–18 months, IDA and ID, 4 months of therapy, BSID, design extended intervention, randomized, double blind, with placebo and nonanemic controls*

Importance This is a very important study because it is the first to use a placebo-control for an extended period of treatment

Design This was a double-blind intervention trial with IDA, ID, and nonanemic control subjects randomly assigned to receive treatment or placebo for 4 months The authors made a concerted effort to match their subjects for confounding variables

Baseline At baseline, the well-documented association between IDA (not ID) and lower scores on tests of development was replicated, with IDA children scoring lower than ID and nonanemic control children on MDI and PDI

Follow-up After 4 months of treatment, the iron-treated IDA children improved significantly more than the nonanemic group in MDI and PDI Baseline differences between these groups were eliminated

Conclusions The hypothesis that the association between iron and development is causal receives strong support and, again, it seems that the only detectable effect is to be found in IDA and not ID children This is the first study to show that pooerer PDI and MDI test performance in infants is reversible following 4 months of iron treatment There is a need for the results to be replicated

Other The authors offer a short discussion of the ways in which poorer psychomotor performance may mediate poorer cognitive development

---

*16 Lozoff et al, (1996b) * Key Words Costa-Rica, age 12–23 months, IDA, 6 months of therapy, BSID & IBR, design extended double-blind intervention, nonanemic controls randomly assigned treatment or placebo, IDA treated*

Importance This study was conducted to replicate the findings of Idjradinata and Pollitt (1993) [Ref 15] However, for ethical reasons, the authors did not randomly assign the IDA group to treatment or placebo Therefore, the two study designs are not directly comparable

Design This was a double-blind intervention trial in which the IDA group received oral iron treatment for 6 months and the nonanemic controls were randomly assigned to treatment or placebo BSID and IBR were assessed at baseline and repeated 3 and 6 months after the start of treatment

Baseline IDA infants scored significantly lower (mean 6 1 points) than the nonanemic controls on the MDI There was no significant difference on the PDI On the IBR, IDA infants were significantly more fearful, unhappy and hesitant with the examiner

Follow-up Children who received treatment showed a good hematological response The differences observed at baseline in MDI between IDA and nonanemic controls were still present at the 3 and 6 months follow-up

There was no change in PDI The IBR of IDA children improved significantly more than that of the nonanemic controls such that the initial differences were no longer present after 6 months of treatment

Conclusions IDA children scored significantly worse at baseline on the IBR rating and MDI but not PDI Iron treatment did not significantly improve the MDI of children but it did lead to a signficant improvement in the IBR rating However, in this study, the improvement in IBR could not be considered a direct result of treatment because there was no IDA placebo group with which to compare results

Other The paper provides a good discussion of the effects of IDA on MDI, PDI and IBR and gives several hypothesises as to why benefits from treatment are not consistently observed

Short-term Effects: Preventative Trials

---

17 Heywood et al (1989) † Key Words Papua New Guinea, age 1 year, IDA, one iron dextran injection at 2 months, total and mean fixation time, habituation, and dishabituation tested, design extended intervention, randomized, double blind, with placebo control

---

Importance The primary importance of this study is that it is the first trial to investigate the benefits to infants from preventing IDA Preventative trials permit the investigation of the causality of the relationship between IDA and development in circumstances where benefits of iron treatment have not been observed The study also measured specific functions within attention rather than more global measures of development

Design This study was a double-blind randomized preventative trial of iron supplementation and placebo in IDA infants, with no nonanemic control group included At age 2 months, the children were randomly assigned to receive IM either iron dextran or placebo, and the effects of this supplementation on hematology and attention were assessed at 1 year

The number of fixations and total fixation time were assessed, as well as rates of habituation and dishabituation A higher rate of habituation is thought to reflect the rate at which an internal model of a stimulus is acquired Dishabituation rates are thought to measure schema acquisition

Follow-up The results of this study are confused by the presence of malaria infection, which interacted with iron status in the treatment group when attention scores were assessed The main result of this study was that aparasitemic IDA infants who received iron treatment had higher total fixation times than did aparasitaemic IDA placebo-treated infants, suggesting that iron treatment leads to longer visual exploration of stimuli Iron treatment did not eliminate anemia, although it did significantly improve the iron status of the treated children in the aparasitemic group There was no evidence of a relationship between socioeconomic variables and this measure of attention

Conclusion There is some evidence that preventing IDA in infants can result in a beneficial effect on attention However, the results are confounded by the concurrent effects of malaria on the iron status of children in this study The results are interesting in the light of reports from other studies, using more global measures, of difficulties on attentional items (Review by Deinard et al (1976))

---

18 Moffatt et al (1994)† Key Words Canada, 2–15 months, at risk of IDA, 13 months of iron-fortified infant formula, BSID, design preventative trial, double-blind, randomized, with placebo-control

---

Importance This was a well designed preventative trial where children's iron status was manipulated from age 2 months All children came from the same disadvantaged background and did not differ sociodemographically or in the amount of stimulation available to them as measured by the HOME Inventory An association was demonstrated between iron deficiency and PDI without any effect on cognition Thus, it is possible that motor disturbance precedes and may cause cognitive disturbance

Design This was a double-blind, randomized, prospective iron status manipulation, where infants at age 6 months were randomly assigned to receive either iron fortified infant formula or regular formula The fortification was continued until age 15 months, with hematologic and developmental assessments at ages 6, 9, 12, and 15 months

Results There were significant hematologic differences between groups at all ages No difference on MDI or IBR was found between the groups at any age At ages 6 and 15 months, there were no intergroup PDI differences, but at ages 9 and 12 months there was a decline in the PDI scores of the regular-formula group, making their scores significantly lower than those of the iron fortified-formula group

Conclusions The prospective nature of this study and the randomizing procedure indicate that strong support is leant to the hypothesis that the association between IDA and motor disturbance is causal The lack of difference between these groups on potentially intervening variables also supports this hypothesis The fact that, at age 15 months, the 9- and 12-month PDI score differences had disappeared suggests that the developmental effect associated with IDA may be transitory

---

19 Lozoff et al (personal communication, 1996a) Key Words Chile, 6–12 months, IDA, 6 months of supplemental iron, BSID, design preventative trial, double blind, randomized, with placebo control

---

Importance This abstract describes another preventative trial that, like Moffet et al (1994) [Ref 18], used a strong experimental design to investigate the nature of the relationship between iron and cognition in infants The studies are comparable except that Moffatt et al (1994) [Ref 18] looked at infants in a very impoverished area of Canada, whereas in this study, the infants were from less impoverished homes in Chile

Design This was a randomized, double-blind, placebo-controlled preventative trial, in which 944 healthy Chilean 6-month-old infants, with normal Hb levels from similar socio-economic backgrounds and with similar anthropometric status, were randomly assigned to receive supplemental iron or no added iron until age 12 months At age 12 months, the infants' hematologic status was assessed for a second time and all infants completed the BSID

Results At age 12 months, fewer of the iron supplemented children were anemic and fewer were iron deficient However, the supplemented children did not have higher BSID scores

Conclusions There is no conclusive evidence of a benefit to children's development resulting from preventing IDA These results are in contrast to those of Moffatt et al (1994) [Ref 18] where the population was more socio-economically disadvantaged Lozoff et al state that the lower BSID scores observed in IDA infants may result from factors other than IDA, including environmental disadvantage, lack of breast-feeding, birth weight of less than 3 kg, IDA onset before 6 months or after 12 months, or IDA lasting longer than 6 months

A failure to find a protective advantage of prophylactic iron treatment may be only be in situations where infants are already at risk of other biological, social, or environmental stressors that are manifested by ID or IDA

Long-term Effects: Observational Studies

---

*20 Palti et al (1985) * Key Words Israel, children 0 to 10–13 years, questionnaire based on the Shaefer Classroom Behavior Inventory, supplemented with learning achievement items, design observational, double blind*

Importance This study assessed the effects of IDA experienced at age 9 months on the educational achievement and behavior of school children aged 10–13 years Because this was a longitudinal prospective study and not a preventative trial, the subjects who were anemic at age 9 months are very likely to have differed from the nonanemic control group for other variables other than iron status However, as with the Palti et al (1983) study [Ref 23], care was taken to assess the extent to which any differences in test scores were attributable to intervening variables Because the children were monitored yearly after the first year of life, the possibility is greatly reduced that educational achievement and behavior at school is a function of some intervening period of anemia rather than anemia in the first year

Design Although infants with Hb less than 11 g/dL at age 9 months received iron treatment to correct their anemia, this study investigated the association between iron status before treatment and school performance and behavior at school It did not assess differences between treated and untreated children when they were infants or when they were of school-age Therefore the study is classed as observational

Baseline After maternal education and the sex of the child were controlled for, IDA children scored lower than nonanemic control children on educational achievement and on positive task orientation, but there was no effect on negative task orientation or on mood Maternal education and the sex of the child also contributed to learning achievement, task orientation, and mood score

Conclusions The authors conclude that although maternal education is still the single best predictor of the child's achievement on development and intelligence tests, IDA in infancy is also significantly associated with poorer performance in the school years The hypothesis that iron status in infancy is associated with long-term effects on school performance and behavior receives support That the association is causal is unclear for two reasons First, although the involvement of potentially intervening variables was assessed, the choice of maternal education as the only indicator of SES may have been inadequate Second, there was no analysis of the results of giving iron treatment

Other Biochemical mechanisms, the findings of studies of IDA in animals, and clinical and public health implications of the findings to date are discussed

---

21 Wasserman et al (1992) Key Words Yugoslavia, age 2 years, Hb levels, some IDA, prospective study, MDI subscale of BSID, design observational*

Importance One of the key features of this study is its comprehensive assessment of the role of various potentially confounding variables (including lead exposure) in the development of infants and young children

Design In this prospective study MDI scores, lead measurements, and Hb measurements were taken at ages 6, 12, 18, and 24 months The number of children anemic at each time and the extent of their anemia are not stated, but the authors noted that Hb values varied from below 9 0 g/dL to greater than 13 0 g/dL The study assessed the extent to which a 2 g/dL decrease in Hb at each time predicted the MDI decrement observed at 24 months

Results Ethnic group and HOME status accounted for a great deal of the variance in MDI, but even after controlling for these variables, the authors found that at 18 months, a 2 g/dL decrease in Hb was a statistically significant predictor of 24-month MDI Moreover, the authors report that Hb concentrations measured at ages 12 and 18 months were better predictors of MDI decrements at 24 months than was the Hb concentration at 24 months This is interesting given the number of studies that concentrate on assessing development as a function of current Hb levels

Conclusions This study implies that decreases in Hb are associated with decreases in MDI (although the extent of the anemia in the children showing these decreases is not given) and that this association is causal, given the care taken to control for confounding variables Furthermore, decreases in Hb levels up to a year before testing were better predictors of MDI decrements than were Hb decreases at the time of testing

More information about the Hb values for children whose Hb decreases predicted MDI decreases is needed before a definite statement can be made about the nature of the association being observed

Other In general this paper is confusing in its report of the findings, in particular it is unclear about the mean Hb levels at each time, about when the children became anemic, and about the uniformity and extent of the decline in Hb

---

22 Hurtado (1995) Key Words USA, 0–10 years, ID in infancy, children assessed with test of cognitive development, design observational*

Importance This abstract reports on a study where a dose-response relationship between hemoglobin and test score and an interaction between test score, iron status and maternal education was observed

Design Subjects were enrolled at birth in a nutritional supplementation program and followed until age 10 years Children's cognitive performance was tested at age 10 years to determine differences in development between children who were ID and children who were iron sufficient in infancy and early childhood The precise design of the study is not given, it is not clear whether all children were supplemented or whether there was a placebo group No report of a randomization procedure is made and no information on the SES of the subjects is given

Follow-up At age 10 years, children were assessed with a test of cognitive performance No levels of statistical significance are reported in the abstract, but the author states that there were indications of an increased risk of disability resulting from ID, especially when it was severe, and that additive interactions with maternal education were also observed

Conclusions This is a potentially crucial study, but more information is needed on the exact design and the data analysis Without this information, it is still possible that the children showing disability at age 10 years did so as a result of factors other than the presence of ID It is unclear whether the children in this study had ID or IDA They are described as ID, but the dose-response relation reported is "between *hemoglobin* and disability"

Long-term Effects: Follow-up of Intervention Trials

23 Palti et al (1983) Key Words Israel, ages 2, 3, and 5 years, IDA and intermediate at 9 months, 3 months of therapy, Brunet-Lezine's Developmental Quotient, MILI IQ test, and Wechsler Scale, design follow-up of previous intervention trial*

Importance The authors distinguished between children who were moderately anemic and children who were mildly anemic The long-term outcomes for these two groups of anemic children are of particular interest, given the studies of Lozoff et al (1987) [Ref 13] and Walter et al (1989) [Ref 14]

Design Developmental assessments were carried out at ages 2, 3, and 5 years as a function of Hb status at age 9 months Children who had been anemic at age 9 months were given iron treatment, with no placebo control, whereas the intermediate and nonanemic children received no treatment

Results At the first developmental assessment and then at 3 years, the initially, moderately IDA children scored lower than did nonanemic control children on the Brunet-Lezine and the MILI, respectively However, these differences were not significant after maternal education and birth weight were controlled for At age 5 years, however, the lower scores in the moderately IDA children persisted, and this time the difference was significant even after the confounding variables were controlled for Because this was not a double-blind study, it is possible that measurements were biased in the direction of the experimental hypothesis

Conclusions The strong implication is that anemia in infancy, in particular moderate anemia, will lead to a poorer performance on tests of cognitive development in the long term

24 Walter et al (1990) Key Words Chile, age 5 years, previously moderately IDA, ID before and after therapy, or ID corrected by therapy, Stanford-Binet IQ test, an assessment of fine and gross motor coordination, an assessment of psycholinguistic ability, a test of visual motor integration, and a preschool educational scale, design follow-up of previous intervention*

Importance This abstract reports a study that is a follow-up of Walter et al (1989) [Ref 14] No separate analysis was conducted as a function of the severity and duration of anemia at age 12 months as was done in the earlier study

Results Anemic infants, at 12 months, scored significantly lower on IQ, motor scores, psycholinguistic items, visuomotor coordination, and the educational preschool assessment even though hematology problems had been completely corrected earlier in childhood

Conclusions Anemia was corrected in infancy yet lower developmental test scores persisted Because no assessment is made of whether or not the children included in the follow-up had been anemic between the two developmental assessments, the lower scores here may have been due to a further period of anemia later in childhood It is at least likely that, if a child's environment early on influences whether or not the child will become anemic, continuing to live in such an environment means continued risk of anemia Therefore firm conclusions cannot be drawn about the long-term developmental risk to children anemic in infancy, although this study does at least suggest that these risks are to be taken as a serious possibility

---

25 Lozoff et al (1991) Key Words Costa Rica, age 5 years, IDA in infancy, psychoeducational measures, a test of visual motor integration, the Draw a Man IQ test, a motor proficiency test, and the Wechsler Preschool and Primary Scale of Intelligence, design follow-up of a previous intervention*

Importance This paper reports a follow-up of Lozoff et al's Costa Rica studies, which compared the developmental status of children at age 5 years who were either mildly anemic, moderately anemic, or nonanemic at age 12–23 months

Results At age 5 years, the authors reported all children to be comparable in terms of their hematology regardless of their hematologic status at the end of the previous short-term study Children who were moderately anemic in the earlier study and children who were mildly anemic but experienced no hematologic correction scored lower on tests of development at age 5 years

At age 5 years, children scored lower on all measures except verbal IQ, visual auditory subtests of the Woodcock test, and the Goodenough Draw a Man test Generally, between-group score differences were greatest on tasks requiring nonverbal skills, visuomotor coordination, and motor coordination and less pronounced on tasks requiring purely verbal skills

The effects on developmental test scores were strongly influenced by intervening variables Another problem with this study, as for Walter et al (1990) [Ref 24],was the failure of the authors to investigate the hematologic history of the children between the end of the previous study and the long-term follow-up The reason why children had persistently lower scores at 5 years may not only be because of their hematologic status in early childhood, but also because they were subsequently anemic between studies As noted above in the review of Walter et al (1990) [Ref 24], it is very likely that the factors predisposing children to hematologic impairment persist

Long-term Effects: Preventative Trials

---

26 Cantwell (1974) Key Words USA, age 0–7 years, IDA at 6–18 months, neurologic evaluation and the Stanford-Binet IQ test, design, preventative*

Importance This study is important in its assessment of the long-term developmental consequences of anemia in earlier childhood

Design This abstract describes a prospective iron status manipulation study, where the developmental assessment at 6–7 years was blind to the iron status of the child in infancy

Results The group of children who had become anemic between ages 6 and 18 months showed difficulty at 6–7 years with clumsiness in balancing on one foot, problems with tandem walking, and difficulty with repetitive hand and foot movements These motor coordination problems, thought to be a long-term developmental outcome of anemia in earlier childhood, may be seen as paralleling the difficulties experienced by the anemic children described by Lozoff et al (1987) [Ref 13] and Walter et al (1989) [Ref 14] As with many of the studies of infants (see those listed in the review by Deinard et al (1976), the children in this study were also rated as more inattentive

Conclusions These results cannot be taken as conclusive proof of the causal relation between infant IDA and long-term poorer performance on tests of development because no placebo group was included, the developmental protection apparently afforded the IM treated infants may have resulted from nonspecific factors Furthermore, no assessment of other differences between the groups was reported, either at baseline or follow-up, and without knowing whether group assignment was randomized, intervening variables such as SES or maternal education may account for the differential effect reported No statistical comparison of the IQ measures was reported

PRESCHOOL CHILDREN (2-5 YEARS)

Summary of Findings

The cognitive benefits of iron treatment in preschool children are more apparent than in infants The reasons for this are not understood but it may be that the tests available for use in older children are inherently more sensitive or that preschool children have passed the critical age at which IDA can have long-lasting effects

Only five studies have looked at the effects of ID or IDA on cognition in preschool children and they each have two notable features First, all are intervention studies with an extended period of intervention (2 6 months) compared with the studies of infants in the previous section Second, in each study there were repeated attempts to measure cognitive function as opposed to development and to determine the locus of a cognitive effect resulting from ID or IDA

Although it is difficult to draw firm conclusions from the results of so few studies, the evidence suggests that children with IDA benefit from iron treatment in terms of improved performance on tests of discrimination and oddity learning/concept acquisition There may also be behavioral differences in that IDA children are observed to be more unhappy and less responsive than iron-sufficient control children (Deinard et al 1986 [Ref 29]) The major influence of IDA on preschool children is thought to be on attention, arousal, and motivation rather than on basic cognitive abilities

In three of the five studies, a battery of tests were designed to distinguish between problems with attention and those with concept acquisition Distinguishing between attention and concept acquisition problems is of particular interest because attentional difficulties may conceal cognitive abilities in children Such difficulties may, in the longer term, result in poorer performance on tests of cognitive function It is also possible that poorer attention and irritability are children's reaction to tasks beyond their capabilities This issue was also relevant in the previous section on infants and young children The type of attentional disturbances seen in preschool children have clear parallels in the behavioral disturbances found in infants and young children, in whom differences in attention, reactivity, and mood on BSID were consistently shown in children with ID and IDA

As with studies in infants, with preschool children the benefits of treatment on attention and cognition are seen only in children who are initially iron deficient with anemia and are not apparent in children who are initially iron deficient but not anemic (see reasons given in infants section)

Evidence to date is limited but has shown that improvements in attention and cognition result from iron treatment of children with IDA suggesting that the relationship is causal and that a program in which iron supplements are given to preschool children could be of benefit to children's attention and cognitive function

Intervention Trials

27 Pollitt et al (1978) H Key Words USA, age approximately 4 years, ID, 4 months of therapy, attention, learning, and memory measured, design extended intervention, double blind, with nonanemic control*

Importance This abstract describes a study of particular interest because it assesses the effects of ID on cognition, comparing ID preschool children with nonanemic, control preschool children before introducing iron therapy The tests are designed to distinguish between control processes and structural capacity

Design This study used a double-blind, iron-treatment-only intervention design and looked at the effects of ID on cognition Both ID children and nonanemic control children were assigned to receive iron treatment

Baseline At baseline, the ID children performed more poorly than did their nonanemic counterparts on tests of attention and memory control processes The results indicate that the effect is at the control level rather than in the capacity of the structures themselves This contradicts Soewondo et al's (1989) paper [Ref 31] which concludes that the effect is also in the capacity of the structures themselves and only in children with IDA, not ID

Follow-up After 4 months of therapy, the relatively poorer performance of the ID group compared to the nonanemic control group was no longer apparent

Conclusions This study indicates that ID is associated with lower scores on cognitive development tests in children of approximately 4 years of age and that performance returns to an optimal level after at least 4 months of therapy However, the paper does not report that any steps were taken to assess the role of potentially intervening variables that may have distinguished the two groups at baseline This, combined with the lack of inclusion of a placebo group, means that the unique effects of iron deficiency and iron therapy on cognition cannot be determined

---

28 Pollitt et al (1983) † Key Words USA, age 3–6 years, IDA, 3 months of therapy, discrimination learning tests, design extended intervention*

Importance This study's importance probably lies in its contradiction of the findings of the studies by Pollitt et al (1986) [Ref 30] and Soewondo et al (1989) [Ref 31] with respect to whether infants are scoring lower on attentional or concept acquisition tasks

Design This study was an intervention trial where IDA children were given treatment for 3 months whereas the nonanemic control children received no treatment There was no placebo control

Baseline As with the Pollitt et al (1978) study [Ref 27], the IDA children had lower scores than nonanemic controls on tests of discrimination learning, thought to tap attentional processes, and also on the attention based items of the memory task However, there was no difference in tests of concept acquisition

Follow-up There was a significant improvement after treatment in the IDA group compared to the nonanemic placebo group in the tests of discrimination but not in the tests of concept acquisition

Conclusion This study suggests that treatment can lead to improvements in attention However, children did not experience structural difficulties in contrast to the studies of Soewondo et al (1989) [Ref 31] and Pollitt et al (1986) [Ref 30]

---

29 Deinard et al (1986) † Key Words USA, age 18–60 months, IDA and ID, 6 months of therapy, BSID or Stanford-Binet IQ, design extended intervention, double blind, partially placebo controlled

---

Importance This study was very well designed yet in contrast to most studies, no differences between IDA, ID and nonanemic controls were observed at baseline in performance on the MDI or Standford Binet There was also no improvement in the IDA or ID group after treatment The study was also important in its direct comparison of the effects on development of ID and IDA

Design This was a double-blind intervention study with a nonanemic control group matched to IDA and ID groups for maternal education and, separately, for baseline MDI scores The IDA group received iron treatment for 6 months, the ID group received treatment or placebo, and the nonanemic control group received a placebo

Baseline Overall, the authors reported no differences in MDI or Stanford-Binet between the ID, IDA and nonanemic control groups at baseline The authors did report that the IDA group was more unhappy and less responsive than the nonanemic control group, again confirming the emerging pattern of behavior found in IDA and ID infants, young children, and preschool children (see Deinard et al 1981 [Ref 1])

Follow-up After 3 months of therapy, neither the IDA nor ID group improved on MDI or Stanford-Binet whereas the nonanemic control children tended to increase their scores, thus creating significant differences between the nonanemic control children and the IDA and ID children

After 6 months of therapy, the pattern was the same, with neither the treated IDA nor the treated ID children improving their MDI or Standford-Binet scores, and the control children improving as before

Conclusions Despite the failure to detect baseline cognition differences between groups, this study supports a hypothesis of an association between iron deficiency (with or without anemia) and poorer performance on tests of cognitive development, given the failure of the IDA and ID groups to match the improvements on MDI and Stanford-Binet seen in the nonanemic control group The authors suggest the lack of improvement in the IDA group could reflect the fact that these children were less testable despite repeated testings (as reflected in the behavioral differences between groups) and perhaps this is because of some irreversible behavioral deficit or because they were more susceptible to adverse environmental conditions such as stress

The absence of a developmental improvement in the IDA and ID groups after 6 months of iron treatment suggests that either the association between IDA and development is noncausal or that the effect is irreversible Because the IDA and ID children were matched to nonanemic control children for maternal education and the control group improved on MDI at 3 and 6 months, the failure of the IDA group to improve does not appear to be a function of maternal education but rather because the effect was not reversible with treatment

Other The authors offer an excellent discussion of the findings of other studies

---

*30 Pollitt et al (1986) * † Key Words Guatemala, age 3–6 years, IDA, 3 months of therapy, three discrimination learning tests, two short-term memory tests, and four oddity learning tasks, design extended intervention with nonanemic control*

Importance This paper provides further evidence that IDA children experience difficulties in the structural or control processes involved in cognition See also Pollitt et al (1978) [Ref 27] and Soewondo et al (1989) [Ref 31]

Design An intervention trial comparing the cognitive function of ID children with nonanemic controls The ID group received treatment for 11-12 weeks Cognitive function was assessed at baseline and immediately after treatment in both groups There was no placebo control

Baseline At baseline, the IDA children needed more trials to reach criterion on the discrimination learning tests No differences were found between the groups on oddity learning / concept acquisition or on memory The results indicate a difficulty in IDA children in attending to relevant information This agrees with the Pollitt et al (1978) [Ref 27] and Pollitt et al (1983) [Ref 28] studies and also with the studies in the Infants and Young Children category, where IBR patterning has been found (Lozoff et al 1985 [Ref 11], Oski and Honig 1978 [Ref 5], Walter et al 1983 [Ref 9])

Follow-up After treatment, the baseline difference in discrimination / attention in the IDA children relative to the control children was eliminated However, after treatment, the IDA children made more errors than the nonanemic control group on the oddity learning task, and this task is thought to tap conceptual acquisition

Conclusions This study provides further evidence in support of an effect of IDA on attention Because no placebo control group was included and post hoc statistical controls focused on possible anthropometric and nutritional differences between groups and not on, for example, SES or maternal education, the baseline differences between ID/IDA children and nonanemic children may be attributable to intervening variables and the changes at follow-up to nonspecific therapy effects

The effects of IDA on concept acquisition in this study are only suggestive In the Pollitt et al (1978 and 1983) studies [Refs 27 and 28], there was no evidence that children were experiencing concept acquisition difficulties whereas in the study of IDA children by Soewondo et al (1989) [Ref 31], concept acquisition was adversely affected Why the group treated with iron showed relatively poorer scores at follow-up but not at baseline in this study is unclear, but it is possible, as with the Deinard et al (1986) study [Ref 29], that the IDA children were more sensitive to the stressful testing conditions and therefore less able to improve with practice than nonanemic control children

Other There is an extensive review of the field in particular, an excellent discussion of the findings concerning ID and a comparison of these findings with the those concerning IDA

31 Soewondo et al (1989) † Key words Indonesia, age approximately 4 5 years, IDA and ID, 2 months of therapy, 2 x 2 choice discrimination learning tests, 3 oddity learning tests, and the Peabody Picture Vocabulary Test, design extended intervention, double blind, randomized, with placebo and nonanemic controls*

Importance This investigation is complementary to the studies of Pollitt et al (1978, 1986) [Refs 27, 30] in its attempt to determine whether lower developmental test scores associated with iron deficiency are to be attributed to structural or control process difficulties

Design The study was a double-blind intervention trial with IDA, ID, and nonanemic control children randomly assigned to receive either treatment or placebo for 8 weeks

Baseline At baseline, of the small number of children who reached the learning criterion on reversal discrimination color tasks, the IDA children learned more slowly than did the nonanemic control children On the oddity learning task, the IDA children's performance was worse than that of the nonanemic control children on the twice- and thrice-repeated versions Thus detectably lower developmental test scores were found in IDA children on tests of attention and conceptual ability The attentional deficits in the IDA children, but not the effects on concept acquisition, confirm findings of Pollitt et al (1978, 1983 and 1986) [Refs 27, 28, 30]

Follow-up After 8 weeks of iron treatment, the iron-treated IDA children learned more quickly on the color discrimination and performed better on the twice- and thrice-repeated items of the oddity learning task than either the nonanemic control children treated with iron or the IDA children who received placebo No benefits of treatment were observed in the ID group

Conclusions The strong implication of this study is that IDA but not ID is associated with lower developmental test scores This is the first study to shows effects of IDA on both attentional control processes and on concept acquisition structural processes Improvement in cognitive function of IDA children after iron treatment suggests that iron supplementation programs would benefit children of pre-school age

SCHOOL-AGE CHILDREN AND ADOLESCENTS (5-16 YEARS)

Summary of Findings

There is strong evidence that among school-age children, initially lower scores on tests of cognition or school achievement due to IDA can be improved and in some instances even reversed after iron treatment One reason for this evidence might be the large number of placebo-controlled trials, which are more able to pick up treatment effects Another reason might be the increased sensitivity of the tests used Alternatively, it could be that the effects of IDA in school-age children are more transitory than in infants and thus more responsive to the effects of iron treatment

Eleven studies have examined the effects of iron supplementation on the cognitive function or educational achievement of school-age children with ID or IDA Of these, nine used placebo-controlled experimental designs, thus permitting the causal effect of iron on cognition to be investigated All but one study (Pollitt et al 1989) [Ref 41] showed significant improvements in the cognitive function or educational achievement of children who received iron supplementation compared with those who received placebo Furthermore, the one study (Bruner et al 1996) [Ref 42] that investigated the effects of treating adolescent girls with ID also found significant cognitive benefits These results are in contrast with those observed with infants where benefits of treatment on development are rarely observed As with studies with infants and preschool children, there seems to be an indication of disturbances in attention and behavior in children with IDA

Note that none of the studies with school-age children documented the hematologic history of the children It is possible, therefore, that the lower scores at baseline in cognitive functioning in children with ID and IDA were a result of hematologic impairment earlier in life Indeed, if the factors that predispose school-age children to ID or IDA are not recent, there is an increased likelihood that these children had been anemic before, as infants and as young children

The adverse effects on cognitive and educational test performance due to IDA in preschool and school-age children appear more transitory in nature than the effects on development in infants and imply that treatment of IDA in preschool and school-age children through iron supplementation programs may be beneficial and have immediate effects This is in contrast to the effects of IDA on infants, for whom poorer performance on developmental tests may not be reversible with treatment and where programs aimed at the prevention of IDA may be the most appropriate action

Observational Studies

*32 Webb and Oski (1973a) * Key Words USA, age 12–14 years, IDA, cross sectional, Iowa Basic Skills, levels A-F, form F, design observational*

Importance This study was carried out to assess the relation between the presence of anemia and school performance, as measured by the Iowa Basic Skills test

Design A cross-sectional comparison of IDA with nonanemic control children

Baseline Although all subjects performed poorly relative to national norms, the anemic children scored significantly lower than did the nonanemic control children The anemic males demonstrated a "progressive departure" in performance with increased age

Conclusion It is not clear whether the assessment was double blind, and no attempt was made to match the subjects for intervening variables Thus, although IDA schoolchildren scored lower on school achievement tests than the nonanemic control group, this may have been due to some other variable related to iron but not iron itself

Other A short discussion of possible biochemical mechanisms is given

---

*33 Webb and Oski (1973b) **

This abstract reports on the same Webb and Oski (1973a) study [Ref 32], giving the results of a teachers' behavioral assessment of the subjects Again, attentional, behavioral, and perceptual mechanisms are implicated as possible factors mediating effects on cognitive performance (See discussions in previous sections and by Soemantri et al (1985) [Ref 36])

The teachers' assessment is not reported to have been blind to the children's hematologic status, and although the children were described as all coming from a socially homogenous background, the behavioral disturbances in the IDA group may not have been due to differences in iron status alone

Intervention Trials

---

34 Seshadri et al (1982) Study 1 † Key Words India, age 5–8 years, IDA, 2 months of therapy, verbal and performance tests from the Wechsler Intelligence Scale for Children (WNAC), design extended intervention, randomized

---

Design This intervention study stratified subjects by age and randomly assigned them to treatment or no treatment before their iron status was determined No placebo control was included and it is not clear that assessment was double blind

Baseline The between-groups comparisons at baseline are not reported

Follow-up After treatment, iron-treated children improved their WNAC scores more than did the nontreated children for all iron status groups Disaggregation by the presence and absence of anemia showed that IDA children only improved more than the nonanemic control children in the 7–8-year age group, and this was across treatments

Conclusion The lack of placebo control means that improvements in cognition at follow-up in the IDA group could be due to a practice effect

---

34 Seshadri et al (1982) Study 2 † Key Words India, age 5–6 years (boys), children IDA, 2 months of therapy, WISC verbal and performance tests, design extended intervention, double blind, randomized, with placebo control

---

Design This was a double-blind intervention study with anemic male subjects only Subjects were pair-matched at baseline for Hb, age, height, weight, Draw a Man IQ, WISC, per capita income, and maternal education After matching, one child from each pair was randomly assigned to receive iron treatment or placebo A nonanemic control group was not included

Follow-up After 2 months of treatment, the iron-treated children showed WISC score improvements, and these scores were significantly higher than those of the placebo group The iron-treated group also had significant improved Hb levels compared to the placebo group

The verbal IQ improvements in the iron-treated group were seen in the information, similarities vocabulary, arithmetic, and digit-span subtests However, improvements were also seen in the arithmetic and digit-span subtests in the placbo group

Conclusions The initial matching procedure and the randomization of treatment and placebo means that a hypothesis of causal association between iron status and school performance is strongly supported in this study

---

35 Pollitt et al (1985) † Key Words Egypt, average age 9 5 years, IDA, 4 months of therapy, matching familiar figures test, design extended intervention, double blind, with placebo and nonanemic controls*

Importance This study is notable for its strong experimental design and assessment of specific cognitive effects of ID and IDA in school children

Design This was a double-blind intervention study in whıch IDA and nonanemıc control chıldren were assıgned to receıve treatment or placebo No randomızatıon procedure ıs reported

Baselıne IDA and ID chıldren were less effıcıent and less accurate than nonanemıc control chıldren on the matchıng famılıar figures test However, ıt ıs not clear ıf the groups were sımılar ın terms of SES, maternal education or other potentıal confoundıng varıables

Follow-up After treatment, the ıron-treated anemıc chıldren were more effıcıent than the placebo group, and theır scores were sımılar to those of the nonanemıc, control chıldren

Conclusıon The study supports the hypothesıs that ID and IDA adversely affect learnıng and problem solvıng capacıty ın school-age chıldren and that the effect ıs reversıble wıth treatment

Other It ıs not clear that the test, as used ın thıs study, has cultural valıdıty

---

*36 Soemantrı et al (1985) * † Key Words Indonesıa, age 10–11 years, IDA, 3 months of therapy, educatıonal achıevement, concentratıon, and Ravens Progressıve Colored Matrıces IQ assessment, desıgn extended ınterventıon, double blınd, randomızed, wıth placebo and nonanemıc controls*

Importance The study was conducted after the Pollıtt et al (1985) [Ref 35] study ın Egypt to determıne whether the effects on learnıng and problem solvıng had long-term ımplıcatıons to a chıld's educatıonal achıevement

Desıgn Thıs double-blınd ınterventıon randomly assıgned IDA and nonanemıc control chıldren to receıve treatment or placebo

Baselıne At baselıne, the IDA chıldren dıd not dıffer from the nonanemıc control chıldren on the Ravens IQ test They dıd, however, perform more poorly on measures of educatıonal achıevement The results of the assessment of concentratıon are unclear

There were no dıfferences between groups ın SES or maternal age, but because maternal educatıon was not assessed ıt ıs possıble that dıfferences at baselıne were due to an ıntervenıng varıable

Follow-up After treatment, the ıron-treated group ımproved theır educatıonal achıevement score sıgnıficantly more than dıd the placebo group However, the ımprovement was not enough to catch up wıth the scores of the nonanemıc control group

Conclusıons There ıs evıdence that IDA adversely affects school achıevement and that ıron treatment can lead to sıgnıficant benefits

Other The authors dıscuss the role of concentratıon and attentıonal dısturbances ın medıatıng poor performance on educatıonal achıevement tests and how these dısturbances may be ınfluenced by physıologıcal arousal factors Thıs paper also offers a good dıscussıon of other studıes of school-aged chıldren

---

37 Groner et al (1986)† Key Words USA, pregnant women, age 14–24 years, ID rısk, 1 month of therapy, arıthmetıc, total dıgıt span, dıgıt symbols, vocabulary, consonant trıgrams, Rey audıtory verbal learnıng test, desıgn extended ınterventıon, double blınd, randomızed, wıth placebo control*

Importance Thıs study ıs notable for ıts examınatıon of pregnant adolescent gırls and young women who are deemed to be at rısk for ıron deficıency The study does not address the ıssue of the ımplıcatıons of maternal ID for bırth outcome, but rather for the cognıtıve performance of the mother herself The findıng of an apparently beneficıal effect of ıron therapy ıs ınterestıng gıven the hematologıc status of the subjects as nonanemıc or, at most, only mıldly ıron deficıent

Desıgn Thıs was a double-blınd ınterventıon study, wıth subjects randomly assıgned to receıve treatment or placebo

Baselıne At baselıne, there were no dıfferences ın cognıtıon or ıron status between the experımental and placebo control group

Follow-up After 1 month of therapy, the hemoglobın level of both the treated and the placebo group declıned but the declıne was less ın the treated group The decreases ın hemoglobın were probably because all subjects were pregnant

After treatment, the treated group improved on the digit symbol test, one subsection of the consonant trigrams test, and two subsections of the Rey test The placebo-control group decreased on arithmetic and increased only on one subsection of the Rey test The treated group's having greater test-retest improvements than did the control group was due to decreasing scores in the placebo-control group Attentional effects are consistent with findings reported elsewhere

Conclusions The study provides evidence that ID affects cognitive functioning and that iron supplementation will prevent a decline in cognitive performance during pregnancy

---

38 Kayshap and Gopaldas (1987)† Key Words India, age 8-15 years (girls), IDA, 4 months of therapy in two 2-month sessions, visual recall, digit span, mazes, and clerical task, design extended intervention, double blind, randomized, with placebo and nonanemic controls

---

Importance This study investigated the effects of iron supplementation on cognition in anemic and nonanemic schoolgirls

Design The study was a double-blind intervention, the girls were pair matched for age, Hb, and individual total cognitive function test scores, after which one member of each pair was randomly assigned to receive treatment or placebo for 8 months No double-blind procedure was described Cognitive assessments were made at baseline, 4, 8 and 12 months after treatment

Baseline There were no baseline differences on cognitive function, even when the subjects were disaggregated from the original experimental and control groups by presence or absence of anemia

Follow-up After 8 months but not after 4 months of therapy, disaggregation of the original groups revealed that the IDA girls given iron had improved significantly more than the placebo group on clerical task, digit span, mazes, and overall score] After 4 months, both the placebo and the iron-treated IDA groups had improved equally

At the 12-month follow-up, 4 months after the completion of supplementation, there was evidence of a sustained beneficial effect of iron supplementation on all but the mazes index Hb had returned to near baseline levels, and only the mazes score had dropped significantly This study is interesting in combination with Soemantri's (1989) [Ref 40] preliminary findings paper reviewed below, because Soemantri also included an assessment after the termination of therapy, which indicated that the benefits of therapy were sustained

Conclusions The selective improvement in the IDA iron-treated group over the placebo group suggests that cognitive improvement is enhanced with iron supplementation in a group performing suboptimally and the benefit is sustained at least 4 months after treatment has finished

Because there were no differences in cognitive scores as a function of iron status at baseline yet the IDA group improved in cognition with treatment, suggests that both groups were scoring lower at baseline than their potential but for different reasons

Other There is a good discussion of the possible biochemical mechanisms supporting the sustained improvement above baseline and of the general biochemical effects of iron deficiency and how these may be associated with poor cognitive performance

---

39 Seshadri and Gopaldas (1989) Study 1 This is a re-report of Seshadri et al (1982) [Ref 34] The reporting of the results for this study is particularly unclear and inconsistent with the tabulation

---

39 Seshadri and Gopaldas (1989) Study 2 This is a re-report of Seshadri et al (1982) [Ref 34]

---

39 Seshadri and Gopaldas (1989) Study 3 † Key Words India, 8–15 years (boys),IDA, 2 months of therapy, WISC, design extended intervention, double blind, randomized, with placebo and nonanemic controls

---

Importance A notable feature of this study is the inclusion of two iron therapy groups given different doses of the iron supplement

Design This was a double-blind intervention study, boys ages 8–15 years (including anemic and nonanemic control subjects) were triplet-matched for age, Hb, and baseline cognitive function before randomly assigning the members of each triplet to receive placebo, 30 mg iron, or 40 mg iron Post hoc disaggregation of the groups was performed to compare IDA subjects with nonanemic control subjects

Baseline No baseline comparison between scores was made for the anemic and nonanemic control groups created post hoc

Follow-up Post hoc analysis found that iron supplementation improved the individual and overall scores on the WISC in IDA children only There was a dose-effect with the 40-mg treatment group showing improvement on more measures It was reported that the WISC baseline scores of the 30-mg group were relatively higher than those of the 40-mg group Therefore it cannot be concluded that the association between iron status and WISC scores is causal

Conclusions No attempt was made to assess whether these post hoc groups were distinguishable from one another on other intervening variables Such differences between groups may have accounted for any baseline differences in cognition but not necessarily for the differential response to iron therapy over placebo

Thus, this study provides strong evidence that IDA is causally associated with lower scores on tests of cognitive functioning and that performance can improve with iron treatment

---

39 Seshadri and Gopaldas (1989) Study 4 This is a re-report of Kayshap and Gopaldas (1987) [Ref 38]

---

40 Soemantri (1989)† Key Words Indonesia, average age 10 5 years, IDA, 3 months of therapy, educational achievement, design extended intervention, double blind, randomized, with placebo and nonanemic controls*

Importance This study assessed cognitive performance 3 months after completion of therapy, as in the Kayshap and Gopaldas (1987) study [Ref 38]

Design This was a double-blind intervention study with IDA and nonanemic control subjects randomly assigned to receive 3 months of treatment or placebo Cognitive function was assessed at baseline and 3 and 6 months after treatment

Baseline There is no statistical analysis of the preliminary data The trends seem to support the hypothesis that children with IDA have lower scores on tests of cognitive performance at baseline than the nonanemic controls

Follow-up The trends also support the existence of a beneficial effect of iron supplementation at 3 months and that the benefit persists at least 3 months after therapy is withdrawn This sustained effect is similar to that found by Kayshap and Gopaldas (1987) [Ref 38] No report is made of attempts to control for the effects of intervening variables such as maternal education or SES, which may have accounted for baseline differences

Conclusions The indication is that IDA is causally related to poorer performance on tests of cognitive development and that performance is responsive to therapy Statistical assessments are obviously required before any conclusions can be drawn from this study

---

41 Pollitt et al (1989) Key Words Thailand, age 9–11 years, IDA and ID, 4 months of therapy, Ravens IQ test and educational achievement, design extended intervention, double blind, randomized, with placebo and nonanemic controls*

Importance This study is important because it includes an ID group with whom IDA and nonanemic control children are compared and because it does not replicate the findings of Soemantri et al (1985) [Ref 36]

Design Before iron status was determined, subjects were randomly assigned to receive treatment or placebo There are similarities between this study and that of Soemantri et al (1985) [Ref 36]

Baseline At baseline, IDA children had lower IQ scores than did nonanemic control children in contrast to Soemantri et al (1985) [Ref 36] and IDA and ID children scored lower than nonanemic children on the Thai Language Test

Follow-up In contrast to Soemantri et al (1985) [Ref 36], there were no significant benefits of treatment in the IDA group compared to the placebo or nonanemic controls

Compared with the Soemantri et al (1985) [Ref 36], the treatment period was longer and the supplement was larger, however, the children were of a similar age, at least some children were moderately anemic, and the nature of the treatment was the same Unlike the Soemantri et al (1985) study [Ref 36], where only the children infected with intestinal worms were given anthelmintic drugs, the children in this study were all given anthelmintic drugs at the start Therefore the failure to demonstrate a treatment effect may have been a result of a beneficial effect, across all subjects, resulting from treating for intestinal worm infections

Conclusions IDA and ID are associated with poorer scores on tests of educational achievement and cognition, but the effect is not reversible with treatment In other studies of this age group, reversibility has been readily demonstrated The inability to replicate the study by Soemantri et al (1985) is not fully understood

Other There is an excellent and systematic discussion of the possible reasons for this negative finding and of the mediators of poor cognitive performance Also included is an incisive comment by Frank Oski concerning the important questions raised by research into iron deficiency in schoolchildren

---

42 Bruner et al (1996)† Key Words USA, age 13–18 years (girls), ID, 8 weeks of ferrous sulfate therapy, Brief Test of Attention (BTA), Symbol Digit Modalities Test (SDMT), Visual Search and Attention Test (VSAT), and Hopkins Verbal Learning Test, design extended period intervention, double blind, randomized, with placebo control

---

Importance This study assessed the effects of ID alone and has adolescent girls as its subjects, a group particularly at risk of iron deficiency It also documents a differential improvement with treatment in learning and memory but not in attention This is interesting given the suggestion from several other studies that attentional disturbances precede and mediate subsequent cognitive disturbances

Design This was a randomized, placebo-controlled intervention There was no nonanemic control group All girls were tested on three attentional measures and one learning and memory test before treatment and after 8 weeks of iron therapy

Baseline At baseline, there were no hematologic or nonhematologic differences between the two groups, indicating that the randomizing procedure had been successful

Follow-up After 8 weeks of iron or placebo, the treated group had higher Hb and serum ferritin levels than did the placebo-treated group, and they showed an improvement on the total recall test However, no improvement was seen on the attentional tests compared with the placebo group

Conclusions The lack of inclusion of an nonanemic control group means that this study offers no support for the hypothesis that ID children perform poorly on developmental tests relative to nonanemic control children However, in the absence of baseline developmental differences before treatment, the difference between groups in the amount of improvement on the learning test indicates that ID girls are indeed performing suboptimally and can only fulfill their potential when this deficiency is corrected This study is unusual in its finding that ID alone may be sufficient to result in cognitive disturbance

Other There is a brief but comprehensive discussion of causal mechanisms by which iron deficiency may alter brain function

SATELLITE ISSUES

IDA is a common nutritional disorder that affects an estimated 25% of the world's infant population (DeMaeyer and Diels-Tegman 1985) This review necessarily focused on a very narrow set of issues associated with IDA However, this section has been included to present a broad overview of satellite fields of research, references are cited throughout, and at the end of the section is a reading list intended to help direct preliminary inquiries into these related issues

Animal Studies and Biological Mechanisms

As Dallman (1987) notes, the literature on this topic has become too large to encompass in a single review Some of the literature documents the poorer performance on behavioral, cognitive, and psychomotor indexes in iron-deficient rats, paralleling the lower test scores described in the studies of humans Various theories have been put forward as to what biochemical effects ID and IDA have, and numerous hypotheses have been suggested for how these biochemical effects are expressed as the lower cognitive, motor, and behavioral test scores described in the literature and reviewed here Work has also been done in an attempt to explain not just the nature of these effects, but also the reasons behind the age and severity dependency of the effects in humans

For each hypothesis there is a huge and ever-increasing body of literature of experimental studies (primarily animal)

To even select central papers for each hypothesis is too great a task to be performed here in the context of a review primarily documenting the effects of ID and IDA on cognitive, psychomotor, and behavioral development Two papers (Chen et al 1995a,b) and two reviews of the field (Beard et al 1993, Beard et al 1995) are suggested for further reading

Beard et al (1993) present a long, comprehensive, and integrative review of the literature that attempts to provide an insight into the biochemical mechanisms at work in iron deficiency and a cautious consideration of how the direct effects of iron deficiency on emotion and cognition may be a consequence of the altered central neurotransmitter metabolism Sections of the review deal with body iron distribution, a model of body iron stores and their respective susceptibilities to iron depletion, the association of iron with disease states, and the roles of iron in brain function (oxidation, reduction, electron transport, synthesis, packaging, uptake, and degradation of neurotransmitters) Beard et al (1993) look at all the major hypotheses concerned to explain the probably interrelated biochemical effects of iron deficiency, specifically they consider the association of iron with norepinephrine, dopamine, monoamine oxidase activity, (-aminobutyric acid metabolism, endogenous opiate system alterations, and the diurnal cycle The conclusion discusses the nature of the tests of function currently used and how the sensitivity of these tests might be improved Beard et al (1993) cite 193 references, which readers can use to pursue experimental papers first hand

Adult Iron Deficiency

Although this review focuses on the effects of ID and IDA on the cognitive, psychomotor, and behavioral status of infants, preschool children, and schoolchildren, it cannot be forgotten that IDA is a life cycle issue Adult iron deficiency has direct and indirect effects on children, as well as on adults The anemia frequently observed in pregnant women is considered to be a normal physiological change, however, severe anemia seems to affect not only the physiological status of the mother, but also the fetus during pregnancy and the infant after birth (Achadi et al 1995, Felt and Lozoff 1995, Gebre Medhin and Birgegard 1981, Godfrey et al 1991, Larkin and Rao 1990, Morgane et al 1993, Tojyo 1983) At risk are the infant's normal growth and possibly also levels of activity and early emotional development

If infant IDA is truly a threat to the cognitive, psychomotor, and behavioral development of the individual, then maternal iron status during pregnancy and lactation needs to be addressed to make programs comprehensive for the prevention of IDA in infants The young women studied in the papers discussed above in the section School-Age Children and Adolescents are themselves of child-bearing age, as becomes apparent in Groner et al 's (1986) study [Ref 37] Pregnancy in adolescence, when menstruation has only recently begun, puts the individual at even greater risk of anemia (Nelson 1996)

Adults with IDA are at risk of failure to fulfill their cognitive potential, and because many new parents are themselves in their late school years, they are also subject to the developmental risks associated with iron deficiency If it is accepted that parental schooling is an important determinant of a child's cognitive development (reviewed in bibliography Deinard et al 1986, Palti et al 1983), the successful prevention and treatment of IDA in all those of a child-rearing age are highly important Iron deficiency in parents must be treated and prevented for the sake of the cognitive and physical productivity of both parents and children

Other Outcomes of Iron Deficiency

Physical Fitness Adult iron deficiency may also detrimentally affect physical fitness and productivity (Davies 1973, Viteri and Torin 1974, Basta et al 1979, Ohira et al 1979, Bhati and Seshadri 1987) The repercussions of such effects are manifold When parents are fatigued, the child-parent interaction will be impeded, and this in itself could affect children's emotional, motor, behavioral, and cognitive health Adult physical fitness itself is also a concern, not only may iron deficiency be preventing individuals from fulfilling their individual potential, but when a nation of adults suffers physical effects of iron deficiency, work productivity is compromised and the economic potential of the nation goes unfulfilled

Infections There is extensive experimental literature describing the effects of iron deficiency on processes involved in host defence mechanisms, and it is commonly thought that infants and children who have moderate to severe iron deficiency tend to have more infections than those who do not However, although this widespread belief exists, there is some clinical and much experimental evidence to the contrary For a comprehensive list of experimental studies, readers are directed to the reference sections of these reviews (Pearson and Robinson 1976, Brock and Mainou-Fowler 1986, Dallman 1987)

Not only may iron deficiency increase the risk of infection, but certain infections (specifically worm infections such as schistosomiasis) may also result in IDA Dallman (1987) begins by describing the laboratory abnormalities in immune function that appear the most convincing and distinguishes these from other components of the immune system about which there is uncertainty or that seem to be normal during iron deficiency He then categorizes the epidemiologic studies aimed at determining whether there is an increased prevalence of infection in individuals with iron deficiency He looks at cell- and antibody-mediated immunity and phagocytosis Although most of the 59 studies reviewed deal with human subjects, there is also a short section on the findings of animal studies

Pearson and Robinson (1976) review studies indicating that an excess of iron facilitates growth and multiplication of a number of microorganisms in various biogenic fluids, specifically studies in which sickle-cell anemia, overwhelming sepsis, and salmonellosis are associated with hyperferremia They also review the literature concerned with the connection between iron deficiency and increased susceptibility to infection There are subsections on phagocytic function, cell-mediated immunity and iron deficiency, and iron deficiency as associated with clinical infection Pearson and Robinson cite 119 references

Confounding and Covarying Factors

That iron deficiency can impede cognitive development has been a very controversial hypothesis, especially in the light of the data concerning the effects of iron deficiency on infants, where the causal nature of the association postulated cannot be concluded because of the lack of iron treatment effects on infant cognition and behavior It has been frequently suggested that some other factor closely related to or covarying with iron deficiency is responsible for the documented poorer developmental test scores

As mentioned above in the context of the implications of adult iron deficiency, parental schooling may well be a stronger determinant of infant cognitive development than iron deficiency Parents with less education were suggested to covary with an environment in which nutritional iron is not readily available The elements here are inextricably entangled low SES and home environmental stress may be responsible for pressure to leave school early or for lack of adequate education accounting for lower educational achievement among children who go on to become parents themselves (Willerman et al 1970, Lieblichet al 1972, Czajka-Narins et al 1978, Escalona 1982) Low-SES parents will have a lower income, less per capita to spend on food, and less time to interact in a positive way with their children and so could have children who are nutritionally, behaviorally, and educationally disadvantaged

School absence has been suggested to be more responsible than nutritional status for lower cognitive test scores in children (Powell and Grantham-McGregor 1980) However, although there may be many determining factors of increased absenteeism among children, including factors again associated with a low-SES background, one factor may well be poor health resulting from nutritional deficiencies School absence is particularly worrisome because children's cognitive and social development depends largely on the provision of adequate educational stimulation.

With all of these factors, it is probably misleading to suggest that any one potential cause of lower scores on tests of development confounds the involvement of another Such disadvantageous factors almost necessarily coexist and likely have an additive and even possibly multiplicative effect For example, when undernourished children go to school without breakfast, the adverse effects on cognitive function are greater than in well nourished children (Simeon and Grantham-McGregor 1989, Simeon et al 1994, Chandler et al 1995, Pollitt 1995)

Given the complex interrelation of low SES, poor nutrition, lack of educational and psychosocial stimulation, and increased illness it may be that iron treatment or nutritional supplementation is not enough Rather, an all-embracing program of environmental enrichment may be more appropriate (Lozoff 1990, Grantham-McGregor et al 1991, Lansdown and Wharton 1995, Brown and Pollitt 1996)

References

Achadi EL, Hansell MJ Sloan NL Anderson MA (1995) Women s nutritional status iron consumption and weight gain during pregnancy in relation to neonatal weight and length in West Java Indonesia Int J Gynaecol Obstet 48 S103 S119

Basta S Soekirman S, Karayadi D, Scrimshaw NS (1979) Iron deficiency anemia and the productivity of adult males in Indonesia Am J Clin Nutr 32 916 925

Beard JL Connor JD, Jones BC (1993) Brain iron location and function Prog Food Nutr Sci 17 183 221

Beard JL Zhan CS Brigham DE (1995) Growth in ID rats Proc Soc Exp Biol Med 209 65 72

Bhati D Seshadri S (1987) Anaemia undernutrition and physical work capacity of young boys Indian J Paediatr 24 133 139

Brock H Mainou Fowler T (1986) Iron and immunity Proc Nutr Soc 45 305 315

Brown L Pollitt E (1996) Malnutrition poverty and intellectual development Sci Am February 26 31

Chandler AM Walker SP Conolloy K Grantham McGregor SM (1995) School breakfast improves verbal fluency in undernourished Jamaican children J Nutr 125 894-900

Chen Q Beard JL Jones BC (1995) Abnormal rat brain monoamine metabolism in iron deficiency anemia J Nutr Biochem 6 486 493

Chen Q Connor JR Beard JL (1995) Brain iron transferrin and ferritin concentrations are altered in developing iron deficient rats J Nutr 125 1529 1535

Czajka Narins DM Haddy TB Kallen DJ (1978) Nutrition and social correlates in iron deficiency anemia Am J Clin Nutr 31 955-960

Dallman PR (1987) Iron deficiency and the immune response Am J Clin Nutr 46 329 334

Dallman PR (1986) Biochemical basis for manifestation of iron deficiency Annu Rev Nutr 6 13 40

Davies CTM (1973) Physiological responses to exercise in East African children II The effects of schistosomiasis anaemia and malnutrition Environ Child Health 19 2 115 119

DeMaeyer E Diels-Tegman M (1985) The prevalence of anaemia in the world World Health Stat Q 38 302 316

Escalona SK (1982) Babies at double hazard early development of infants at biologic and social risk Pediatrics 70 670 676

Felt BT Lozoff B (1995) Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development J Nutr 126 693 701

Gebre Medhin M Birgegard G (1981) Serum ferritin in Ethiopian mothers and their newborn infants Relation of iron intake and socio economic conditions Scand J Haematol 27 247 252

Godfrey KM Redman CWG Barker DJP Osmond C (1991) The effect of maternal anaemia on the ratio of fetal weight to placental weight Br J Obstet Gynaecol 98 886 891

Grantham McGregor SM Powell CA Walker SP Himes JH (1991) Nutritional supplementation psychosocial stimulation and mental development of stunted children the Jamaican study Lancet 338 1 5

Lansdown R Wharton B (1995) Iron and mental and motor behaviour in childhood iron nutritional and physiological significance Chapman and Hall New York pp 65 180

Larkin EC Rao GA (1990) Importance of fetal and neonatal iron adequacy for normal development of central nervous system In Dobbing J (ed) Brain behaviour and iron in the infant diet Springer-Verlag London pp 43 62

Lieblich A Ninio A Kugelmass S (1972) Effects of ethnic origin and parental SES on WPPSI performance of pre school children in Israel J Cross Cult Psychol 3 159 168

Lozoff B (1990) Has iron deficiency been shown to cause altered behavior in infants? In Dobbing J (ed) Brain behaviour and iron in the infant diet Springer-Verlag, London pp 107 131

Morgane PJ, Austin-LaFrance A Bronzino J et al (1993) Prenatal malnutrition and development of the brain Neurosci Biobehav Rev 17 91 128

Nelson M (1996) Anaemia in adolescent girls effects on cognitive function and activity Proc Nutr Soc 55 359 367

Ohira Y Edgerton VR, Gardner GW, et al (1979) Work capacity heart rate and blood lactate responses to iron treatment Br J Haematol 41 365 72

Pearson HA Robinson JE (1976)The role of iron in host resistance Adv Pediatr 23 1 3

Pollitt E (1995) Does breakfast make a difference in school? J Am Diet Assoc 95 1134-1139

Powell C Grantham McGregor SM (1980) The associations between nutritional status school achievement and school attendance in twelve year old children at a Jamaican school W I Med J 29 247 253

Simeon DT Grantham McGregor S (1989) Effects of missing breakfast on the cognitive functions of school children of differing nutritional status Am J Clin Nutr 49 646 653

Simeon DT Callender J Wong M et al (1994) School performance nutritional status and Trichuriasis in Jamaican school children Acta Paediatr 83 1188 1193

Tojyo H (1983) Effect of different intensities of iron deficient anemia in pregnant rats on maternal tissue iron and fetal development J Nutr Sci Vitaminol (Tokyo) 29 339 351

Viteri F Torin B (1974) Anaemia and physical work capacity Clin Haematol 3 609 626

Willerman L Broman SH (1970) Infant development preschool IQ and social class Child Dev 41 69 77

World Health Organization (1972) Nutritional anaemia report of a WHO group of experts Technical Report Series no 503 Geneva WHO

READING LIST

Reviews on the effects of ID and IDA on mental and motor performance, cognition, behaviour and school achievement in children

Avramidis L (1983) Developmental deficits in iron deficient infants J Pediatr 103 339 340

Beard J (1995) One person s view of iron deficiency development and cognitive function Am J Clin Nutr 62 709 710

Brown JL Pollitt E (1986) Malnutrition poverty and intellectual development Scientific American Feb 26 31

Deinard AS Murray MJ Egeland B (1976) Childhood iron deficiency and impaired attentional development or scholastic performance Is the evidence sufficient to establish causality? J Pediatr 88 162

Galler JR ed (1984) Nutrition and Behavior Plenum Press, New York

Grantham McGregor SM (1990) Malnutrition mental function and development In Suskind RM Lewinter Suskind L (eds) The Malnourished Child Vol 19 Raven Press New York pp 197 212

Horowitz FD (1989) Using developmental theory to guide the search for the effects of biological risk factors on the development of children Am J Clin Nutr 50 509 597

Lansdown R Wharton B (1995) Iron and mental and motor behaviour in childhood In Iron Nutritional and Physiological Significance Clapham and Hall pp 65 180

Leibel RL Pollitt E Kim I Viteri FE (1982) Studies regarding the impact of micronutrient status on behaviour in man iron deficiency as a model Am J Clin Nutr 35 1211 1221

Lozoff B (1989) Methodologic issues in studying behavioural effects of infant iron deficiency anemia Am J Clin Nutr (suppl) 50 641 654

Lozoff B (1990) Has iron deficiency been shown to cause altered behaviour in infants? In Dobbing J (ed) Brain, Behaviour and Iron in the Infant Springer Verlag London pp 107 131

Lozoff B (1994) Iron deficiency and infant development J Pediatr 125 577 578

Nelson M (1996) Anemia in adolescent girls effects on cognitive function and activity Proc Nutr Soc 55 359 367

Oski FA (1993) Iron deficiency in infancy and childhood New Eng J Med 329 190 193

Pollitt E Leibel RL (1976) Iron deficiency and behaviour J Pediatr 88 372 281

Pollitt E Gorman K (1990) Long term developmental implications of motor maturation and physical activity in infancy in a nutritionally at risk population In Schurz B, Scrimshaw NS (eds) Activity energy expenditure and energy requirements of infants and children Proceedings of International Dietary Energy Consultative Group Lausanne, Switzerland (IDECG) pp 279-296

Pollitt E Metallinos Katsaras E (1990) Iron deficiency and behaviour constructs methods, and validity of the findings In Wurtman RJ Wurtman JJ (eds) Nutrition and brain Vol 8 Raven Press New York

Read MS (1975) Anaemia and behaviour nutrition growth and development Mod Probl Pediatr 14 189-202

Scrimshaw NS (1984) Functional consequences of iron deficiency in human populations J Nutr Sci Vitaminol 30 47 63

Simeon DT Grantham McGregor S (1990) Nutritional deficiencies and children s behaviour and mental development Nutrition Research Reviews 3 1 24

APPENDIX A

Tabulated summary of studies investigating the effects of iron deficiency (with and without anemia) on the development of infants and young children, preschool children, and school-age children and adolescents

Studies of the effects of iron deficiency (with and without anemia) on cognitive motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow up	Measures	Results at baseline	Results at follow up period
			SHORT TERM EFFECTS OBSERVATIONAL STUDIES				
1 Deinard et al 1981 USA	15 months	double blind observational	ID severe n=34 (SF≤9 ng/mL) [mean SF 8 85±1 58] ID mild n=21 (SF 10 19 ng/mL) [mean SF 16 10±2 91] NA n=157 (SF⊕20 ng/mL) [mean SF 50 72±22 8] nonanemic=Hct >34%		BSID habituation U/HSPD	None noted overall ID severe group shows a systematic pattern of difficulties on the IBR	
2 Johnson and McGowan, 1983 Study 1 USA	12 months	observational NA control	IDA n=31 (Hb<10 5 g/dL) [mean Hb 8 7±0 9 moderate] NA n=31 (Hb⊕11 5) [mean Hb 12 2 g/dL]		tests of mother child interaction activity reactivity emotional tone attention span	No significant group differences on any of the measures	
2 Johnson and McGowan, 1983 Study 2 USA	12 months	double blind observational	IDA n=25 (Hb<10 5 g/dL) [mean Hb 8 7±0 9 moderate] NA n=25 (Hb⊕11 5) [mean Hb12 2 g/dL		IBR of BSID	No significant differences noted between groups	

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
			SHORT TERM EFFECTS OBSERVATIONAL STUDIES				
3 Grindulis et al 1986 UK	22 months	double blind observational NA control	IDA n=80 (Hb < 11 0 g/dL) [not given] NA n=54 (Hb > 11 0 g/dL)		Sheridan developmental sequences, testing psycho motor develop ment	IDA children showed significant difficulties on fine motor and social development items	
4 Lozoff et al 1986 Guatemala	6 24 months	double blind observational NA control	IDA n=21 (Hb<10 5 g/dL plus 2 of 3 abnormal biochemical measures) [mean Hb 9 6 g/dL] NA n=21 (Hb⊕12 0 g/dL) [mean Hb 12 6 g/dL]		-assessment of behavior frequencies and quality by use of a computer compatible even recording system -BSID	After other variables were controlled for the anemic infants initiated and maintained more contact with their mothers than did the NA control infants, and the mothers of IDA infants spent less time beyond arm s length of their children were less likely to break close contact with their children, and were more likely to reestablish close contact	
			SHORT TERM EFFECTS INTERVENTION TRIALS				
5 Oski and Honig 1978 USA	9 26 months	double blind intervention IDA subjects randomly assigned to treatment or placebo no NA control	IDA n=24 (Hb<10 5 g/dL plus two measures of iron deficiency) [iron treated group Hb range 6 2 10 3 Hb mean = 8 85±0 86 placebo treated group Hb range 7 6 10 2 Hb [mean 8 73 ± 1 09]	5 8 days of IM iron dose calculated according to child s specific hematologic status	BSID	No significant differences noted between treatment and placebo group on MDI or PDI All subjects showed similar difficulties on IBR and poorer gross and fine motor coordination	Iron treated IDA children improve on MDI but this improvement was not significantly different from the improvement in the placebo treated group Initial Hb (not other hematologic measures) correlated with amount of MDI improvement within this group Nonsignificant change noted on PDI Iron treated IDA children improve on reactivity (IBR) and on fine and gross motor coordination

6 and 7 Lozoff et al 1982 (b and c) Guatemala	6 24 months	double blind intervention IDA and NA control children randomly assigned to receive treatment or placebo	IDA n=28 (Hb≤10 5 g/dl plus three abnormal biochemical measures) [mean Hb 9 5 ± 0 9 nonspecifiable] NA n=40 (Hb⊕12 0 g/dL plus three normal biochemical measures)	1 week of ferrous ascorbate dose calculated according to each child s specific hematologic status	BSID	IDA children s MDI scores were significantly lower in 19 24 month olds than those of the NA children of the same age Severity of IDA was positively associated with the extent of the difficulty experienced on motor tasks IDA children s PDI scores were nonsignificantly lower in all age subgroups than those of NA children Compared with infants aged 6 18 months IDA children at 19 24 months showed disproportionate difficulty on language items and on 11 of 12 items shown to predict later IQ	Previous deficits persisted in iron status groups All groups improved their MDI scores with no differences in amount of improvement between iron and placebo treated infants
8 Lozoff et al 1982a (same study as Lozoff et al 1982 b and c above)	see above	see above	see above	see above	BSID IBR	IDA children show a consistent pattern of difficulties on the IBR	Behavioral differences between IDA and NA infants disappeared at follow up in both iron treated and placebo treated IDA subjects
9 Walter et al 1983 Chile	15 months	double blind intervention IDA ID and NA control children given treatment (no placebo control)	IDA n=10 (Hb <11 0 g/dL >8 5 g/dL plus two abnormal biochemical measures and treatment response) [mean Hb 9 8 ± 0 8 nonspecifiable] ID n=12 (Hb⊕11 0 g/dL and at least one abnormal biochemical measure with treatment response) NA n=15	10 days of 3 4 mg ferrous sulfate/kg per day	BSID	IDA children scored lower on MDI than did control children No differences noted between groups on PDI IDA children were more unhappy than were other groups	IDA infants improved significantly on MDI NA control subjects show no significant improve ment on MDI Improvement on MDI in the IDA group coincided with IBR improvements in cooperativeness and attention span Only ID children with two or more abnormal biochemical measures showed improvement No improvement noted on PDI

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
SHORT-TERM EFFECTS INTERVENTION TRIALS							
10 Oski et al 1983 USA	9 12 months	double blind intervention ID, Idepl, and NA subjects matched on sex and color given treatment no placebo control	ID (biochemical and cellular) n=8 (⊕11 0 g/dL + abnormal biochemical measures and abnormal MCV) [mean SF = 9 8±2 0 nonspecifiable severity] ID(biochemical) n=10 (⊕11 0 g/dL + 3 abnormal biochemical measures) [mean SF = 10 2±1 3 nonspecifiable severity] Idepl n=10 (⊕11 0 g/dL + abnormal SF) NA n=10	7 days of 50 mg iron dextran IM	BSID	No differences noted between groups on MDI	MDI scores increased significantly in all ID children but not in NA children or Idepl children No patterning of areas of improvement noted on MDI or IBR
11 Lozoff et al 1985 Guatemala	6 24 months	double blind intervention IDA and NA infants randomly assignee to iron or placebo	IDA n=28 (Hb<10 5 g/dL plus two of three abnormal biochemical measures) [not given] NA n=40 (Hb⊕12 0 g/dL)	iron or placebo twice daily for 1 week	BSID (particular focus on the test affect and task orientation factors of the IBR)	IDA infants showed more behavioral disturbance and lower MDI and PDI scores than the did NA infants The lower MDI scores were found in the infants with abnormal ratings on test affect The lowei PDI scores were found in the infants with abnormal ratings on test affect and task orientation Hb was directly related to abnormal IBR ratings and only indirectly related to MDI scores	There was no evidence of a treatment effect after 1 week The affectively disturbed IDA infants tended to improve their behavioral ratings regardless of treatment group Affectively disturbed IDA infants whose IBR ratings improved also improved their MDI scores There was no differential improvement in PDI scores

12 Aukett et al 1986 UK	17 19 months	double blind intervention DA subjects randomly assigned to receive treatment or placebo no NA control	IDA + iron and vitamin C n=48 (Hb < 11 0 g/dL) [nonspecifiable severity] IDA + vitaminC n=49 (Hb<11 0)	2 months of therapy with 24 mg ferrous sulfate 10 mg vitamin C or both	Denver developmental screening test for psychomotor development	Baseline Denver scores were not assessed	Significantly more of the children whose Hb values rose more than 2 g/dL achieved the standard change in Denver score than did children whose Hb values did not rise
13 Lozoff et al 1987 Costa Rica	12 23 months	double blind intervention randomized assignment of IDA ID Idepl, and NA control children to receive treatment or placebo (partial)	IDA n=52 (Hb≤10 5 g/dL plus 2 abnormal biochemical measures) [mean Hb 9 5 ± 0 1 moderate IDA] Intermediate ID n=45 (Hb >10 6<11 9 + 2 abnormal bio chemical measures) ID n=21 (Hb⊕12 0 + two abnormal biochemical measures) Idepl n=28 (Hb⊕12 0 + abnormal serum ferritin) NA n=35 (Hb⊕12 0 + normal biochemical measures)	1 week of $FeSO_4$ oral or parenteral intervention IDA and intermediate children assigned to receive oral or parenteral iron oi placebo NA children assigned to receive oral iron or placebo 12 weeks of $FeSO_4$ oral iron for all iron deficient children previously given oral iron, all parenterally treated or iron sufficient children given placebo	BSID	within the anemic group the authors distinguished between moderately and mildly anemic children moderately anemic infants (Hb≤10 0) scored lower on the MDI than all other groups both mild (Hb 10 0 10 5) and moderately anemic infants scored lower than the other groups on the PDI anemic children consis tently failed on certain items of the MDI and PDI scales	At 1 week no differences noted on MDI and PDI between parenteral and orally treated groups, significant effect of iron therapy seen on iron status and all groups improved their MDI scores, regardless of their iron status or whether they were given treatment or placebo At 12 weeks there was no improve ment in MDI scores in the anemic group (mild or moderate) moderately anemic children showing no Hb correction or persistence of abnormal biochemical measures still showed significantly lower PDI scores than did mildly anemic children anemic children whose Hb value was corrected showed PDI score improvement and were no longer different from the NA group mildly anemic children were more likely to show hematologic correction and improvements in the IDA group could not be compared with effects in a placebo group because no such group was included in the design

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow-up period
			SHORT TERM EFFECTS INTERVENTION TRIALS				
14 Walter et al 1989 Chile	0 15 months	double blind intervention IDA ID and NA children assigned to receive treatment or placebo for the first 10 days after which time all children received treatment IDA n=39	(Hb<11 0 g/dL+ two or more abnormal biochemical measures an abnormal cellular index and a response to therapy of⊕1 g/dL) [mean Hb=10 0 ± 0 9 nonspecifiable] ID n=127 (Hb⊕11 0 g/dL plus abnormal biochemical measures) NA n=30 (Hb⊕11 0 g/dL plus normal biochemical measures with lack of response to supple mentation)	at age 9 months hematologic assessment made at age 12 months 3 months of 0 6 mL ferrous sulfate suspen sion given three times a day with assessments made at 10 days and 3 months	BSID	At age 12 months IDA children had lower MDI and PDI score than did NA control and ID children the authors reported a sigmoid distribution of MDI scores as a function of increasing Hb with the lowest developmental test scores to be found in infants with the lowest Hb infants with Hb > 10 9 showed no evidence of poorer performance, there was patterning on MDI PDI and IBR scales there was a significant effect of duration and severity of anemia, i e children who at initial developmental assessment had been anemic 3 months earlier had much lower scores than did IDA children who had become anemic in the past 3 months at the age 12-months assessment children who had become anemic in the past 3 months were less severely anemic than children who were anemic at initial assessment	At the 10 day assesment all groups improved on MDI and PDI regardless of iron status or whether they were given placebo or iron treatment and no change in IBR At the 3 months assess ment there were no changes in any of the children s BSID scores (including IBR ratings) between follow up 1 and follow up 2 and IDA children were still scoring low on language items and on showing shoes clothing or own toy and were less able to stand from sitting or stand on left foot with help

15 Idjradinata and Pollitt 1993 Indonesia	12 18 months	double blind intervention IDA ID, and NA subjects randomly assigned to receive treatment or placebo	IDA n=50 (Hb≤105 g/L + two abnormal biochemical measures) [iron treated children s Hb mean =95 7±1 1 placebo treated children s Hb mean = 98 0±1 0 moderate IDA] ID n=29 (Hb⊕120 g/L + two abnormal biochemical measures) NA, n=47 (Hb⊕120 g/L + normal biochemical measures)	4 months of 3 mg/kg per day of oral ferrous sulfate	BSID	IDA children scored lower than did ID and NA children on MDI and PDI No significant difference noted between ID and NA children IDA children s mothers had achieved significantly lower maximum school grade than had mothers in ID or NA groups	-Iron treated IDA children showed significant MDI and PDI improvements The improvements on MDI and PDI in the iron treated IDA children were larger than improvements seen in NA and IDA placebo treated children The baseline differences in MDI between iron treated IDA children and ID or NA children were eliminated, thus the poorer test performance observed at baseline was reversed There were no significant differences in the amount of MDI and PDI improve ment between iron or placebo treated ID children Correction of Hb values noted in iron treated IDA and ID children
16 Lozoff et al (1996b) Costa Rica	12–23 months	Double blind intervention IDA gives treatment NA randomly assigned to receive treatment or placebo	IDA n=32 (Hb ≤100 g/L + two of three abnormal biochemic measures) NA n=54 (Hb ⊕12 5 g/L)	6 months of oral ferrous sulphate given 3mg/kg per dose, twice a day	BSID & IBR	At baseline IDA infants scored significantly lower (mean 6 1 points) than NA on MDI No significant difference on PDI IDA infants on IBR were significantly more fearful, unhappy and hesitant with examiner	Good hematological response to treatment Differences in MDI between IDA and NA remained at the 3 and 6 months follow up No change in PDI No differences in IBR between IDA and NA The significant improvement in IBR is not considered to benefit directly from iron treatment

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
SHORT-TERM EFFECTS INTERVENTION TRIALS							
17 Heywood et al 1989 Papua New Guinea	1 year	double blind intervention IDA children randomly assigned at age 2 months to receive treatment or placebo no NA control	IDA, malaria positive + iron n=18 [mean Hb 84 1 g/dL range 70 5 97 6 moderate] IDA malaria negative + iron n= 30 [mean Hb 100 5 g/dL range 92 3 108 9 unspecifiable] IDA malaria positive + placebo n= 11 [mean Hb 80 0 g/dL range 65 9 94 1 moderate] IDA malaria negative + placebo n=36 [mean Hb 92 9 g/dL range 80 2 105 5 unspecifiable]	1 x 3 mL IM dextran treatment at age 2 months with tests of attention given at age 1 year	attention total fixation time mean fixation time habituation dishabituation	No baseline assessment made of attention	Iron treated IDA malaria negative infants had significantly longer total fixation times than did placebo treated malaria negative infants

SHORT TERM EFFECTS PREVENTATIVE TRIALS							
18 Moffatt et al 1994 Canada	2 15 months	double blind preventative infants randomly assigned at age 2 months to receive iron fortified or regular formula assessments at 6 9, 12 and 15 months	6 months n=225 regular [Hb 107 7±5 3 nonspecifiable] fortified [Hb 113 5±5 3] 9 months n=204 regular [Hb 111 6±5 6 nonspecifiable] fortified [Hb 116 4±5 6] 12 months n=186 regular [Hb 111 8±5 7 nonspecifiable] fortified [Hb 117 5±5 6] 15 months n=154 regular [Hb 115 1±5 7 nonspecifiable] fortified [Hb 118 6±5 7]	13 months of iron fortified formula (12 8 mg) or regular formula (1 1 mg)	BSID (including IBR), attention paid to the test affect and task orientation clusters of items		Overall all measures of iron status were significantly different between the two groups and mental development and behavior were not affected At 6 months PDI values were similar in all groups At 9 months PDI scores for the regular formula group fell significantly and gave this group a score significantly lower than that of the fortified formula group At 12 months intergroup PDI differ ences persisted At 15 months the group means were closer again and the difference was nonsignifi cant
19 Lozoff et al 1996a Chile	6 12 months	double blind preventative infants randomly assigned at age 6 months to receive supple mental iron or no added iron until age 12 months	supplemental iron n=625 no supplemental iron n=319 anemia [Hb< 110 g/L + 2 of three abnormal biochemical measures]	6 months of supplemental iron	BSID	No significant differences noted between the supplemented and nonsupplemented groups	At 12 months the supplemented infants had less anemia and less iron deficiency than did the nonsupplemented groups There were no significant differences in BSID scores between the groups

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow up	Measures	Results at baseline	Results at follow-up period
			LONG-TERM EFFECTS OBSERVATIONAL STUDIES				
20 Palti et al 1985 Israel	10 13 years	single blind observational children intermediate and NA at 9 months followed yearly until 10 13 years and assessed	At 9 months intermediate n=20 (Hb<10 5 g/dL) [not given] NA n=56 (Hb>11 5 g/dL) [not given]		subsection of the Shaefer Classroom Behavior Inventory with educational achievement items		After maternal education and sex of the child were controlled for, children IDA at 9 months scored lower on educational achievement and positive task orientation with no effect on negative task orientation or mood Maternal education and sex of the child were also significant predictors of educational achievement task orientation and mood
21 Wasserman et al 1992 Yugoslavia	2 years	prospective MDI decrements at 24 months measured as a function of Hb decreases at 6, 12 18 and 24 months	n = 392 Hb measurements at four time periods not given		MDI		Significant MDI decrements at 18 24 months predicted by Hb decrease of 2 g/dL at 18 months MDI decrement at 24 months predicted better by Hb decrease of 2 g/dL at 12 and 18 months than by Hb decrease at 24 months
22 Hurtado 1995	0 10 years	preventative no note made of groups randomization procedure or use of a placebo	n=5411 groups not described	dose or length of treatment not given	test of cognitive development		At 10 years iron deficiency was associated with poorer performance on a cognitive test with a dose response relation between Hb and performance and interaction with maternal education reported

LONG TERM EFFECTS FOLLOW UP OF INTERVENTION TRIALS

23 Palti et al 1983 Israel	0 5 years	intervention children with IDA at 9 10 months given treatment no placebo control IDA and NA children given neither treat ment nor placebo developmental assessments conducted at 2 3 and 5 years as a function of hematology at 9 months	IDA moderate at 9 months 3 years n=32 5 years n=29 (Hb≤9 9) [moderate] IDA mild at 9 months 2 years n=84 5 years n=52 (Hb 10 10 9)[mild] IDA at 9 months 3 years n=149 5 years n= 99 (Hb 11 11 9) iron sufficient at 9 months 3 years n=123 5 years n= 59 (Hb⊕12 0)	2 years (baseline) 3 years 5 years	BLDQ at 2 years Mili Israeli IQ Test at 3 years Wechsler WPPSI (Israeli version)	(Baseline is taken as developmental measure ments at age 2) Initially moderate IDA children scored lower on BLDQ than did other three groups but this difference was not significant after maternal education and birth weight were controlled for	At 3 years the initially moderately IDA infants still scored lower than did all other groups this time on the Mili test but again the between groups difference only approached significance after maternal education and birth weight were controlled for At 5 years the initially IDA infants still scored lower than all othei groups but at 5 yeais these differences between groups on IQ were significant even after maternal education and birth weight were controlled for
24 Walter et al 1990 (abstract) Chile	5 years	see Walter et al 1989 above note that it is not clear whether the assessments of iron status at 4 years or the developmental assessments at 5 years were double blind	IDA n=43 [severity of anemia in infancy was not specifiable] NA n=29	see Walter et al 1989 above	SBIQ Bruininks Oseretsky fine/ gross motor assess ment Illinois psycholinguistic assessment visual motor integration Woodcock educational preschool scale	see Waltei et al 1989 above	Infants with IDA at 12 months of age (who showed poorer develop mental test performance at the time of original assessment) showed persistence of lower test scores at age 5 years regardless of the hemato logic correction that occurred after 3 months of subsequent iron therapy
25 Lozoff et al 1991 Costa Rica follow up of subjects from Lozoff et al 1987	5 years	see Lozoff et al 1987 above note that is not clear whether the 5 year follow-up assessment was double blind	initially moderately IDA initially iron deficient before and after therapy initially iron deficient corrected by therapy	5 years	Woodcock Johnson psychoeducational battery test of visual motor integra tion Goodenough Harris Draw a Man test Bruininks Oseretsky test of motor profi ciency WPPSI	see Lozoff et al 1987 above	Infants originally with moderate IDA or mild IDA uncorrected by therapy showed persistently lower scores on developmental tests at age 5 years

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in infants and young children (6–24 months)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
LONG-TERM EFFECTS PREVENTATIVE TRIALS							
26 Cantwell 1974 (abstract) USA	0 7 years	double blind preventative no note made of randomization procedure no placebo control	neonatal IM iron dextran NA at 6 18 months n=28 IDA, n=32 (criteria not given) [Hb range = 6 1 9 5 moderate]	IM dextran treatment dose and length of treatment not specified, developmental assessments made at 6 7 years	neurological evaluation SBIQ		At 6 7 years children who were IDA as infants showed clumsiness balancing on one foot tandem walking, and repetitive hand and foot movements and were more inattentive and hyperactive and the Stanford Binet mean score for IDA children was 92 and for NA children was 98

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in preschool children (2–5 years)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
INTERVENTION TRIALS							
27 Pollitt et al 1978 USA	44 45 months	double blind intervention ID and NA control given treatment	ID n= 23 (criteria not given) [mean Hb =11 5, MCV=79 7 SI/TIBC ratio =13 4 serum iron= 35 0 severity not specifiable] NA n= 23 (criteria not given)	4 months of iron therapy (dose not specified)	three discrimi nation learning tests two short term memory tests four oddity learning tasks	ID children perform worse on tests of their attention and memory control processes but not on tests of the capacity of the structures themselves	Differences in scores between groups at baseline eliminated
28 Pollitt et al 1983 USA	3 6 years	intervention IDA children given treatment NA control children not treated no placebo control	IDA n=15 NA control n=15	3 months of oral iron	discrimination learning short term memory oddity learning	IDA children performed worse than NA control on three discrimination learning tests	After treatment the differences between the IDA and NA control children had been eliminated
29 Deinard et al 1986 USA	18 60 months	double blind intervention IDA given treatment only ID group assigned to treatment or placebo and NA group given placebo only NA control matched twice to experimental group on 1)maternal education sex and age and 2) baseline MDI score	IDA, n=25 (≤11 0 g/dL plus three abnormal biochemical measures and abnormal cellular index) [mean group Hb = 10 4 g/dL SD not given but potentially categorizable as mild anemia] ID n=45 (⊕11 0 g/dL plus two abnormal biochemical measures and abnormal cellular index) NA n=? (⊕11 0 g/dL plus three normal biochemical measures and normal cellular index)	6 months of oral iron (6 mg/kg per day) with follow up assessments at 3 months and 6 months	BSID MDI for children under age 2 years SBIQ forms L M for children over age 2 years	No significant difference noted between the IDA children and their NA maternal education control on MDI and SBIQ There were no significant differences between IDA children and their NA controls matched on maternal education on 8 of 10 IBR measures The IDA group was more unhappy and less responsive to their environment than were their NA controls matched on maternal education Similar patterns emerged between the IDA children and their controls matched for MDI baseline	At 3 months the IDA group did not improve on MDI and SBIQ neither of the ID groups improved on MDI and SBIQ -overall all NA control groups tended to increase their scores on the MDI and SBIQ from baseline creating significant differences between the ID and IDA groups and their NA controls At 6 months IDA children showed no MDI and SBIQ increase, ID treated children showed no increase over baseline in MDI and SBIQ ID children given placebo increased on MDI SBIQ, and -again, NA control children tended to significantly increase their scores

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in preschool children (2–5 years)

Author	Age	Study design	Groups, n (hematologic selection criteria) [hematologic group mean and mild vs moderate classification]	Length of treatment and follow-up	Measures	Results at baseline	Results at follow up period
			INTERVENTION TRIALS				
30 Pollitt et al 1986 Guatemala	3 6 years	intervention IDA and NA control given treatment no placebo control	IDA n=25 (Hb≤10 g/dL plus one abnormal biochemical measure and Hb response to therapy >2 g/dL) [mean Hb = 8 96 ± 0 98 moderate IDA] NA n=25 (Hb >11 g/dL plus one normal biochemical measure and no Hb response to therapy)	11 12 weeks of 30 mg/kg per day oral ferrous sulfate	three discrimi nation learning tests two short term memory tests four oddity learning tasks	Discrimination learning IDA children needed more trials to criterion no differences on oddity learning no differences on memory	Discrimination learning IDA group improved on trials to criterion after treatment eliminating the baseline differences between IDA and NA groups on trials needed to reach criterion Oddity learning both groups improved the NA group improved significantly more than the IDA group and there were no significant differences on memory
31 Soewondo et al 1989 Indonesia	NA mean age 57 5 months IDA mean age 54 2 months	double blind intervention IDA ID and NA subjects randomly assigned to receive treatment or placebo	IDA n=49 (Hb <110 g/L plus two abnormal biochemical measures) [group Hb mean = 106 0 ±0 7 mild] ID n=60 (Hb⊕110 g/L plus two abnormal biochemical measures) NA n=70 (Hb⊕110 g/L plus two normal biochemical measures)	8 weeks 50 mg oral elemental Fe	2 x two choice discrimination learning tests 3 x oddity learning tasks PPVT	Among the small number of children who reached learning criterion on reversal discrimination color tasks there was a significant difference between groups in number of trials to criterion with NA children learning faster NA children performed better than IDA children on repeated twice and thrice variations of the oddity learning task	Of children who reached criterion on trials to learning on color discrimi nation the IDA+iron children learned more quickly than did the NA+ iron children On the repeated twice and thrice versions of the oddity learning task iron treated IDA children performed better than iron treated NA children There was no significant improvement in the performance of the IDA children treated with placebo Iron treated IDA children showed significant improvement in all iron measures but the improvement was small and it is probable that ID was not fully reversed

Studies of the effects of iron deficiency (with and without anemia) on cognitive motor, and behavioral indexes in school age children and adolescents (5–16 years)							
Author	**Age**	**Design**	**Groups, n (hematologic selection criteria) [hematologic group means]**	**Baseline to follow-up**	**Measures**	**Baseline differences**	**Differences at follow up**
OBSERVATIONAL STUDIES							
32 Webb and Oski 1973a USA	12 14	observational trial with no double blind procedure data were analyzed as a function of age subclass (12 13 and 14 years)	IDA n=92 (Hb 10 1 11 4 g/dL) [lowest Hb was 10 6 ± 0 4 mild anemia] NA n=101 (Hb 14 0 14 9 g/dL)		Iowa Tests of Basic Skills levels A F form 3	IDA children scored lower than did NA children The older anemic males showed a progressive departure from their controls	
33 Webb and Oski 1973b USA abstract report of Webb and Oski 1973 above	same as Webb and Oski 1973 above				Peterson Quay Behaviour Problem Checklist visual after image task	Anemic males showed more conduct disturbance than did their controls including distractibility (see Soemantri et al 1985 above for a similar concentration finding) overactivity disruptiveness and negativism IDA subjects showed longer latency to after image report than did control subjects	
INTERVENTION TRIALS							
34 Seshadri et al 1982 India Study 1	5 8 years	intervention before disaggregation into IDA and NA control groups children stratified by age and randomly assigned to receive treatment or no treatment no placebo control blind status of the trial not reported	Experimental groups 5 6 years n=23 6 7 years n 21 7 8 years n=19 Control groups 5 6 years n=12 6 7 years n=12 7 8 years n=10 IDA, n=39 (Hb <110 g/L) [means not given] NA, n=24 (Hb>110 g/L)	2 months of 20 mg oral elemental Fe and folic acid	WNAC six verbal tests six performance tests	Between groups comparisons on initial developmental scores were not reported	Iron treated children improve in Hb and WNAC and control shildren do not regardless of hematologic status In children aged 7 8 years only WNAC score improvement was higher for IDA than NA groups (across treatments)

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in school age children and adolescents (5–16 years)

Author	Age	Design	Groups, n (hematologic selection criteria) [hematologic group means]	Baseline to follow-up	Measures	Baseline differences	Differences at follow up
OBSERVATIONAL STUDIES							
34 Seshadri et al 1982 India Study 2	5 6 years	double blind intervention after these IDA children were pair matched on weight Hb DAM IQ per capita income and maternal education one child from each pair was randomly assigned to receive treatment or placebo no NA control included	treated n=14 [mean Hb = 96 2±2 7 moderate] placebo control n=14 (mean Hb = 98 2±2 3 nonspecifiable] (IDA Hb < 105 g/L + post hoc Hb increase > 15 g/L)	2 months of 40 mg elemental Fe and folic acid	WNAC verbal and performance tests	No differences as matched were noted	Only the treated group showed WNAC score improvements WNAC scores of the treated group were higher than those of the control group The experimental group showed Hb increase of 23 g/L whereas the control group showed a decrease of 2 g/L
35 Pollitt et al reported 1985 Egypt	average 9 5 years	double blind intervention IDA and NA control children given treatment or placebo no report of randomization procedure	IDA n=28 (Hb≤11 5 g/dL plus one abnormal biochemical measure and response to therapy) [not specified] NA n=40 (Hb >13 g/d plus a normal biochemical measure and no Hb response to iron therapy)	4 months of 50 mg oral ferrous sulfate	form F of the matching familiar figure test (assessment is of speed and accuracy)	NA children were faster and more accurate at baseline	Only the anemic children who were treated with iron became more efficient Efficiency scores for the treated anemic children were similar to the scores of the control children
36 Soemantri et al 1985 Indonesia	10 11 years	double blind intervention IDA and NA control randomly assigned to receive treatment or placebo	IDA n=78 (Hb≤11 0 g/dL plus one abnormal biochemical measure) [mean Hb= 9 74 ± 1 31 nonspecifiable] NA n=41 (Hb⊕12 0 g/dL plus normal measurements in the biochemical index)	3 months of 10 mg oral ferrous sulfate	educational achievement maths biology social science, and language Bourden Wisconsin concentration test RPCM	No baseline differences noted between IDA and NA on RPCM NA children performed better on educational achievement than did IDA children NA children were heavier and taller than IDA children The results of concentra tion assessment were not clear	Iron treated IDA children had changed Hb values more than did other groups The results of concentration assessment were not clear Iron treated IDA children improved their EA score more than did placebo treated IDA children A difference on EA remained between iron treated IDA children and all NA children No hematologic differences were noted between treated IDA and NA children

37 Groner et al 1986 USA	pregnant women ages 14 24 years assumed to be at risk of ID	double blind intervention randomized assignment to receive treatment or placebo	experimental n=16 (≤16 weeks pregnant Hct⊕31%) [mean Hb 12 2 g/dL normal] control (just prenatal vitamin) n=9 ≤16 weeks pregnant, Hct⊕31%) [mean Hb 12 3 g/dL normal]	1 month of 90 mg ferrous fumerate BID + prenatal vitamin treatment	arithmetic total digit span digit symbol vocabulary consonant trigrams RAVLT	No psychometric differences except on one subsection of the RAVLT with experimental subjects performing better than control subjects No correlation between hematologic status and psychometric test scores	Note that decreases in iron measures were expected because of the dilutional effects of pregnancy Control subjects demonstrated greater hematologic decrease than did experimental subjects Experimental group improved on digit symbol on one subsection of consonant trigrams and on two subsections of RAVLT Control subjects decreased on arithmetic and increased only on one subsection of RAVLT Experimental group showed greater test retest improvements than did control subjects on three tests because of control group score decreases No correlation noted between hematologic status and psychometric test scores No correlation noted between hematologic changes and changes in psychometric test score
38 Kayshap and Gopaldas 1987 India	girls ages 8 15 years	double blind intervention after being pair matched on age Hb and individual total cognitive function test scores one member of each pair was randomly assigned to receive treatment or placebo groups were disaggregated into IDA and NA control groups for further analysis	experimental n=65 control n=65 IDA n=81 (Hb <105 g/L) [placebo 95 0±1 3 moderate experimental 96 0±1 3 moderate] NA n=20	assessments every 4 months for 1 year including assessment at 12 months 4 months after completion of therapy, 60 mg oral $FeSO_4$ treatment as one tablet per day for 2 months at the beginning of each of two 4 month school terms	cognitive function tests visual recall digit span maze clerical task	After disaggregation anemic and NA groups showed no baseline differences in cognitive function	-At 8 months iron supplemented IDA children had improved their Hb and clerical task digital span maze and overall scores more than had placebo treated IDA children The only improvement in the NA children was in the iron treated group and was only on mazes At 12 months there were no differences between placebo and treated groups except on mazes with the iron treated group scoring higher still The only significant drop in scores in the treated group was on mazes

Studies of the effects of iron deficiency (with and without anemia) on cognitive, motor, and behavioral indexes in school age children and adoles cents (5–16 years)

Author	Age	Design	Groups, n (hematologic selection criteria) [hematologic group means]	Baseline to follow-up	Measures	Baseline differences	Differences at follow up
			OBSERVATIONAL STUDIES				
39 Seshadri and Gopaldas 1989 India Study 1 re report of Seshadri et al 1982 Study 1 above							
39 Seshadri and Gopaldas 1989 India Study 2 re report of Seshadri et al 1982 Study 2 above							
39 Seshadri and Gopaldas 1989 Study 3 India	boys ages 8 15 years	double blind intervention after being triplet matched on age Hb and baseline cognitive function scores subjects within each set were randomly assigned to receive 30 mg treatment 40 mg treatment, or placebo groups disaggregated into IDA and NA control groups for further analysis	experimental 30 mg dose (both IDA and NA) n = 16 experimental 40 mg dose (both IDA and NA) n=16 placebo (both IDA and ID), n=16 (IDA Hb<105 g/L) NA (Hb>115 g/L) IDA + iron [98 ± 2 0 moderate] IDA+ placebo [placebo 98 ±2 6 nonspecifiable]	4 months 30 mg or 40 mg oral ferrous sulfate therapy for 2 months	cognitive function tests visual recall digit span maze clerical task		After disaggregation 30 mg and 40 mg iron treated IDA and NA children improved their individual and overall cognitive scores except for the 30 mg group on mazes The overall scores of the iron treated groups were higher than the placebo treated group with the 40 mg group showing more individual child improve ment on visual recall, digit span maze and clerical task and the 30 mg group showing more individual child improvement on clerical task and visual recall These differences resulted from changes in the anemic iron treated group which improved more than did the placebo treated anemic group and all NA groups All subjects given iron responded hematologically with no dose effect
39 Seshadri and Gopaldas 1989 India Study 4 re report of Kayshap and Gopaldas 1987 above							

40 Soemantri 1989 Indonesia	average 10 5 years	double blind intervention IDA and NA control children randomly assigned to receive treatment or placebo	IDA n=58 (Hb <110 plus one abnormal biochemical measure) [IDA + iron mean Hb=97 7 ± 4 0 IDA + placebo Hb=96 8±5 1 nonspecifiable] NA n=72 (Hb > 120 plus one normal biochemical measure)	3 months of 10 mg oral ferrous sulfate treat ment with developmental assessments at 3 months and at 6 months (3 months after therapy completion)	EA maths biology social science language	Note that in this prelimi- nary study no statistical analysis was performed No apparent IQ differ ences noted between groups NA children appear to perform better than IDA children on all EA measures NA children were taller and heavier than IDA children	Note that in this prelimi nary study no statistical analysis was performed Iron treated IDA children appeared to consistently show improvement on all EA measures at all follow ups including 3 months after completion of therapy There was also a similar improving trend in the placebo treated group although this appeared to be of a smaller size The changes in the NA children were not in any consistent direction or of a large size
41 Pollitt et al 1989 Thailand	9 11 years	double blind intervention before iron status had been assessed children were randomly assigned to receive treatment or placebo	IDA n=101 (Hb <120 g/L plus two abnormal measures) [non specifiable] ID n=47 (Hb⊕120 g/L plus two abnormal measures) NA n=1210 (Hb⊕120 g/L plus normal biochemical measures)	2 weeks 50 mg oral ferrous sulfate and 14 weeks 100 mg oral ferrous sulfate	RPCM EA Thai language maths	IDA children scored lower on IQ did than NA control children IDA and ID children scored lower on Thai language than did NA control children	All children improved their scores at follow up regardless of iron status There were no differences in improvement between the iron and placebo treated children
42 Bruner et al 1996 USA	13 18 years	double blind intervention ID girls randomly assigned to receive treatment or placebo no NA control group	ID + treatment n=37 (Hb >12 0 g/dL SF <12 0 µg/L) [Hb 13 1±0 7 SF 9 1±2 2] ID + placebo n=36 (Hb >12 0 g/dL SF <12 0 µg/L) [Hb 13 0±0 7 SF 8 5±2 6]	8 weeks of 325 mg ferrous sulfate twice per day	cognitive functioning Brief Test of Attention Symbol Digit Modalities Test Visual Search and Attention Test Hopkins Verbal Learning Test	Both groups were similar on hematologic and cognitive measures	Iron treated group had higher mean SF and Hb values There was no effect of iron treatment on any of the measures of attention Treated girls performed significantly better than baseline scores and the placebo treated group on the total recall score of the Hopkins Verbal Learning Test

Legend

ID iron deficiency (deficient) IDA, iron deficiency anemia (anemic) Idepl, iron depleted IM intramuscular NA nonanemic control Hb hemoglobin Hct, hematocrit, MCV mean corpuscular volume SF serum ferritin

BLDQ, Brunet Lezine s Developmental Quotient BSID Bayley Scale of Infant Development DAM IQ Draw a Man IQ Test EA Educational Assessment IBR Infant Behaviour Record (subscale of BSID), MDI Mental Development Index (subscale of BSID) PDI Psychomotor Development Index (subscale of BSID) PPVT, Peabody Picture Vocabulary Test RAVLT, Rey Auditory Verbal Learning Test, RPCM Raven Progressive Color Matrices SBIQ, Stanford Binet Intelligence Quotient U/HSPD Uzgiris and Hunt Ordinal Scales of Psychological Development WNAC Wechsler Intelligence Scale for Children WPPSI Wechsler Preschool and Primary Scale of Intelligence

Observational baseline hematologic and nonhematologic measurements only are taken from groups to be compared intervention the IDA and ID groups are given iron supplementation usually after baseline hematologic and nonhematologic assessment preventative IDA and ID in a risk population are prevented with prophylactic supplementation from an early age, and the development of the subjects is compared with the development of subjects from the same population not given supplements placebo control a subgroup of the IDA or ID children are given a placebo according to the same procedure as the administration of the iron supplement randomized subjects are randomly assigned to treatment or placebo groups NA control an NA group is included, usually matched to the IDA or ID group for age (as a minimum) and given the same developmental assessments Here the NA control group often receives the same iron supplementation or placebo administration as do the IDA and ID groups

To convert from conventional values to SI values, use the following factors for ferritin, multiply by 1 to convert from ng/mL to µg/L for hemoglobin multiply by 10 to convert from g/dL to g/L, for hematocrit multiply by 0 01 and delete the percent sign

APPENDIX B

List of studies used in the bibliography, by category

Studies of the Short-term Effects of IDA and ID Infants and Young Children (6B24 Months)

Aukett et al (1986) Reference 12

Deinard et al (1981) Reference 1

Grindulis et al (1986) Reference 3

Heywood et al (1989) Reference 17

Idjradinata and Pollitt (1993) Reference 15

Johnson and McGowan (1983) Reference 2

Lozoff et al (1982a) Reference 8

Lozoff et al (1982b) Reference 7

Lozoff et al (1982c) Reference 6

Lozoff et al (1985) Reference 11

Lozoff et al (1986) Reference 4

Lozoff et al (1987) Reference 13

Lozoff et al (personal communication, 1996) Reference 19

Moffat et al (1994) Reference 18

Oski and Honig (1978) Reference 5

Oski et al (1983) Reference 10

Walter et al (1983) Reference 9

Walter et al (1989) Reference 14

Studies of the Long-term Effects of IDA and ID: Infants and Young Children (6B24 Months)

Cantwell (1974) Reference 26

Hurtado (1995) Reference 22

Lozoff et al (1991) Reference 25

Palti et al (1983) Reference 23

Palti et al (1985) Reference 20

Walter et al (1990) Reference 24

Wasserman et al (1992) Reference 21

Studies of the Effects of IDA and ID: Preschool Children (2B5 Years)

Deinard et al (1986) Reference 29

Pollitt et al (1978) Reference 27

Pollitt et al (1983) Reference 28

Pollitt et al (1986) Reference 30

Soewondo et al (1989) Reference 31

Studies of the Effects of IDA and ID: School-age Children and Adolescents (5B16 Years)

Bruner et al (1996) Reference 42

Groner et al (1986) Reference 37

Kayshap and Gopaldas (1987) Reference 38

Pollitt et al (1989) Reference 41

Pollitt et al (1985) Reference 35

Seshadri and Gopaldas (1989) Reference 39

Seshadri et al (1982) Reference 34

Soemantri (1989) Reference 40

Soemantri et al (1985) Reference 36

Webb and Oski (1973a) Reference 32

Webb and Oski (1973b) Reference 33

APPENDIX C

A brief description of the test instruments used in the study of ID/IDA on cognition, behavior, development, and educational achievement

Tests are listed in alphabetical order A description of each test is given and/or the name of the test publisher

1. Tests of Development, Behavior, and Intelligence

Bayley Scale of Mental Development

Bayley N (1969) Bayley Scales of Infant Development Manual New York Psychological Corporation

The scales give three complementary tools for assessing a child's developmental status between the ages of 2 months and 2 years The test is given individually

1 The Mental Scale (MDI) Measures perception, memory, learning, problem solving, vocalization, the beginnings of verbal communication, and rudimentary abstract thinking

2 The Motor Scale (PDI) Measures gross motor abilities, such as sitting, standing, walking, and stair climbing Also measures manipulatory skills of hands and fingers At the infant level, these abilities are considered to play an important part in children's interactions with the environment and thus in the development of their mental processes

3 The Infant Behavior Record (IBR) This is a rating scale completed by the examiner after the other two parts have been given It assesses various aspects of personality development such as emotional and social behavior, attention span persistence, and goal directedness

U S norms were developed for children 2 to 30 months old The MDI and PDI give separate developmental indexes expressed as normalized standard scores with a mean of 100 and a standard deviation of 16 (as in the Stanford-Binet) Raw scores on individual subtests may also be used

The scales are advised for assessing current developmental status and not for predicting future abilities They may be useful in the early detection of sensory and neurological defects, emotional disturbances, and environmental deficits

Beery Test of Visual Motor Integration

Beery KE (1982) Administration, scoring, and teaching manual for the developmental test of visual-motor integration Cleveland, OH Modern Curriculum Press

Bourden-Wisconsin Card Sorting Test

Heaton RK (1981) A manual for the Wisconsin Card Sorting Test Odessa, FL Psychological Assessment Resources

The test was originally developed to measure conceptual levels of the normal adult population It has, however, become very popular in clinical neuropsychology and is regarded as sensitive in revealing behavioral rigidity, which is typically exhibited by patients with frontal lobe syndrome Adult-level performance in the test emerges at the age of approximately 10 years

The test is given individually It consists of two identical packs of cards which the subject has to categorize with the help of four stimulus cards and cued feedback given by the experimenter When a particular sorting criterion (color, form, or number) is established, the experimenter changes it unexpectedly The test is finished when six categories have been identified or all (128) cards have been used Successful performance requires reasoning ability and flexibility to alter sorting strategies

Bruininks-Oseretsky Test of Motor Proficiency

Herrick VE (1959) The Iowa School Performance Test In Buros OK, ed The fifth mental measurements handbook Highland Park, NJ Gryphon, p 311 (also published by American Guidance Service in 1978)

Originally published in Russia in 1923 The most recent version was published in 1978 Designed to cover all major types of motor behavior and used for testing mentally retarded children (who frequently have motor impairment) and children with motor handicaps, minimal brain dysfunction, or learning disabilities Standardized for ages 4 to 14 years The complete battery consists of 46 items grouped into eight subtests It takes 45–60 minutes to complete and gives three scores a Gross Motor Composite, which measures performance of the large muscles (shoulders, trunk, and legs), a Fine Motor Composite, which measures performance of the small muscles (fingers, hands, and forearm), and a total Battery Composite Score There is also a 14-item Short Form, which gives a single index of general motor proficiency

Brunet-Lezine's IQ Test

Brunet O, Lezine I (1951) Le developpement psychologique de l'enfant Paris Presse Universitaire de France

A French version of Gesell's developmental schedule The test consists of 10 items for each age (birth, 3, 6, 9, 12, 18, and 24 months) Psychomotor development is measured by four subscales (1) motor development, (2) coordination development, (3) language development, and (3) social-personal development

Denver Developmental Screening Test

Frankenburg WK, Dodds JB, Fandal AW (1973) Denver Developmental Screening Test manual workbook for nursing and paramedical personnel Denver, CO University of Colorado Medical Center

The test was designed for use with children from birth to 6 years of age It measures infant and child development and is divided into four parts (1) personal-social, e g , ability to put on and remove clothes, (2) fine-motor–adaptive, e g , ability to draw, (3) language, e g , ability to use plurals, opposite analogies, define words, and (4) gross motor skills, e g , ability to throw a ball

U S age-standardized scores are available The test has been validated against the Bayley Scale of Infant Development and the Stanford-Binet and also standardized for use in multiracial communities

Goodenough-Harris Draw-a-Man Test

Harris DB (1962) Children's drawings as measures of intellectual maturity a revision and extension of the Goodenough Draw-a-Man Test New York Harcourt Brace and World

Draw-a-Man Test was first standardized in 1929 Current version was restandardized by Harris in 1962 The test instructions are simply, "Make a picture of a man, make the very best picture that you can" There are also instructions for drawing a woman and for drawing oneself It may be given individually or in groups Emphasis is placed on the child's accuracy of observation and on the development of conceptual thinking, rather than on artistic skill Points are given for the inclusion of individual body parts, clothing details, proportion, perspective, etc The maximum number of points for the man or the woman is 73 and 71, respectively These are transformed into standardized scores based on U S norms with a mean of 100 and a standard deviation of 15 An alternative, simplified scoring system called the Quality Scale may be used where the child's drawing is matched to the one it resembles most closely in a graded series of 12 sample pictures

In older children, performance on the test is said to correlate well with tests of reasoning, spatial ability, and perceptual accuracy, whereas in pre-school-age children it correlates best with numerical aptitude Performance on the test is quite heavily influenced by cultural background

Illinois Test of Psycholinguistic Abilities Revised (ITPA-R)

Champaign, IL University of Illinois Press

This is an individually administered test for children 2 to 10 years old The test was designed to follow a three-dimensional model of the process of communication The model has two *channels* (auditory-vocal and visual-motor), three *processes* (receptive, organizing, and expressive), and two *levels* (representational and automatic) The abilities covered by the test are located at the intersections of the three dimensions E g , the Manual Expression Test asks children to perform a manual gesture to "show what we do with" each pictured object such as a telephone This task includes the following dimensions visual-motor channel, expressive process, and representational level

The ITPA is considered very culturally restricted in that it was developed for U S middle- class children, so its use is not recommended for lower-socioeconomic or minority groups

Iowa Tests of Basic Skills Levels A–F, Form 3

Chicago Riverside Publishing Company

This is a test of educational achievement in U S children in kindergarten to grade 9 The battery gives a profile of scores on the major academic areas of reading, writing, and arithmetic The three domains tested are (1) language (vocabulary, reading comprehension, spelling, capitalization, punctuation, language usage), (2) work-study skills (visual materials, reference materials), and (3) mathematics (mathematical concepts, problems solving, computation)

Performance on the test at different grades can be directly compared

Multi-Level Informal Language Inventory (MILI) Intelligence Scale for Preschool Children

Developed by C Goldsworthy and W Secord in 1982, the test measures language growth and development in Israeli children 4–6 years old

Peabody Picture Vocabulary Test. Revised (PPVT-R)

Dunn LM (1981) Peabody Picture Vocabulary Test—Revised Circle Pines, MN American Guidance Service

The test provides a quick measure of the "use" of vocabulary It takes around 15 minutes to complete and consists of a series of 175 plates, each containing four pictures As each plate is presented, the examiner provides a stimulus word orally The test taker responds by pointing to the picture on the plate that best illustrates the meaning of the stimulus word It is especially useful for testing vocabulary use among people who are not literate, who are not able to vocalize well, or who are deaf In studies investigating the effects of iron deficiency anemia on children's cognitive/motor/mental development, it is sometimes used as a relative measure of the educational level of parents Performance in the United States and the United Kingdom correlates well with other vocabulary tests and also reasonably well with verbal intelligence, educational achievement, and scholastic aptitude

Peterson-Quay Behavior Problem Checklist

Peterson DR, Quay HC (1967) Manual for the Behavior Problem Checklist Unpublished manuscript, University of Illinois

Ravens Coloured Progressive Matrices

London HK Lewis & Co Ltd , San Antonio, TX Psychological Corporation

This is an easier version than the Ravens Progressive Matrices (RPM) RPM was designed in 1983 as a measure of intelligence, specifically Spearman's *g* factor Performance is based on an ability to analyze/interpret abstract items The colored version has three parts, each with 12 items Each item consists of a picture of a pattern at the top or a series of pictures arranged in a matrix from which a piece is missing Children are asked to pick from six choices the picture that completes the pattern or matrix The easier items measure accuracy of discrimination, and the more difficult items measure analogies and logical relations It can be given individually or in groups There is no time limit, although children usually complete it in 10 to 40 minutes

---

Shaefer Classroom Behavior Inventory

Shaefer ES, Droppleman LE, Kalverboer AF (1965) Development of classroom behavior checklist and factor analyses of children's behavior in the United States and the Netherlands Proceedings of a Conference of the Society for Research in Child Development, Minneapolis, MN

The Classroom Behavior questionnaire was designed for use as a routine screening procedure for learning and behavioral problems of children Children are assessed by their teachers There are 60 questions on sections including (1) learning achievement (assessed by reading, writing, spelling, arithmetic, and general knowledge), (2) task orientation—(2a) positive task orientation (comprehension, persistence, and self-control) and (2b) negative task orientation (distractibility, lack of discipline, and motor restlessness)—and (3) mood (anxiety, depression, aggressiveness, and mood swings) Each question is scored on a four-point scale (0–3) The questions have equal weight

---

Sheridan Developmental Sequences

Sheridan M (1978) Children's developmental progress Windsor NFER, pp 1–55 (currently out of print)

Stanford-Binet Intelligence Scale

Chicago Riverside Publishing Company

Originally designed in 1905 as a measure of IQ/general intelligence The current (fourth) edition was published in 1986 It is administered individually Fifteen tests measure four cognitive domains (1) verbal reasoning, e g , vocabulary, comprehension, (2) abstract/visual reasoning, e g , number series, equation building, (3) quantitative reasoning, e g , pattern analysis, copying paper folding, and cutting, and (4) short-term memory, e g , bead, sentence, digit, or object memory The items are given in a mixed order to retain a child's interest and attention Six of the tests are used for all ages, whereas the remaining nine tests either begin or end at a higher level

Although the overall score gives a useful measure of IQ, the scores on the individual subtests provide information on specific learning difficulties U S normalized age-standardized scores are available for individuals 2 to 23 years old The overall score has a mean of 50 and a standard deviation of 8, whereas the scores for each of the four cognitive domains have a mean of 100 and a standard deviation of 16 Raw scores on individual subtests can also be used

---

Uzgiris and Hunt Ordinal Scales of Psychological Development

Uzgiris IC, Hunt J McV (1975) Assessment in infancy Ordinal Scales of Psychological Development Urbana, IL University of Illinois Press

---

Wechsler Intelligence Scales

Wechsler Adult Intelligence Scales—Revised (WAIS-R)

Wechsler Intelligence Scale for Children—Revised (WISC-R)

Wechsler Pre-school and Primary Scale of Intelligence—Revised (WPPSI-R)

New York Psychological Corporation

There are three scale (1) WAIS for adults (>16 years) published in 1939, (2) WISC-R for school-age children (ages 6 to 16 years) published in 1974, and (3) the WPPSI-R for preschool children (ages 4 to 6 years) published in 1989 Each scale is used as measures of general intelligence and sometimes as an aid in psychiatric diagnosis, and is given individually

Within each scale there are two main parts (1) Verbal Scale In the WISC-R, this constitutes six subtests Information, Similarities, Arithmetic, Vocabulary, Comprehension, and Memory (Digit-Span) (2) Performance Scale In the WISC this constitutes five subtests Picture Completion, Picture Arrangement, Block Design, Object Assembly, and Coding (or Mazes) Performance on individual subtests can give information about specific learning difficulties Subtests that have been used in studies on iron deficiency anemia and cognition are described individually below

The scores may be age standardized to U S norms, with a mean of 100 and a standard deviation of 15 However, raw scores or standardized scores on individual subtests can also be used Performance correlates highly (0 80) with the Stanford-Binet The full battery takes around 60 minutes to give

Woodcock-Johnson Psycho-educational Battery

McGrew KS, Werder JK, Woodcock RW (1991) WJ-R technical manual Allen, TX DLM

2. Tests of Cognitive Function

A Brief Test of Attention

Schretlen D, Bobholz J, Brandt J (1996) Development and psychometric properties of the Brief Test of Attention Clinical Neuropsychology *10 80–89*

This is a measure of auditory divided attention in which participants listen to a tape of letters and numbers (e g , 4-A-8-G-3-2) and are asked to report how many letters or numbers they hear

Hopkins Verbal Learning Test

Brandt J (1991) The Hopkins Verbal Learning Test development of a new memory test with six equivalent forms Clinical Neuropsychology *5 125–142*

This is a test of cognitive function It is a 12-item semantically categorized word-list learning test There are three free recall trials, a delayed recall trial, and a yes/no recognition test Participants are read the same list of words three times, and each time they are asked to repeat as many words as they can recall Twenty minutes later they are asked to say which words they remember and are read 24 words that include the original 12 words plus 12 semantically related and unrelated words

Symbol Digit Modalities Test

Smith A (1973) Symbol Digit Modalities Test manual Los Angeles Western Psychological Services

This is a timed measure of visual attention, motor speed, and rapid coding in which participants print the number that corresponds to a written symbol listed at the top of the test page The task is then repeated with the participant saying the digits

Visual Search and Attention Test

Psychological Assessment Resources (1990) Visual Search and Attention Test professional manual Odessa, FL Psychological Assessment Resources Inc

This is a timed test of visual scanning, target detection, and cancellation in which participants locate and cross out letters or symbols that look like the target

Test of Attention in Infants—Habituation/Fixation

Test reported by Heywood et al (1989)

The child was seated on its mother's lap Two meters in front of the mother and child was a screen with a peephole in the middle The observer sat behind the screen out of sight of the child and observed and timed the visual fixation of the child to the stimulus with a cumulative stopwatch and recorded the number of looking episodes The stimuli were presented in front of the screen Two stimuli were used a brightly colored blown-up plastic fish or doll The fish was presented for four trials, each lasting 30 seconds, with a 15-second interval The doll was presented on the fifth trial for 30 seconds At the start of each trial, the stimulus was pressed so it would squeak

Consonant Trigrams

Test used in Groner et al (1986) No reference provided

Rey Auditory Verbal Learning Test

Test used in Groner et al (1986) No reference provided

3. Discrimination Learning

(1) Two choices with three-dimensional objects

The child is presented two three-dimensional objects (toy car, toy whistle, etc) mounted on wooden bases A yellow happy face is pasted on the bottom of only one of the bases The child's task is to discover which stimulus hides the happy face underneath it After each trial the stimuli are rearranged out of the child's view, and the procedure continues until a criterion of seven correct responses in a row is met The reverse problem is then administered with the same criterion

(2) Two choices with two-dimensional objects

The task is identical to the three-dimensional task except that the happy face is pasted on the bottom of a cardboard picture cut from a child's book

Short-Term Memory Task

A large number of two-choice visual discrimination learning problems consisting of two-dimensional pictures are presented concurrently for a total of four trials each Trials 1 and 2 are consecutive Trials 2 and 3 have either zero, four, or eight interpolated items separating them Trial 4 occurs 24 hours later A happy face is posted on the back of the correct stimulus

Oddity Learning

Three two-dimensional pictures (stimuli) are presented simultaneously on a black card, and two of the stimuli are identical The only instructions given are "to find the winner" The correct answer/winner is the picture that is different from the other two (oddity) In the first trials, new stimuli are used each time In the remaining trials the same stimuli are repeated each time in an AAB, ABB manner Thus, the specific character of a stimulus does not determine its correctness, rather, it is the relationship of a character to other stimuli in the array

Matching Familiar Figures Test—Form F

The child is shown two cards one card, the standard, has a picture on it, and the other card has pictures of six variants of the standard The child has to match the standard and one of the alternatives The time taken for the first response and the errors made before a perfect match is achieved are recorded

The remaining cognitive tests mentioned in the Bibliography are all tests within the Wechsler Scales These include Mazes, Clerical Task, Visual Recall, Digit-Span, Digit-Symbol, Arithmetic, and Vocabulary