Paediatric and Perinatal Epidemiology 1998, **12,** 313–333

Study designs

The Treatment of Lead-exposed Children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers

Treatment of Lead-exposed Children Trial Group
Participants are listed in the Appendix

Summary. Exposure to lead impairs cognitive development in young children, but the benefits of lowering blood lead pharmacologically are not clear. This report describes the design, recruitment, enrolment and baseline results of the Treatment of Lead-Exposed Children (TLC) trial, a randomised, multicentre, placebo-controlled, double-blind clinical trial of the effects of treating lead-exposed children with succimer, a drug that enhances urinary excretion of lead, on cognitive, behavioural and physical development. TLC clinical sites were in Baltimore, Cincinnati and Columbus, Newark and Philadelphia. Children were eligible for TLC if they were between 12 and 33 months of age, had a confirmed blood lead concentration between 20 and 44 μg/dL and lived in a residence suitable for lead dust reduction. Randomised children received up to three 26-day courses of succimer or placebo, and were then followed for 3 years. The study can detect a three-point difference in full-scale IQ at 3-year follow-up. Statistical power for the other end points is more difficult to estimate. A total of 1854 children were evaluated and 780 children were randomised between August 1994 and January 1997. The mean age of randomised children was 24 months and mean blood lead level 26 μg/dL. Three-quarters were African–American. Most children had poor, single mothers who had completed 12 or fewer years of school and who lived in older, poorly maintained residences.

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Introduction

Exposure to lead produces dose-related impairment of cognitive development in young children.[1,2] Prospective epidemiological studies have shown that peak blood lead levels, which occur at 20–30 months of age, are inversely associated with developmental test scores measured at ages 4–10 years.[3–7] This association has been found at blood lead levels achieved by 1 000 000 or more children in the United States,[8] and at levels that produce no symptoms or laboratory abnormalities. Exposure to small amounts of lead during childhood may also affect growth, hearing, behaviour and blood pressure. Although the toxicity of lead to all levels of the nervous system is very well studied, the mechanism by which lead delays development is not known, nor is it known whether these effects can be reversed or attenuated once exposure has taken place.

In 1991, the Centers for Disease Control and Prevention (CDC) recommended universal screening of children for elevated blood lead concentration.[9] All children with blood lead levels above 15 μg/dL were to have their source of lead identified and reduced. For children whose blood lead concentration was between 20 and 44 μg/dL, the CDC left open the options of lowering blood lead pharmacologically, not doing so, or participation in trials of such therapy. The drugs for lowering blood lead do so by chelation, that is they form a non-covalent bond between the drug and the metal, and the complex or chelate is more soluble and thus readily excreted in urine. About 1% of US children below the age of 6 years had blood lead levels greater than 20 μg/dL,[8] and 4.4% of children aged between 1 and 5 years had blood lead levels greater than 10 μg/dL.[10] Before 1991, all drugs labelled for lead chelation were injectables, and most lead-poisoned children were admitted to specialised centres for chelation treatment. In that year, however, the oral chelating drug Chemet® (succimer) was licensed in the United States for treatment of young children with blood lead levels $\geqslant 45$ μg/dL. The combination of increased screening activity, the availability of an oral drug and the lack of data showing efficacy of any form of therapy for prevention of latent developmental delay stimulated the initiation of a randomised clinical trial of oral chelation sponsored by the National Institute of Environmental Health Sciences (NIEHS) and supported in part by the Office of Research on Minority Health of the US National Institutes of Health. The trial was designed to test the hypothesis that children with moderate blood lead concentrations who were treated with succimer would have higher scores than untreated children on a range of tests measuring cognitive and behavioural development 3 years after treatment. We also hypothesised that treatment would have favourable effects on blood pressure and stature. This paper presents the design of the study, recruitment results, and the characteristics of the randomised children and their families.

Methods

Introduction and organisation

The Treatment of Lead-exposed Children (TLC) Trial is a placebo-controlled, double-blind, randomised clinical trial of the effect of succimer treatment on growth, behaviour and development of lead-exposed children. Children were enrolled at four clinical centres, located in Baltimore MD, Cincinnati/Columbus OH, Newark NJ, and Philadelphia PA. The data-coordinating centre was at the Harvard School of Public Health, the central laboratory was at the CDC, Atlanta GA, and the central pharmacy was the Program Support Center of the US Department of Health and Human Services, Perry Point, MD. The TLC trial enrolled children between August 1994 and January 1997. The core study design was approved by the Institutional Review Boards at all clinical sites, the Harvard School of Public Health, NIEHS and the CDC. There were minor differences in the wording of the consent form among centres. The Newark centre also had Spanish consent forms, which were approved by the Institutional Review Boards at Newark and the NIEHS.

The TLC provided vitamin and mineral supplementation to all enrolled children, and in order to reduce exposure to lead in settled dust or deteriorated paint, the TLC either cleaned the families' homes or helped them to move. A steering committee – consisting of all principal investigators, the NIEHS project officer, and other participating investigators and a representative of the drug manufacturer as needed – established the protocol and monitored recruitment, treatment and follow-up. The study's protocol and performance were reviewed independently by a data and safety monitoring committee (see Appendix).

The TLC trial intervened with families that were burdened with major social and economic disadvantages. It was as family-friendly as possible, providing transportation, food, day care and small gifts on clinic days. The crews responsible for the cleaning of study homes were visible in the communities, the families welcomed them and their activities resulted in further recruitment of families from the same or adjacent buildings.

Initial eligibility

Children were eligible for the initial TLC visit if they were expected to be between 12 and 33 months of age at randomisation (about 5 weeks from the first visit), had a referral blood lead between 20 and 44 μg/dL and if psychometric tests could be administered in English (or Spanish in the Newark centre).

Recruitment

The TLC recruited in several ways. Staff made presentations to local medical and community groups, cooperated with local health departments, and sought out

individual physicians and clinics with an interest in lead poisoning. All TLC centres operated at sites that had experience with management of lead poisoning and that had established referral patterns. Most children were referred to TLC clinics for management of their elevated blood leads. Some TLC clinics enrolled children with elevated blood lead concentrations from their own primary care clinics. The Cincinnati centre screened in the community and at health fairs. The Newark centre recruited at several sites in northern New Jersey and the Cincinnati centre recruited in northern Kentucky. Because the TLC sought referrals from many sources, and because there were no lists of lead-poisoned children in the catchment areas, it is not possible to characterise the children referred to the TLC in terms of the population from which they were drawn.

First clinic visit

At the first clinic visit, TLC staff described the trial to parents or guardians and obtained their written consent to participate in the first stage of the study, which included all activities up to randomisation. The child's parent or care giver was asked whether the child had any disqualifying medical conditions (significant developmental delay, autism or any disorder prohibiting psychological testing, significant renal or hepatic disease, cyanotic congenital heart disease, anaemia not due to iron deficiency, reported birthweight under 3 pounds or previous chelation therapy) and the child was examined. If no disqualifying condition was noted from the history and physical examination, blood was drawn for measurement of blood lead, ferritin, complete blood count, and other indices were selected either

Table 1. Laboratory results before treatment in randomised children

	Placebo			Active drug		
	n	Mean	SD	*n*	Mean	SD
Haemoglobin (g/dL)	384	11.7	0.9	393	11.7	0.9
Red cell distribution width (%)	384	14.4	1.9	390	14.3	2.0
Serum creatinine (mg/dL)	381	0.4	0.1	392	0.4	0.1
Platelets (count/mm^3)	384	358	91	392	354	85
Alkaline phosphatase (IU/L)	383	270	111	393	277	136
Alanine aminotransferase (IU/L)	383	18	9	394	19	10
Aspartate aminotransferase (IU/L)	383	38	10	393	38	13
Absolute neutrophil count (count/mm^3)	377	2770	1576	389	2733	1489

SD, standard deviation.

because they had been reported to be affected by the drug or because they affected disposition of the drug (Table 1). If the results were abnormal according to specific criteria, these tests were repeated at a later visit. If the abnormality did not resolve, the child was disqualified. Urine was checked for protein and glucose. The central laboratory at CDC measured blood lead and ferritin, and local laboratories carried out the other tests.

Lead in blood was measured by atomic absorption spectrometry based on the method described by Miller *et al*.[11] Lead content was determined using a Perkin-Elmer Model 4100-ZL graphite furnace atomic absorption spectrophotometer with Zeeman-effect background correction. Ferritin was measured using the Bio-Rad Laboratories Quantimmune Ferritin IRMA kit, which is a single-incubation two-site ^{125}I-immunoradiometric assay (IRMA) based on the general principles of assays as described by Addison *et al*.[12] and Miles,[13] and modified by Jeong *et al*.[14] Height and weight were measured using a standard protocol and dedicated scales and stadiometers. Blood pressure was measured using a Dinamap Vital Signs Monitor. The Dinamap monitor determines blood pressure using an oscillometric technique, based on the principle that pulsatile blood flow through an artery produces vessel-wall oscillations that transmit to the blood pressure cuff. The Dinamap has been found to be more accurate than auscultation when compared with intra-arterial measurement. The instrument eliminates inter observer variability and, compared with auscultation, depends less on patient cooperation or a quiet environment.[15]

Each family meeting the study criteria at the initial clinical evaluation received a month's supply of TLC vitamins and minerals, which included iron, zinc, calcium and copper. We used this formulation because of the possibility of a mild cation diuresis during treatment. As such formulations are available only in chewable form, the TLC provided pill crushers and advised parents to crush the tablets for safer administration. The TLC also provided a vitamin diary, both to accustom the family to keeping a medication diary and for assessment of compliance.

Home inspection

Between the first and second clinic screening visits, TLC staff inspected the child's home or homes using a standard protocol. The TLC required that children had no more than two residences where they spent more than 8 h a day on a regular basis. It was assumed that these children were exposed to lead in their homes, and therefore lead in the paint was not measured. The home inspection identified potential sources of lead, especially painted surfaces that were accessible to the child. The homes were required to be in sufficiently good repair that the TLC clean-up regimen could be expected to minimise exposure to lead dust for 6 months, the period during which the child might be taking succimer. This requirement was based on the concern that succimer therapy might increase the child's propensity to absorb lead.

Second clinic visit

Children with blood lead levels between 20 and 44 μg/dL in the blood sample were scheduled for a second clinic visit 3–4 weeks after the first. At the second visit, results from the laboratory tests and the home inspection were reviewed by clinic staff to check eligibility. If none of the laboratory tests exceeded prespecified boundaries, and the child's residence or residences met study criteria, then a second blood sample was drawn for blood lead measurement. If possible, a clean-up visit was scheduled so that if the child's blood lead remained in the eligible range on the second TLC blood lead measurement, then the home would be cleaned before randomisation. If the child qualified but was iron deficient, a 30-day course of oral iron was prescribed and the child was scheduled to return in 1 month.

A randomisation visit was scheduled if the child's second blood lead measurement was also between 20 and 44 μg/dL and the family had achieved reasonable compliance with appointments and vitamin regimens. Clinic staff explained the treatment and follow-up schedule for the study, and the families were asked to sign a second consent form. The second blood lead measurement was used as the baseline value for evaluation of treatment effects and for identifying increases in blood lead level requiring additional intervention.

Home clean-up

Each family whose child was initially eligible and whose housing was cleanable according to TLC standards was offered professional clean-up. All TLC clean-up activities were in addition to any lead-based paint abatement or repair activities mandated by state or city law, or undertaken by local lead poisoning prevention programmes or local public health agencies in the absence of relevant statutes and regulations. The objective of the home clean-up was reduction in lead exposure during succimer treatment and whenever possible was scheduled after the second clinic visit and before the child was randomised. When this was impossible, homes were scheduled either before the second clinic visit or within 1 week after treatment began. The TLC would clean up to two homes per child and would clean any new home if the family moved during the treatment period. In some cases, principally in Baltimore, families were moved to housing that reduced the child's exposure to lead.

Clean-up consisted, at a minimum, of vacuuming all accessible horizontal surfaces (e.g. floors, window sills, window wells) with a vacuum cleaner fitted with a high-efficiency particle air (HEPA) filter (designed to trap fine particles down to 0.3 μm in size), damp mopping or wiping uncarpeted surfaces with a solution containing tri-sodium phosphate or equivalent cleaning substance, and then vacuuming again. Areas with peeling paint were also vacuumed with the HEPA vacuum cleaner. Before and after cleaning surface wipes were taken from a

sample of residences. TLC cleaning crews performed minor repairs to stabilise paint on small surfaces but did not undertake lead paint abatement, except in Baltimore. There, approximately one-third of families had access to special state loan funds for more extensive abatement activities in private housing. The cleaning crews also recommended that old or damaged carpets be discarded and provided instruction in lead dust suppression, floor mats and cleaning materials to the families.

All TLC cleaning crews were trained in and followed National Institute of Occupational Safety and Health procedures for minimising their own exposure. Families were not allowed in the room being cleaned but sometimes remained in the home. Whenever possible, male–female cleaning crews were assigned to the houses of single female parents. TLC housing staff worked in pairs and never went into homes alone.

Randomisation

Treatment assignments were blocked by centre, six categories of body surface area, two strata of blood lead level at the second clinic visit (20–24 μg/dL or 25–44 μg/dL) and, in Newark, English or Spanish language. Half the children were given succimer, and half were given placebo. Clinics obtained treatment assignments from the data-coordinating centre by telephone, usually on the day before the scheduled visit at which the succimer or placebo would be dispensed. The data-coordinating centre assigned a study number corresponding to a blinded bottle of drug or placebo stored at the clinical site containing the number of capsules appropriate for the child's body surface area. Randomisation was completed only if the child returned to the clinic to begin treatment within 2 weeks of the second qualifying blood lead measurement. When treatment could not be started during this period, study personnel repeated the measurement of blood lead and randomised the child again only if that blood lead measurement was between 20 and 44 μg/dL.

Baseline behavioural and psychometric assessment

Baseline behavioural assessment and psychometric testing, consisting of the Child Development Inventory (CDI)[16] and the Bayley Scales of Infant Development-II (BSID2),[17] were performed on the same day as the first treatment visit by examiners blinded to treatment assignment. No blood was drawn at this visit and the parent did not begin to administer the capsules until the next day. The CDI is a shortened and revised version of the Minnesota Child Development Inventory.[18] The General Development subscale consists of the 70 most age-discriminating items from the CDI. These items describe the behaviour of children in the first 78 months of life. The parent is read simple statements describing behaviour, and

states whether their child exhibits them. Raw scores, which are the number of positive responses, are compared with age-specific standards. This is carried out clinically by graphing the child's scores on a scaled profile sheet that comes with the test. A child performing at 25% or 30% below the age standard is thought to require further evaluation. An earlier version of the scale was shown to have concurrent validity when applied to a population of minority, high-risk children.[19]

The BSID2 is a revision and restandardisation of the well-known Bayley Scales of Infant Development.[20] The Bayley Scales are the most widely used and precisely constructed of all published infant intelligence tests. The BSID2 yields a mental development index (MDI) and psychomotor development index (PDI) analogous to an IQ score with a mean of 100 and standard deviation of 15. The MDI is designed to evaluate the development of sensory and perceptual acuities and discriminations, acquisition of object constancy, memory, learning, problem solving, vocalisation, beginning of verbal communication, early forms of abstract thinking, habituation, mental mapping, complex language, and mathematical concept formation. The PDI is designed to evaluate the development of postural control, coordination of the large muscles, manipulatory skills of the hands and fingers, dynamic movement, dynamic praxis, postural imitation and stereognosis. The BSID2 also provides estimates of developmental age in the cognitive, linguistic and motor domains. These are based on the child's ability to perform individual items, which have standard ages at which the child is expected to be able to complete them.

The BSID2 includes a Behaviour Rating Scale (known as the Infant Behaviour Record in the original Bayley scales) with which the examiner rates the child's affective, attentional and motivational behaviour. The Behaviour Rating Scale assesses the nature of the child's social interactions, environmental orientations, interests, activity level and quality of motor performance. Higher scores on the Behaviour Rating Scale usually indicate optimal performance. The scale yields a total raw and percentile score and subscale scores for Orientation/Engagement, Emotional Regulation and Motor Quality.

Treatment

McNeil Consumer Products provided 100 mg Chemet® (succimer) and placebo capsules of identical appearance. Because succimer has a strong mercaptan odour, the central pharmacy packaged 200 mg of active drug in a vented plastic cylinder in each bottle of placebo and active drug. Although this did not provide the placebo bottles with the room-filling odour of the active drug, it did give the placebo an obvious aroma.

TLC children were assigned to one of six dosing regimens based on an estimate of body surface area calculated from height and weight at the beginning of each course of treatment (Table 2). Dose regimens were designed to come as close as possible to the dose rate on the Chemet® label, which is 1050 mg/m^2/ day for the

Table 2. Dose by body surface area and day of treatment

	Day of treatment			
	1–7		8–26	
Body surface area (m^2)	Daily dose (mg)	Range of delivered dose (mg/m^2/ day)	Daily dose (mg)	Range of delivered dose (mg/m^2/day)
0.357–0.428	400	1120–935	300	840–701
0.429–0.499	500	1166–1002	300	699–601
0.500–0.523	500	1000–956	400	800–765
0.524–0.618	600	1145–971	400	763–647
0.619–0.642	700	1131–1090	400	646–623
0.643–0.713	700	1089–982	500	778–701
0.714–0.770[a]	800	1120–1039	500	700–649
0.771–0.809[a]	800	1038–989	600	778–742

[a]The last two dosing regimens were used during retreatment courses only for children who had grown out of our original six body surface area classes.

first 5 days, and then 700 mg/m^2/ day for the rest of the 19-day course, without using fractions of capsules. Note that, although the Chemet® label provides doses both by body surface area and by weight, young children such as the ones in the TLC get much more drug using the body surface area method.

Treatment courses in the TLC trial were 26 days in length, 7 days longer than the 19 days specified by the label. The 1050 mg/m^2/ day dose regimen was used for 7 days, rather than the 5 days on the label. Treatment periods were lengthened to reduce the magnitude of rebound in blood lead level after cessation of treatment and thereby to achieve a larger and more prolonged reduction of blood lead level. Participants could receive up to three courses of treatment. Because the children continued to grow, doses were recalculated for each course. Children returned for clinic visits at 7, 28 and 42 days after the beginning of each course of therapy. At each of these treatment visits, blood lead, neutrophils, platelets and serum enzymes ('liver function tests') were measured. All of these values were potentially affected by succimer, so the results were not given to the treating physician. A designated physician at each site who was not involved in the child's clinical care received the results of the laboratory tests and checked whether any result violated predetermined boundaries. In addition, the data-coordinating centre reviewed blood lead levels, which they received electronically from CDC within 3–5 days of measurement. If a child's blood lead level increased by more than 15 μg/dL from the baseline value, the data-coordinating centre notified the clinical centre to repeat the blood lead measurement. If the child's blood lead ever exceeded 44 μg/dL, study treatment was interrupted and the child was managed according to the clinical centre's local standards of care.

Chemet® capsules are too large for small children to swallow. Hence, at the first treatment visit, staff instructed the parents on how to open the capsules and sprinkle the coated beads onto apple sauce. All instructional capsules were placebo. Families were given a medication diary, information about overdose or ingestion, and a telephone number where they could reach study staff. Families were instructed to stop vitamins while the child was taking the study drug. Parents did not know whether their children had received active drug or placebo. The bottles had a scratch-off area on a detachable label that identified the contents as succimer or placebo. This label was kept at the clinical centre in an area with 24-h access in case it was necessary to identify the capsules immediately. Families were told that pills would be counted at subsequent clinic visits. The Cincinnati/Columbus site used bottles with the Medical Event Monitoring System (MEMS) (APREX Corporation, Freemont, CA, USA), a bottle cap with a sensing device that recorded bottle openings. The cap also beeped to remind parents of the prescribed time to administer drug.

If a child receiving active drug had blood lead concentration of 15 μg/dL or higher at the day-42 visit of the first or second course, an additional course of treatment was initiated. An approximately equal number of children in the placebo group were selected at random for retreatment to retain blinding. Seventy-five per cent of children required a second course of drug, and 81% of those receiving a second course of treatment required a third.

Succimer was prescribed under an Investigational New Drug permit (IND no. 45 248) from the Food and Drug Administration (FDA). All serious adverse events were reported to the FDA, the other clinicians, the NIEHS and the drug's manufacturer, irrespective of whether they were known or suspected to be due to succimer. All hospitalisations occurring in TLC children were regarded by the TLC as potentially due to drug, and all were discussed by the steering committee at regularly scheduled phone calls. No serious drug-related events were identified.

Post-treatment follow-up, monitoring and psychometric assessment

After treatment was completed, children were seen at 3-month intervals for clinical examination and blood lead measurement during the first 2 years of follow-up, and at about 4-month intervals in the third follow-up year. Follow-up visits followed the 1991 CDC guidelines for frequency of visits at these blood lead levels. Although clinical centres were blinded to blood lead levels during treatment, post-treatment levels were available to them. However, the treatment assignment was not revealed, and for an individual child, was not obvious from the blood lead levels. After treatment, vitamins were provided for participating children for the duration of the study.

Follow-up psychometric assessments were performed at 6 months, 18 months and 3 years after randomisation. The assessment included the BSID2 up to the age

of 42 months. Thereafter, we administered the Wechsler Primary and Preschool Scales of Intelligence – Revised[21] (WPPSI-R), a revision of the original Wechsler Preschool and Primary Scale of Intelligence.[22] It possesses the best psychometric properties of all published tests of preschool intelligence and is the test most frequently used to establish the construct and criterion-based validity of other measures of preschool intellectual attainment. It consists of a collection of 12 subtests organised into two scales: a Verbal Scale, which uses language-based items, and a Performance Scale, which uses visual–motor items that are somewhat less dependent upon language. The WPPSI-R yields scale scores for the 12 subtests as well as Verbal, Performance and Full-Scale Deviation IQs that have a mean of 100 and a standard deviation of 15. The General Development subscale of the CDI is also administered at all follow-up psychometric assessments. Because parental IQ predicts the child's IQ so strongly, the power of the study can be increased by adjustment for parental IQ in the comparison of treatment groups. Parental (in most cases maternal) IQ was tested once, usually after 1 year of follow-up, using the Wechsler Adult Intelligence Scale–Revised, Short Form (WAIS-RSF)[23] in English or Spanish. The two-subtest short-form includes vocabulary and block design and yields a full-scale IQ score.

At the 3 year follow-up visit, the children were between 48 and 69 months old and had a much greater range of competencies. Thus, the 3-year follow-up assessment included testing in more domains. This included the Conners' Parent Rating Scale–Revised, Short Form[24] and the Developmental Assessment of Neuropsychological Functioning (NEuroPSYchological, or NEPSY).[25]

The Conners' Parent Rating Scale–Revised, Short Form is a 27-item rating scale used to characterise patterns of child behaviour. The 27 items yield standard scores on three subscales: Oppositional, Cognitive Problems and Hyperactivity. The NEPSY is the first standardised neuropsychological examination developed specifically for preschool and primary school children. It is designed to identify underlying neurocognitive deficiencies that interfere with learning. The subtests of the NEPSY are divided into five functional domains: Executive Functions (including attention, planning and problem solving), Language and Communication, Sensorimotor Functions, Visuospatial Functions, and Learning and Memory. We believe that the results of the NEPSY will provide needed insight into the neuropsychological bases of lead-associated intellectual deficits. Because of the length of the test battery carried out at 36 months of follow-up, the NEPSY was administered during a separate testing session $\approx$ 14 days after the initial 3-year follow-up assessment.

Statistical methods

Among the tests of cognitive development and behaviour that the TLC will use at follow-up, the WPPSI-R provides the most reliable and understood measure of

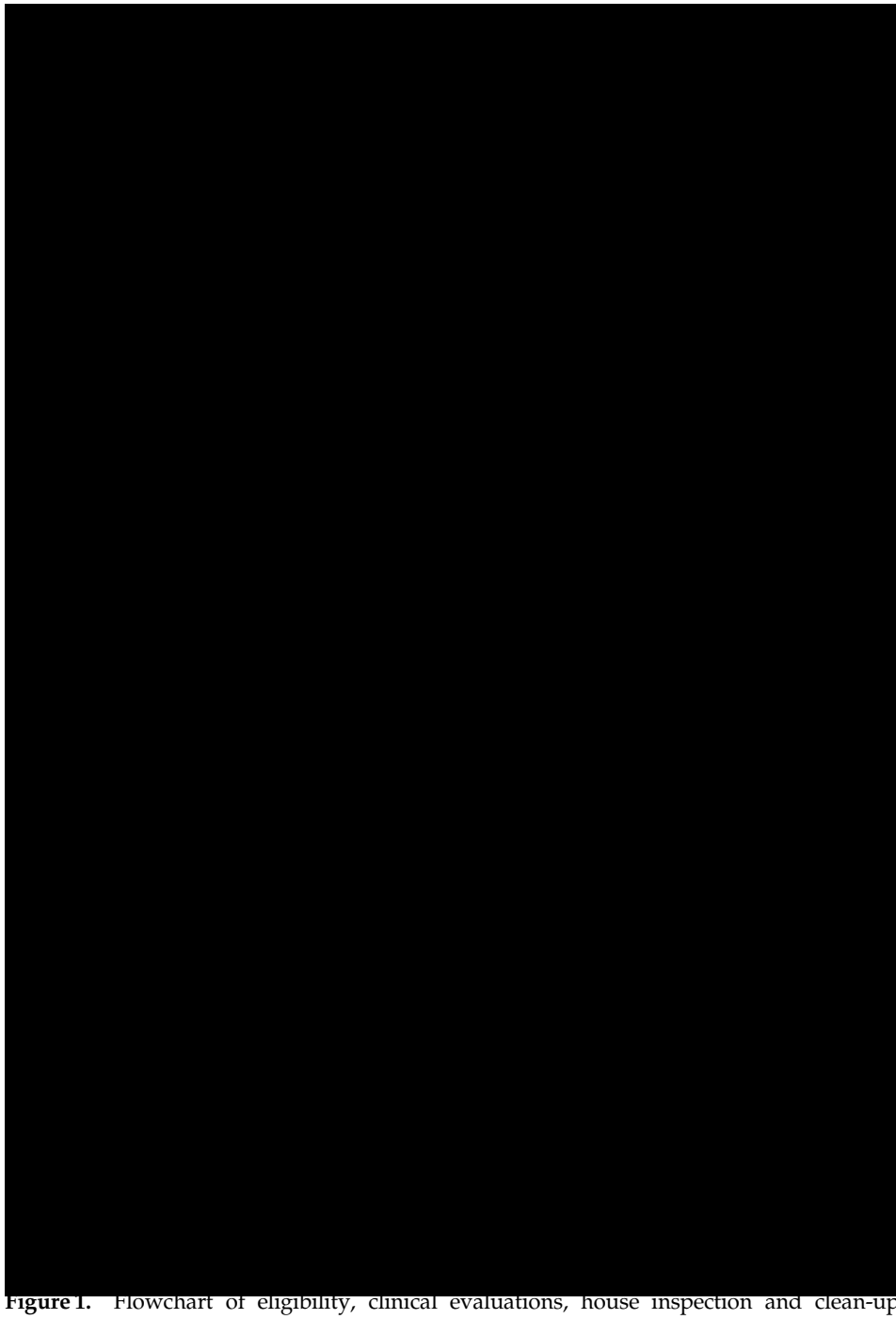

Figure 1. Flowchart of eligibility, clinical evaluations, house inspection and clean-up, and randomisation.

overall cognitive status. Thus, power calculations and the primary statistical analysis plan are based on hypothesised effects of treatment on the full-scale IQ from the WPPSI-R. The hypothesis that children who have received active drug will score higher on the WPPSI-R will be tested by analysis of covariance, using the WPPSI-R IQ score as the outcome variable, treatment group as the covariate of interest and adjusting for baseline IQ, as measured by the MDI score from the BSID2, maternal IQ, clinic and other predictors of IQ. Each study participant for whom a WPPSI-R score is available will be included in the analysis according to their treatment assignment (an 'intent-to-treat' analysis). Assuming that the 36-month WPPSI-R score will have a standard deviation of 14 in this sample, that 78% of the 780 randomised children will be tested successfully at 36 months and that adjustment for baseline IQ and maternal IQ will explain 16% of the variance of 36-month IQ, the TLC Trial has the power of 0.82 to detect a difference of three IQ points between treatment groups at 36 months. In observational data, a 10 μg/dL difference in blood lead is associated with as much as a three-point IQ difference.[1,2] In the trial, the mean blood lead at the beginning of therapy is 26 μg/dL, and the treatment goal is 15 μg/dL.

Secondary TLC end points include increase in stature and decrease in blood pressure over 3 years. Results for these end points at 3 years will also be evaluated by analysis of covariance. All end points measured repeatedly during follow-up will also be analysed using growth curve methods to test the hypothesis that the linear trend in mean scores differs between treatment groups.[26]

Table 3. Age, gender, race and primary language of children at the first three clinic visits

	First clinic visit ($n = 1854$)	Second clinic visit ($n = 1009$)	First treatment–randomisation ($n = 780$)
Age (months)			
Mean	23	24	24
SD	6	6	6
% Females	45	45	44
Race[a]			
% African–American	–	77	77
% Hispanic	–	6	6
% Other	–	5	5
% White	–	12	12
% Spanish speaking[b]	4	5	5

SD, standard deviation.
[a]Self-designated race/ethnicity; data not collected until second clinic visit.
[b]Care givers who signed Spanish consent documents. All Spanish-speaking children were enrolled at the Newark Clinic and comprised 19% of the randomised children at that site.

Results

A total of 1854 children had an initial TLC clinic visit between 10th August 1994 and 20th December 1996 (Fig. 1). At the first clinic visit, 35% of children had non-qualifying blood lead levels and 1% of children were ineligible for other reasons. An additional 3% of children were eligible at this visit but did not continue to participate. Of those continuing, 5% failed the house inspection. An additional 5% of children whose homes were eligible did not continue to participate. Of the 1009 children who came to the second clinic visit, 19% had non-qualifying blood lead levels and less than 1% were ineligible for other reasons. Four per cent of fully eligible children were not randomised, usually because of failure to return for the initial treatment visit. Most children had their housing inspected before the second clinic visit; however, 3% had the second clinic visit before the house inspection and subsequently were either ineligible or did not continue. Three of these children were randomised without their housing inspected by the TLC: one had moved elsewhere with relatives during scheduled inspection, one had a health department inspection and one was a family refusal. Two per cent of the homes of randomised children were never cleaned by the TLC, usually because of family refusal.

The proportion of children who are female, African–American and Spanish-speaking remains the same between the second clinic visit and randomization at the first treatment visit. All children are, of course, older at the second clinic visit, but there is no tendency for older or younger children to continue preferentially (Table 3). Of the 780 randomised subjects, 77% were African–American and 12% were white. In the Newark centre, 19% of mothers of randomised children spoke Spanish as their primary language. No differences were observed between

Fig. 2. [illegible] ment.

Table 4. Characteristics of randomised subjects at baseline by treatment assignment

	Placebo			Active drug		
	n	Mean	SD	*n*	Mean	SD
Age (months)	384	24	6	396	24	6
Baseline PbB (μg/dL)	384	26	5	396	26	5
Blood pressure (mmHg)						
Systolic	350	101	13	354	100	14
Diastolic	350	60	12	354	60	11
Height (cm)	384	86	6	396	86	6
Weight (kg)	384	12.3	1.9	396	12.3	2.0
BSA (m^2)	384	0.53	0.06	396	0.52	0.06
Head circumference (cm)	378	48	2	391	48	2
Birthweight (g)	361	3169	620	380	3135	551
	n	%		*n*	%	
% Female	384	43		396	45	
Race[a]	384			396		
% African–American		76			78	
% Hispanic		7			6	
% Other		6			4	
% White		11			12	
% Spanish-speaking[b]	384	5		396	5	

SD, standard deviation; BSA, body surface area.
[a]Self-designated race/ethnicity.
[b]Care givers who signed Spanish consent documents. All Spanish-speaking children were enrolled at the Newark Clinic and comprised 19% of the randomised children at that site.

treatment groups in the demographic characteristics of the families and anthropometric and physiological characteristics of the children.

The TLC protocol permitted treatment of children before housing clean-up if scheduling difficulties were extreme; although most such children had their housing cleaned up within 1 week of beginning treatment, 2% of randomised children never had their housing cleaned, usually because of parental refusal. The management of children after randomisation will be reported in a subsequent paper.

Nearly one-half of enrolled children had blood lead levels of 20–24 μg/dL at baseline (the second clinic visit) and 30% had blood levels between 25 and 29 μg/dL (Fig. 2). This distribution, heavily weighted near the low end of eligibility, was expected, given that the mean lead levels in the participating communities were below 10 μg/dL. The mean blood lead level at baseline was 26 μg/dL. The mean blood lead concentrations in the two treatment groups did not differ at baseline. Height, weight and consequently body surface area were similar in the two treated groups (Table 4) as were laboratory values (Table 1).

Table 5. Developmental status of randomised subjects at baseline by treatment assignment

	Placebo			Active drug		
	n	Mean	SD	*n*	Mean	SD
Bayley Scales of Infant Development II						
Mental Development Index	374	82	14	389	84	14
Psychomotor Development Index	334	93	13	347	93	14
Developmental age (months)[a]						
Cognitive	364	21	7	386	22	7
Language	358	21	8	374	21	8
Motor	365	23	8	379	23	8
Behaviour ratings (percentiles)						
Orientation/engagement	376	40	28	391	38	28
Emotional	376	41	29	391	44	29
Motor quality	376	44	27	391	45	29
Overall	376	38	27	391	39	28
Child Developmental Inventory						
General Development Subscale	380	29	10	393	29	10

SD, standard deviation.
[a]Mean calendar age of children at testing was 24 months.

The baseline developmental test scores of randomised children were far below age-based norms. The mean baseline MDI score on the BSID2 was 82.3, more than one standard deviation below the normed population mean of 100, whereas the mean baseline PDI score was 91.7. The mean developmental ages – cognitive, language and motor – were all below the mean calendar ages. The Behaviour Rating Scale scores were well below the 50th percentile. The CDI scores on the General Development subscale are at the age-appropriate level of 27 for 24-month-old children. The mean scores did not differ between treatment groups (Table 5). This dissociation between estimates of mental development based on testing (the BSID2) and estimates based on parental reports (the CDI) has been reported previously in studies of disadvantaged families using another instrument; however, another study using the CDI did not find the dissociation from developmental test scores.[27]

The families of randomised children consisted predominantly of single parents, usually mothers living without a partner (72%), with at most a high-school education (84%), and low mean maternal IQ (80). Most families participated in several assistance programmes (Table 6).

Discussion

Recruitment and eligibility

Approximately 45% of children seen in the TLC Trial did not qualify because of failure to meet the blood lead criteria at either the first or second clinic visit. Most

Table 6. Socio-economic characteristics and IQ of families of randomised subjects at baseline by treatment assignment

	Placebo		Active drug	
	n[a]	%	*n*	%
Parent without partner[b]	380	73	390	72
Highest grade achieved by either parent	383		396	
< High school		40		41
High school		43		41
> High school		17		18
Either parent employed	384	43	394	41
Family income ($000)	384		394	
< 10		36		39
⩾ 10		27		27
Don't know		37		34
Assistance received by family				
No public assistance	382	3	391	4
Aid to families with dependent children	372	67	394	66
Food stamps	382	84	392	78
WIC	379	72	392	72
Medicaid	378	81	386	82
	n	Mean (SD)	*n*	Mean (SD)
Household size	382	5.2 (2.0)	394	5.5 (2.0)
Parental IQ[c]	312	79 (10)	306	81 (11)

SD, standard deviation; WIC, Women, Infants and Children.
[a]*n* is the number of families on whom information is available for each item.
[b]Parents (usually mothers) who are single, divorced, separated or widowed.
[c]Parental IQ (usually maternal) assessed on or after 1 year of follow-up.

children with qualifying blood lead levels met the other eligibility criteria. High rates of ineligibility because of blood lead levels below 20 μg/dL are a natural consequence of regression to the mean when children with blood lead levels of 20–44 μg/dL are identified in a population with mean lead levels below 10 μg/dL. For the TLC, this problem was most severe in the Philadelphia centre, where almost all candidates were identified from a primary care population. In Philadelphia, 52% of screened children were ineligible because of non-qualifying blood lead levels. Centres that relied more heavily on referrals, such as Cincinnati and Newark, lost fewer children. Referred children often had had several high blood lead readings before they were referred.

The second most frequent single reason for ineligibility was housing. As explained above, we did not undertake a full lead paint abatement of homes, but instead attempted to minimise the child's exposure to lead in house dust and deteriorated paint by a combination of professional cleaning and minor repair work, or by relocating children to better housing. Only homes that could be cleaned

without causing further dust exposure and which our inspectors deemed stable enough to permit a reduction in lead in dust during the period of chelation treatment were eligible. Although this was not found to be a major barrier to recruitment, 5% of homes assessed failed to meet this criterion. Very few children had unexpected laboratory abnormalities or were excluded for other medical reasons. Approximately 6% of otherwise eligible children discontinued participation at some point before randomisation, usually because of poor compliance, refusal to give informed consent or incomplete eligibility determination at close of the recruitment period.

Characteristics of treated children

The mean age of the children at randomisation, 24 months, reflects the eligibility criteria and corresponds to the age at which peak blood lead levels are observed. The slight excess of males is also consistent with previous experience. The racial make-up of the sample, 77% African–American, reflects the catchment area populations of these urban clinics and the demography of lead poisoning in the US. The CDC has recently reported that 11.2% of black children have blood lead levels greater than 10 μg/dL compared with 2.3% of white, non-Hispanic children.[10]

The majority of the families have one parent, the mother, at home. Most of these mothers do not work outside the home and have family incomes of less than $10 000 per year. More than 40% of the mothers have not finished high school. They live mostly in older multi family houses or apartments, many of which are not well maintained.

Lead poisoning is a preventable illness, but its disappearance is probably another generation away. Meanwhile, if a simple oral treatment regimen in the context of inexpensive but effective residential lead hazard reduction or relocation of the family could prevent lead-associated developmental delay, it would be a useful adjunct to primary prevention until all children live in lead-safe housing. If lowering blood lead levels after they have been found to be high does not prevent the latent consequences of lead poisoning, then it has little to recommend it at levels below 45 μg/dL. Because cognitive impairment can have life-long consequences and many children will continue to be exposed to lead, information about the efficacy and safety of chelation therapy is necessary both for clinicians caring for the lead-exposed child and for policy makers.

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Acknowledgements

T. Shaffer, Program Support Center, US Department of Health and Human Services, Perry Point, MD, and E. Helzner, McNeil Consumer Products, Fort Washington, PA. Chemet® and placebo were gifts from McNeil. The TLC was supported by contracts and intra-agency agreements from NIEHS in cooperation with the Office of Research on Minority Health, NIH.

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