Chapter 8. Appraisal of Impact in Man

Treatment. The management of clinical and subclinical plumbism consists of two interrelated components: A. Chelation therapy and B. Control of excessive exposure. Chelation therapy does effect sharp and prompt reduction in tissue levels of lead; however, there is no evidence that it can even under prolonged administration remove all of the lead in the body. Experimental evidence would indicate that lead incorporated into calcareous bone is not accessible to chelating agents. Chelating agents therefore seem indicated and effective for reducing potentially toxic levels of lead, principally in the soft tissues, rapidly to less toxic or nontoxic levels. Three chelating agents are now in wide use. They are the calcium disodium salt of Ca versinate (CaEDTA), 2,3-dimercaptopropanol (BAL), and d-penicillamine (d-pen, PCA). DPTA and DMS have received brief clinical trials but their effectiveness relative to the agents in wide use in humans has not been adequately assessed. The preliminary data indicate that they are not significantly more effective. As discussed elsewhere (1) an adequate molar excess of chelating agent over lead is apparently essential for effective therapy. Under this principle the higher the estimate of body lead content the higher the dosage and intensity of chelation therapy. In the patients with the most severe degree of acute plumbism the highest doses of chelating agents consistent with safety are indicated.

An example of the effectiveness of prolonged calcium versinate therapy is shown in the two figures which illustrates the major laboratory changes that occurred in a sixty year old man who had had a seventeen-year exposure to lead dust and fumes while employed at a smelting plant.

Fig I
Fig II

The patient presented to the hospital with a myelopathy and peripheral neuropathy affecting the shoulder girdle bilaterally and the distal muscle groups of both upper extremities. His whole blood lead concentration was 67 μg%. Following an extensive evaluation of his endocrine status he was given sixty-four grams of calcium EDTA intravenously in two-gram doses and his response to therapy observed. Electromyographic studies demonstrated a disappearence of increased insertional potentials and fibrillations which had been present initially. His strength improved markedly in muscle groups which had been quite weak on admission. His hematocrit and mean corpuscular hemoglobin concentration rose to normal (Figure I), while his reticulocyte count which was as high as 4.0% initially when his red cell survival time was decreased to 17 days, decreased to the normal range.

Patient With Industrial Lead Intoxication

Figure 1

Response to Ca-EDTA THERAPY

Effect on Urinary Lead Excretion; Hematocrit, Reticulocytes, MCHC, BUN, and Serum Creatinine

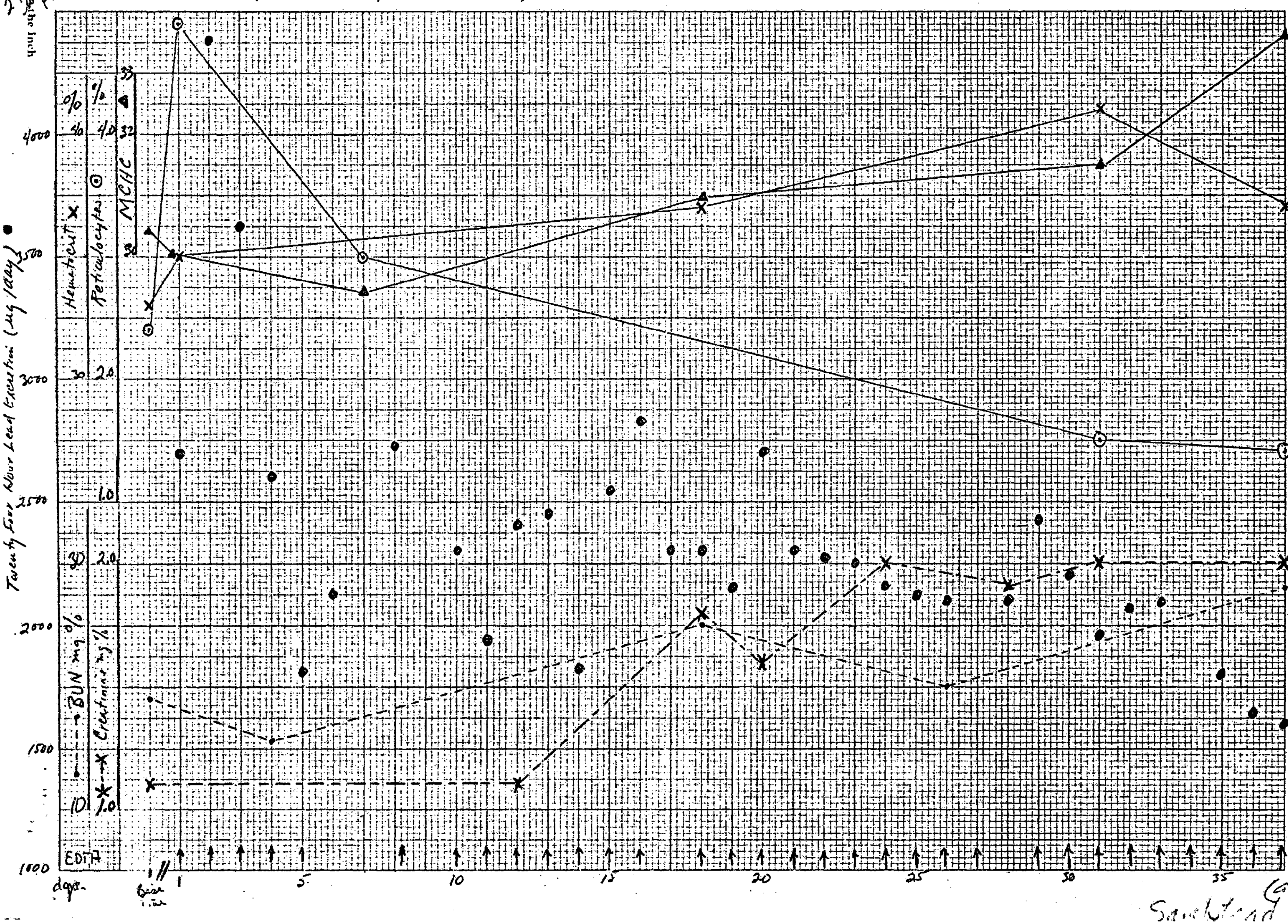

Fig. 11

It appeared that therapy was associated with a mild increase in impairment of his renal function as judged by an increase in his blood urea nitrogren and serum creatinine concentration from the initial levels. Excretions of lead appeared to be decreasing by the end of the thirty-seven days, but was still greater than 1500 μg / 24 hours. Figure II illustrates his plasma renin response to acute sodium deprivation and erect posture, before and following therapy. Both supine and erect plasma renin activity increased into the normal range following removal of lead. This finding [~~which has been submitted for publication~~] suggests that lead may impair the normal metabolism of the juxtaglomerular apparatus.

From the treatment point of view, these observations illustrate that responses to therapy may be slow in occuring in patients with large body burdens of lead. They also suggest that renal functional impairment may occur, and that renal function should be carefully monitored while giving therapy. Even though our previous experience suggests that these impairments are temporary, caution is certainly indicated.

The control of hazardous exposure is in the long run a far more important aspect of therapy. Repeated brief courses of chelation therapy instituted after the onset of severe clinical symptoms will apparently not prevent the occurrence of permanent injury to the nervous system and the kidney. No therapeutic agent is currently available which could be safely administered on a long term basis for the purpose of minimizing the absorption in the face of continued hazardous exposure. Current therapy may now be evaluated in terms of its efficacy, direct medical cost for acute and after care, and damage costs.

Efficacy of Chelation Therapy. The efficacy of chelating agents may be evaluated in terms of their influence on the mortality and known adverse health effects of lead on the nervous system, kidney and hematopoietic system. Prior to the advent of chelating agents in 1946 the mortality of severe acute lead encephalopathy was 66%. With BAL first and ~~EDTAx~~ Ca-EDTA a few years later the mortality from encephalopathy was reduced to 25 to 35%. With combined administration of BAL and Ca-EDTA this mortality can apparently be reduced to less than 5% provided that certain important supportive measures are incorporated in the therapeutic regime.[1,2] These critical supportive measures are as follows:

1. Prompt institution of chelation therapy, 2. Withholding of all oral fluids and restriction of parenteral fluid administration to basal requirements and minimal estimates for the replacement of fluid losses, 3. Prompt adequate and continuous control of seizures and 4. Maintenance of a patent airway and adequate ventilation.[3,4]

Severe lead encephalopathy may be defined as the presence of intractible seizures for a period of 24 hours or longer. In such patients the immediate threat to life abates after 48 to 72 hours except in those maintained in a vegetative state by means of artificial cardiopulmonary assistance. Acute illness of lesser severity (gastrointestinal symptoms, peripheral neuropathy) and subclinical manifestations of lead toxicity do not pose an immediate threat to life and can be treated satisfactorily with either Ca-EDTA (parenteral administration) or d-penicillamine (parenteral or oral administration) in lesser dose than that required for those patients with higher tissue levels of lead with or without central nervous system symptoms.[1,5,6] Since several of the biochemical and metabolic parameters of acute lead toxicity are promptly suppressed toward normal levels the duration of a course of chelation therapy is best monitored by quantitative measurement of urinary lead excretion during therapy.[6] When the

diuresis of lead under the influence of chelation therapy has largely subsided the course of therapy is terminated. Adverse side effects of chelating agents are described elsewhere.[1,5,6] d-penicillamine is widely used in Europe but in the United States its use is currently restricted and when used for the treatment of lead poisoning it is currently considered by the FDA as an investigational drug.

Certain acute toxic biochemical and metabolic effects of lead as well as acute clinical symptoms are rather promptly reversed with chelation therapy within a period of hours. Complete reversal at the subclinical level may require up to two months. (Without therapy such effects may subside slowly over a period of several months provided that excessive exposure is immediately terminated.) But, the anemia of plumbism and the hematopoietic paramenters of lead toxicity (excessive urinary excretion of ALA and coproporphyrin are promptly suppressed and the iron-deficient patient's response to iron therapy is restored.[1,5] The effect of therapy on elevated levels of free erythrocyte as above has not been adequately studied. Long term d-penicillamine therapy in children[1] and adults[6] can maintain normal hematologic indices in the face of continued diuresis of lead. With respect to acute renal injury the Fanconi syndrome (generalized amino aciduria of the renal type, melliturias, and hypophosphatemia with hyperphosphoturia) is also reversed without apparent residual injury.[7]

Normal mineralization of bone is restored following the return of serum phosphorus levels to normal. Similarly subclinical manifestation of deranged endocrine function and metabolism and plasma renin activity return to normal following chelation therapy.[8,9] It should be stated, however, that modern more sophisticated means

of assessing renal function have not been systematically applied on a long term basis in either children or adults to determine whether subclinical impairment of renal function persists following acute renal injury in the absence of continued excessive exposure.

Although the toxic effects of lead on the hematopoietic system are apparently completely reversible certain toxic effects of lead on the nervous system and kidney are not completely reversed by chelation therapy. There is no report in the medical literature of any beneficial effect of chelation therapy on the late lead nephropathy (with or without secondary gout), nor would any beneficial effect be anticipated in view of the profound impairment of renal function and the profound tissue injury found in the kidneys of such patients.[10,11,12,13] The responsiveness of impairment of peripheral nerve conduction[14] to therapy has not yet been assessed in either children or adults. However, the presence of pes cavus deformities in some patients with late lead nephropathy[11] and the preliminary finding of decreased peripheral nerve conduction velocity in the peroneal nerve of 3 institutionalized children 3 to 10 years after chelation therapy for acute lead encephalopathy[15] suggest that there is a point beyond which injury to peripheral nerves is not completely reversible by chelation therapy.

All reported clinical studies in children relative to central nervous system injury are of necessity retrospective in nature. Nevertheless, there is clear clinical evidence that at least 25% of children who survive an episode of acute encephalopathy sustain severe central nervous system injury and that such injury is permanent (profound mental retardation, seizure disorders, gross behavior disorders, ~~phonetic athetoid~~ optic atrophy and paralyses. ~~and~~ paresis). The results of followup studes in 425 children surviving plumbism reported by Perlstein and Attala[18] are summarized in Table III. Perlstein and Attala[18] observed that the severity and frequency of permanent brain damage appeared to be related to the mode of onset of acute plumbism: for example,

III

TABLE

SEQUELAE OF PLUMBISM BY MODE OF ONSET IN 425 PATIENTS

	Total (N = 425)		Mode of Onset: Enceph. (N = 59)		Seizures (N = 43)		Ataxia (N = 17)		G.I. (N = 232)		Febrile (N = 16)		Asymptomatic (N = 58)	
Sequelae	N	%	N	%	N	%	N	%	N	%	N	%	N	%
None	257	61	11	18	14	33	7	41	159	69	13	81	53	91
Present	168	39	48	82	29	67	10	59	73	31	3	19	5	9
Mental retardation	93	22	23	38	14	33	5	29	43	19	3	19	5	9
Seizures	85	20	32	54	17	39	6	35	30	13	0	0	0	0
Cerebral palsy	9	2	8	13	0	0	1	6	0	0	0	0	0	0
Optic atrophy	5	1	4	6	0	0	1	6	0	0	0	0	0	0
Total		106%†		123%†		105%†		117%†		101%†		100%		100%

†Percentages total more than 100% because of multiple sequelae in same patient.

From: Perlstein, M. A. and Attala, R.: Neurologic Sequelae of Plumbism in Children, Clin. Ped. 5:292, 1966.

82% of 59 children presenting with acute encephalopathy were left with permanent and often multiple disabilities, while 13% of 159 children presenting with GI complaints only were left with seizure disorders. These authors concluded that "the nature and incidence of sequelae seems to be unrelated to the type of treatment employed." [18] These reports just cited refer to the analysis of patients treated with either Ca-EDTA or BAL alone. Coffin, et al.[2] found permanent residual nervous system injury in 7 of 21 children with acute encephalopathy who were treated with combined BAL and EDTA. Childholm[16] currently has 10 childhood survivors of childhood encephalopathy treated with BAL and EDTA under followup. Of these 10, 5 are severely damaged despite therapy and despite rigorous prevention of further abnormal environmental exposure. One of the 5 is blind, one institutionalized, two have already been excluded from school while only one of the ten is of above average intelligence and functioning at a superior level in school. There are no detailed reports available which attest the relationship between chelation therapy and persistent but nevertheless significant nervous system handicaps such as perseveration, visual motor coordination, fine motor control, reaction time, etc in either children or adults. Clearly the limits of efficacy of therapy with respect to central and peripheral nervous function in both children and adults remains to be determined.

Control of Exposure. Haeger-Aaronsen[19] reported in occupationally exposed adult workers that urinary ALA excretion was quite sensitive to varying levels of exposure. In serial studies on a few individual workers she noted prompt decrease in ALA output on weekends and during vacations and conversely, she noted sharp increases when available safety procedures at the plant were temporarily disregarded. Salander and Cramer[20] instituted an occupational rotation plan whereby workers alternated on a regular basis between tasks with unavoidable high exposure and no exposure. They were

able to show that mean urinary ALA levels were lower in such rotated groups. But environmental hygiene, automation of hazardous industrial steps, personal good personal hygiene and rotation can apparently minimize metabolic abnormalities and the occurrence of overt illness in occupational situations.

In children it is clear that re-exposure to lead in deteriorated housing following a single known bout of acute encephalopathy increases the risk of permanent brain damage to virtually 100% (Table IV). [21] This observation has been confirmed by Byers[22] and others. Byers and Lord[23] noted the occurrence of mental handicaps in 19 of 20 children who did not have classical clinical encephalopathy: a careful re-reading of this report reveals that at least 13 of the 20 had long continued exposure to lead and recurrent episodes of plumbism throughout the pre-school years. It is likely that the data shown in Table I represent the outcome in children exposed to lead in old housing throughout the pre-school years: Perlstein and Attala report continued pica and continued exposure in many of their patients without stating exact figures. A similar principle applies to the consumers of *moonshine* nontaxpaid whiskey. Brief courses of chelation therapy followed by continued consumption of lead-contaminated moonshine will not prevent the risk of permanent nervous system and renal injury as described by Emmerson[11], Morgan[12] and others.

In some, control of excess exposure is the only known effective means of preventing serious functional impairment due to either very intense or very prolonged hazardous environmental exposure. It is clear that chelation therapy is not fully effective in reversing injury to the nervous system and kidney once it has occurred. In this light, chelating agents are seen as a useful but limited adjunct to adequate environmental hygiene: they are principally useful and effective for rapid reduction in high soft tissue levels of lead and should be administered on the basis of subclinical evidence of lead toxicity and prior to the onset of obvious clinical symptoms. The extent to which they may reverse minor functional impairment if administered at this level is not known at this time.

TABLE ~~V~~ ~~VI~~ IV

RELATION BETWEEN INCIDENCE OF SEVERE SEQUELAE IN THE CENTRAL NERVOUS SYSTEM AND RE-EXPOSURE TO LEAD FOLLOWING RECOVERY FROM AN INITIAL EPISODE OF ACUTE LEAD ENCEPHALOPATHY.

	Acute Lead Encephalopathy			
	Severe Cases†		Mild Cases	
	With Sequelae††	~~No~~ Severe Sequelae Absent	With Sequelae	~~No~~ Severe Sequelae Absent
Known re-exposure to lead	7	0	7	0
No known re-exposure to lead	3	6	2	17
	X^2=4.89; P<0.05		X^2=14.35; P<0.01	

†Four survivors of severe acute lead encephalopathy who sustained sequelae, but in whom reexposure to lead was uncertain, are omitted from the table.

††Sequelae=severe, permanent, residual damage to the brain (severe mental retardation, convulsive disorder, severe behavior disturbance).

From: Chisolm, J.J., Jr. and Harrison, H.E.: The Exposure of Children to Lead, Ped. 18:943, 1956.

Costs. Treatment costs may be divided into four components: 1) direct medical costs for acute and convalescent care, 2) after care, excess school costs and custodial care for the permanently injured, 3) correction of hazards in housing and 4) preventive health supervision. Children and adults are considered separately because of differences in exposure and other etiologic considerations (i.d., pica in children).

In young children since separation from exposure is the essential component of therapy, hospitalization is indicated. Out-patient treatment with daily injections of chelating agents into children with persistent pica and continued in tense environmental exposure cannot be condoned as either effective or humane management. While out-patient treatment may ~~hx~~ reduce public medical expense, it increases costs to parents of the effected children in the form of transportation costs, loss of work and neglect of other members of the family. Thus the epidemiology of childhood plumbism is such that these costs fall most heavily and directly on the poor who are least able to pay. Nevertheless, one treatment center[24] reports the treatment of even mild cases of acute encephalopathy on an ambulatory out-patient basis: presumably, this approach reflects the utter hopelessness and futility on the part of the ~~hx~~ physician that correction of the lead hazard in substandard housing can ever be attained.

The city of Baltimore is unique in the United States in having an "extended pediatric care facility" for convalescent home where children can be replaced and where they remain until a safe dwelling is found for the family.

The term "safe dwelling" is here defined as modern public housing or an adequately repaired old house. Table V lists actual direct medical costs under field operating conditions incurred between 1965 and 1970 in a group of 45 children with increased body lead burden. This group of 45 includes 10 survivors of encephalopathy. In this group average total days of acute and convalescent hospitalization was 100 days - and average direct hospital cost in 34 patients was $2,749. Virtually all of these children were hospitalized at public expense in hospitals that have a blanket basic charge and do not make charges for extras such as special nursing and intensive care. Not shown in Table V are the two highest hospital bills which were over $8,000 a piece. In one instance the high cost resulted from repeated hospitalization for complications of encephalopathy and in the other instance because of an excessively long wait for admission to public housing. This experience is not unique and the cost would be greater in other cities where children are retained in general hospitals for periods of from one to 3 months while an informal quest for safe housing goes on. In view of the rapid rate of rise of hospital costs during the past 5 years it can be estimated that direct hospital costs for the 45 children shown in Table V would in 1970 cost $5,498 on the average. (see Table VI) Chelation therapy with BAL and EDTA followed by oral administration of d-penicillamine requires an average of 10 days of hospitalization only. Asymptomatic dhildren do not require treatment in a general hospital but can be handled in a a convalescent facility at reduced cost. Thus, under this approach hospital costs beyond 10 days are directly attributable to delays in the completion of necessary housing repairs. Baltimore allows up to 6 weeks for completion of housing repairs before legal action is taken. New York and Philadelphia now limit the time allowed for compliance, repair the apartment at municipal expense and take out a lien on the property to recover the costs.

Table V

Title: Total Days of Hospitalization and Estimated Direct Medical Costs in 45 Children with Initial Blood Lead Levels Greater than 80 Micrograms Pb per 100 grams Whole Blood (Including 10 Children with Acute Encephalopathy) Who are not Discharged to Home until after Completion of Removal of Old Lead Pigment Paints from ~~the~~ Home Environment - Baltimore, Maryland, 1965-1970

Days of Hospitalization

	A Acute Care (General Hospital) (days)	B Convalescent Care (Happy Hills Hospital) (days)		Total A + B (days)
No. of Patients (45)				
Total Days	1108	3402	=	4510
Mean (Days/patient)	24.7	75.7	=	100.4
Median (Days/patient)	21	50	=	71
Range (80% of Patients)	4 - 70	20 - 203	=	25 - 253

Actual Costs*
(1965 - 1970)

No. of Patients (34)	
Total	93,377.16
Costs/patient-mean)	2,749.34
median	2,175.00
90% range	1,068.42 - 4,813.95

*Actual costs - Note that basic hospital rates virtually doubled between 1965 and 1970. Most of the 34 children for whom complete hoppital charges could be verified were hospitalized during 1965, 1966, and 1967 at public expense.

Table VI

Estimated Current Average Direct Medical Costs to Above ~~49~~ 45 Children
Based on 1970 Basic Hospital Rates in Baltimore, Maryland

	A Acute Care	B Convalescent Care		Total (A + B)
Unit Cost	$100/day	$40/day		
Total (45 children)	$110,800 (1108 days)	$136,000 (3402 days)	=	$246,800 (4510 days)
Mean cost/child	$2470 (24.7 days)	$3028 (75.7 days)	=	$5,498 (100.4 days)

n.b. Since the above children were handled under general policy that no child is discharged until either home is "deleaded" or family moves into safe modern housing, length of hospitalization is determined by this factor rather than severity of acute illness.

*Actual Costs - Note that basic hospital rates virtually doubled between 1965 and 1970. Most of the 34 children for whom hospital charges could be verified were hospitalized in 1965, 1966, 1967, at public expense.

Sustained medical followup for children with pica who live in substandard old housing is indicated for preventive purposes throughout the years of pica or for an average period of 3 yaars. The current costs for this are estimated at $120 based on a fee of $15 per out-patient clinic visit. For those with plumbism follow-up period ranges from 2 to 10 years for $225 to $675 per patient. The salary of a medical social worker or comparable paramedical personnel at one worker per 50 cases should be added to this figure. For children with moderately severe permanent brain damage who require special schooling excess school costs related to transportation costs and smaller class size are currently estimated at $1200 per pupil per year, for$14,400 for 12 years of school through high school per damaged child. For those children requiring institutionalization for custodial care, current costs at the Rosewood State Hospital in Maryland are approximately $4000 per year per patient. Data for other institutions in Maryland where such patients have been hospitalized in the past are not available and comparable data from other parts of the country are likewise not immediately available to the Committee. During the past 13 years 19 children had been admitted to the Rosewood State Hospital as a result of lead encephalopathy during early childhood [16]; one has died, two have recently been given leave of absence, leaving 16 children in residence at a current cost of $64,000 per annum. These patients have been hospitalized for a total of 148 patient years or 7.7 years per patient. None of the 16 remaining in residence are considered suitable for discharge. Should each one survive to 65 years of age the expenditure of 60 years of institutional care at $4000 per annum is estimated at $240,000 per severely damaged child. The total direct medical cost can therefore be estimated according to the final clinical outcome as follows: 1) asymptomatic increased lead absorption without obvious residual permanent injury - $1500 to $2000 per patient; 2) moderate permanent brain damage (special schooling required) $18,000 per patient and 3) severe permanent brain damage (institutional care required) $245,000 per patient at current medical costs.

These direct treatment costs may be contrasted with the cost of the repairs to substandard housing to eliminate the paint hazard. In Baltimore estimated costs range from $150 to $1200 per apartment depending upon the extent of repairs needed. New York City estimates costs at $1263 per apartment[25]. Since New York City repairs many apartments itself through the municipal emergency repair program, actual figures may shortly be available as the result of the program instituted in April 1970. Adequate housing repair is therefore comparable in dollars to the direct medical costs of treatment of a single asymptomatic child with increased body lead burden. Also repairs to substandard housing can prevent lead intoxication in the total number of children that may live in that house during the remainder of the house's useful existence. Were houses inspected and repaired prior to the onset of pica, direct medical costs could be totally eliminated.

Preventive health care costs for children cannot be precisely estimated at this time. With the exception of New York no comprehensive programs are in existence, at New York City estimates such costs at $12.50 per child for initial case finding and $6.51 per child for each follow-up visit, including blood lead tests. Current research is aimed at reducing the cost of screening both children and housing through improved techniques with a potential for automation and portability for field testing.

Treatment costs for adults can be considerably less. In the case of occupational exposure patients can be treated on an ambulatory basis because they can be easily and quickly separated from excessive exposure. Only in the case of severe illness is hospitalization required. In one instance the total hospitalization cost was $6693.95[27]. In the case of plumbism due to lead contaminated "moonshine" liquor repeated hospitalization occurred because of recurred ingestion and ready availability of "moonshine," specially in the Southeastern part of the United States. Late

lead nepropathy[12] can lead to total costs comparable to those in severely damaged children. Cost in adults might better be estimated on the basis of an impaired working efficiency and productivity were that data available.

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Lou's note. Find Selander and Crame from other reference and change spelling of Crame

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