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Behavioral Effects of Low Level Neonatal Lead Exposure[1]

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HASTINGS, L., G. P. COOPER, R. L. BORNSCHEIN AND J. A. MICHAELSON. *Behavioral effects of low level neonatal lead exposure*. PHARMAC. BIOCHEM. BEHAV. 7(1) 37–42, 1977. – Rats exposed to lead via maternal milk were tested at various stages of development on a number of behavioral tasks. Beginning at paturition, the dams were given either tap water, 0.02%, or 0.10% lead acetate in the drinking water. Pups from all three groups were weaned to normal chow and tap water at 21 days of age. The mean lead concentration of the dam's blood and of neonatal (20 days of age) brain and blood were all below 50 μg/100 ml. No significant differences were found between the high lead-exposed group and controls in general as measured by wheel running over a 21 day period beginning at 30 days of age. However, there was a significant difference in wheel running behavior during the first three hr of testing. Both lead-exposed groups were found to display significantly less aggressive behavior as measured by the shock-elicited aggression test. Low level lead exposure had no discernable effect on the acquisition and subsequent reversal of a successive brightness discrimination task. Lead exposure under these conditions appears to affect some aspects of emotional behavior, while having little effect on general activity or cognitive function.

Lead acetate Lead and activity Lead and aggression Lead and learning

IN RECENT years there has been much concern about the existence of possible subclinical effects in children resulting from low level lead exposure. Although the evidence is by no means substantial, an extensive array of behavioral disturbances, including hyperactivity, impulsiveness, and aggressiveness [1,12] has been imputed to low level lead exposure. In addition, varying degrees of intellectual impairment have also been reported to be associated with early exposures to low levels of lead [9].

Investigations of the effects of lead exposure on behavior using adult rats have yielded very little positive data [8,25], presumably because the CNS of adult rats is much less prone to insult due to decreased absorption of lead from the gut [15] as well as the reduced sensitivity which accompanies neural maturation [13]. Therefore, emphasis has shifted towards early exposure of neonates to lead, usually either via dam's milk or directly via injections or intubation. While in earlier experiments the exposure levels were quite high and produced symptoms of lead encephalopathy [18,19], more recent research has been characterized by exposure levels which produce blood lead levels more comparable to those found in the pediatric population.

One of the most often mentioned alterations in behavior purported to result from early lead exposure is hyperactivity, which has been reported in children [12] as well as rats and mice [21,22]. On the other hand, there are studies which failed to produce any evidence of increased motor activity in rodents exposed to lead [24] and several reports of hypoactivity [14,20]. Low level lead exposure also has been reported to impair performance on a variety of other behavioral tasks. In one study [11] in which lambs were exposed perinatally to lead, acquisition of a visual discrimination task was impaired in lambs with blood lead levels two weeks after birth as low as 25 μg/100 ml. In another study [23], rats exposed postnatally to lead by intubation and having a subsequent blood lead concentration of approximately 23 μg/100 ml at Day 35, showed both altered responsiveness to amphetamines as well as a performance deficit in a two-way shuttle task. In a similar study in which the exposure period lasted only the first 10 days after birth [7], learning deficits were reported for rats in the acquisition of a light–dark discrimination task. This protocol produced rats having elevated blood-lead levels at Day 11 (46 μg/100 ml) but were normal in terms of both body and organ weights by Day 21. Finally, in a recent study [14] it was reported that rats exposed continuously to lead acetate solutions (2000 ppm Pb) showed impaired performance on the initial acquisition of a visual discrimination problem, but not on a reversal procedure. Activity in the open field was also reduced compared to controls, but the lead-exposed rats showed improved performance on a shuttle avoidance problem. Blood or brain lead levels were not given, but lead concentration in both kidney and liver were significantly elevated.

That early low level lead exposure does exert some effect on rodent behavior is fairly well documented [7, 14, 20, 23, 24]. However, because of the wide variety of both exposure protocols and behavioral tests employed, the exact nature and significance of these effects remain obscure. Due to the wide variation in actual exposure that occurs when different routes of administration are used, in conjunction with differences in absorption at different ages, it is imperative that some index of body burden throughout the animal's life be determined if an evaluation of the effect

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of lead on behavior is to be meaningful.

In the experiments reported here we investigated the effects of early low level lead exposure and the resulting body burden on the behavior of developing rats. The exposure paradigm in which rat pups receive lead via the maternal milk supply [6] was used in order to reduce the effects of malnutrition and growth retardation usually associated with other exposure paradigms (e.g., 14,24]). As the rats matured, they were tested for level of general activity, aggressive behavior, and finally reversal learning using a visual discrimination task.

METHOD

Animals

A total of 48 male Long Evans (Charles River) rats were used in the study. They were randomly selected from a larger population composed of the offspring of 9 Charles River timed-pregnant females. The litters of the 9 females were all reduced to 6 male pups each on Day 7. The animals were ear punched at 30 days of age and given food and water ad lib until Day 90.

Treatment

The rat pups were exposed to lead via the dam's milk. Beginning on the day of birth, the dams were assigned to one of three groups and given either (a) tap water (<0.05 ppm Pb); (b) 0.02% Pb $(Ac)_2$ (109 ppm Pb); or (c) 0.1% Pb $(Ac)_2$ (545 ppm Pb). Lead acetate was dissolved in boiling distilled water. Water bottles were positioned so as to be inaccessible to the pups. This exposure paradigm was continued for 21 days, at which time all pups were weaned to tap water and Purina Laboratory Rat Chow, code number 5001 (Pb content, approximately 0.5 ppm) ad lib. Body weights were recorded daily for the first four weeks of life.

Lead Determinations

The amount of lead in milk from each dam, as well as the level in the blood was determined for the three groups. Milk and blood samples were collected on Day 20 and analyzed for lead content using atomic absorption technique. A complete description of the procedures has been published elsewhere [26]. Blood-lead and brain-lead of the offspring were determined for the various groups on Days 20, 60, and 270.

Activity

Due to limitations in the number of instruments available, only 12 rats from the control group and 12 rats from Group 3 (0.1% $Pb(Ac)_2$) were placed in Wahmann running wheels (Model No. LC 34) at 30 days of age. The individual wheels were not isolated from one another, but were located in an animal room removed from the normal flow of laboratory traffic. Purina Lab Chow and tap water were available ad lib; food and water intake as well as body weight were recorded weekly. In order to determine if there were any differences between the groups in response to a novel situation, activity (number of wheel turns) was recorded every hour, beginning at 2 p.m., for the first three hours. Recordings were made daily at 9 a.m. and 5 p.m. for the remainder of the experiment. The cages were cleaned and food and water weighed once a week. Activity from 9–5 was not recorded for these days. A 12-hr light–dark cycle (8 a.m.–8 p.m.) was in force throughout the study and the room temperature kept at 22 ± 1 C.

Aggression Testing

Pairs of animals, approximately 60 days old and housed together since birth (except for three weeks of isolation in the running wheels) were tested for shock-elicited aggression. The individual pairs (same treatment groups) were placed in a 25 × 30 × 38 cm chamber having a stainless steel grid floor. Fifty trials of scrambled AC shock (2 mA, 0.5 sec in duration) and with an intertrial inerval (ITI) averaging 20 sec were run. The resulting behavior between the pairs of animals was scored according to a system that is both concise and easily scored [4]. Briefly, behavior was placed into one of the following categories: (a) both animals fighting, lunging, striking, or biting; (b) only one animal fighting, lunging, striking, or biting; (c) one animal or both animals standing and facing (boxing); (d) no response other than running, jumping or vocalization. During all test sessions the scorer was unaware of the animals' experimental condition.

Flinch-Jump Testing

Since changes in shock-elicited aggression could be related to changes in responsiveness to shock, animals were also examined in a flinch-jump pain threshold determination to ascertain whether changes in shock-elicited aggression were independent of pain sensitivity. To determine pain thresholds, the rats were placed individually into the cage and subjected to an ascending series of shocks. Scrambled AC shock from a Coulbourn Instrument No. E13–16 shocker was administered to the rat beginning at 0.05 mA, then 0.1 mA and continued in increments of 0.1 mA. Shock duration continued for 10 sec with a 20 sec ITI. The shock intensity at which the rats first flinched and first jumped in response to the shock was recorded.

Visual Discrimination Testing

Twelve male rats from each of the three exposure groups were started on the visual discrimination task at approximately 90 days of age. The rats were run in four Coulbourn test cages which were housed in sound attenuated cubicles. Each cage was equipped with two retractable bars, a liquid dipper (0.1 cc reinforcement) and a houselight. All programming was controlled by Coulbourn logic modules.

The rats were first shaped to bar press on a single bar for liquid reinforcement: (1:1 condensed milk and water). Two retractable bars were then introduced one at a time and the rats were given equal practice on each bar.

The cues for the successive discrimination task consisted of onset of the houselight operated at the full 28 VDC (bright) or with a 460 Ω resistor in series (dim). Onset of the light in the bright mode required the rat to press the left bar for reinforcement. A correction procedure was not used, i.e., the trial terminated when an incorrect response was made and the bars retracted. Reinforcement consisted of 0.1 cc of condensed milk with a twenty second interval following reinforcement or termination of the trial.

The rats were run fifty trials a day, 6 days a week. Body weight was maintained at 85% of baseline value. When a rat reached criterion (45 out of 50 correct responses for three days in a row) a reversal procedure was initiated. Testing of

TABLE 1

LEAD CONCENTRATION IN RAT DAM'S BLOOD AND MILK AFTER 20 DAYS OF EXPOSURE DURING LACATATION

Concentration of Lead Acetate in Dam's Water	Dam's Blood Lead (µg%)	Dam's Milk Lead (µg%)
Tap Water	9±3*	<1
0.02%	24±5	21±2
0.10%	41±7	87±7

*All values represent the mean ± SE of 3–5 determinations.

TABLE 2

LEAD CONCENTRATION IN THE BLOOD AND BRAIN OF OFFSPRING AT 20, 60, AND 270 DAYS OF AGE. RATS SACRIFICED AT DAYS 20 AND 60 WERE LITTERMATES OF THOSE TESTED; VALUES AT DAY 270 WERE FROM RATS TESTED

	BLOOD LEAD CONCENTRATION (µg%)		
	20	60	270
Tap Water	11±4*	4±1	9±0.3
0.02%	29±5	5±0	9±0.7
0.10%	42±4	9±3	9±1.0
	BRAIN LEAD CONCENTRATION (µg%)		
Tap Water	12±2	14±0	12±1
0.02%	29±7	8±0	14±0.3
0.10%	47±10	14±0	20±4

*All values represent the mean ± SE of 3–5 determinations.

the rats ended after 96 sessions regardless of whether criterion had been met in the reversal procedure.

RESULTS

Lead Determinations

Both milk and blood lead concentrations for the dams are shown in Table 1. The importance of verifying the level of actual exposure is demonstrated by the fact that while the blood lead concentration of the dams in the 0.1% group was only approximately twice as great as that of those in the 0.02% group, exposure to the pups via the milk was at a level almost four times as high as the 0.02% group. Table 2 contains a summary of the concentration of lead in both blood and brain for the offspring of the three groups at Days 20, 60, and 270. It is quite evident that there exists essentially no difference in the 20-day old rats between blood and brain lead concentration at these exposure levels. Apparently, no barrier exists to prevent the equilibrium of lead between whole blood and brain during the first 20 days of life. By Day 60, however, the concentration of lead in both blood and brain was essentially equal for all three groups. Consequently, learning studies and aggression testing in this study was done on animals having normal concentrations of lead in blood and brain at the time of testing.

Growth

There were no significant differences in growth among the three groups. Mean body weight ± SE at Day 21 was: Control = 52.1 ± 1.6 g; low lead = 55.8 ± 0.6 g; and high lead = 55.3 ± 1.3 g.

Activity

Since the activity measurements were based on number of events per unit time, which results in a Poisson distribution, a square root transformation was used to normalize the data. Results of an analysis of variance of the first three hr showed no significant main effect of treatment, $F(1,19) = 0.41$, $p > 0.05$, but there was a significant main effect of hours, $F(2,28) = 5.41$, $p < 0.01$, reflecting the decrease in activity seen during habituation. Since the treatment X hr interaction was also significant, $F(2,38) = 4.79$, $p < 0.02$, a test for simple main effects on hours for the control group was performed and found significant, $F(2,40) = 12.21$, $p < 0.01$, while a similar test with the lead exposed group was not significant, $F(2,36) = 0.23$, $p > 0.05$. Thus the control group showed a significant decline in activity over the first three hours while the lead-exposed group, starting at a lower level than the controls, showed no significant change (see Fig. 1). Analysis of the activity levels over the total test period revealed that there were no significant differences between the groups in total activity over the three weeks or for activity during the night period only. Food and water intake as well as body weight also showed no significant differences between the groups.

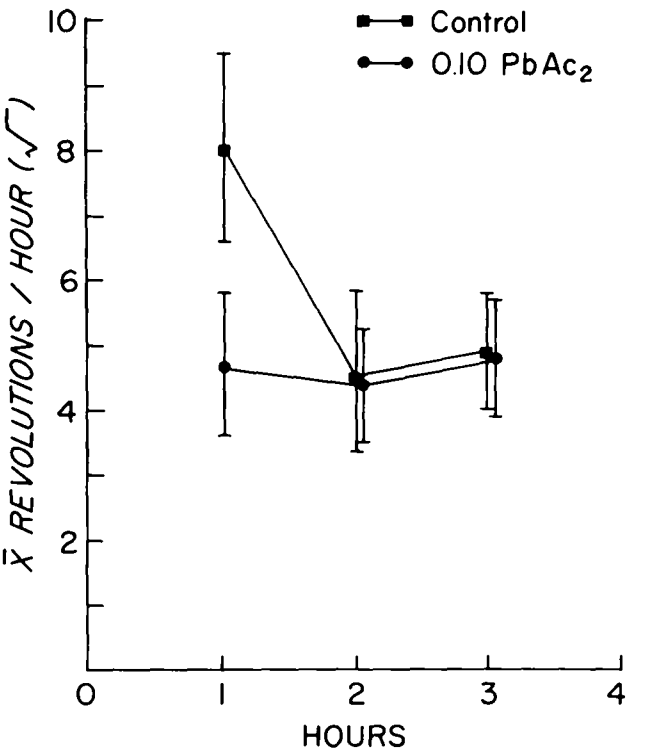

FIG. 1. First 3 hr of wheel running activity in 30 day old rats after initially being placed in running wheels.

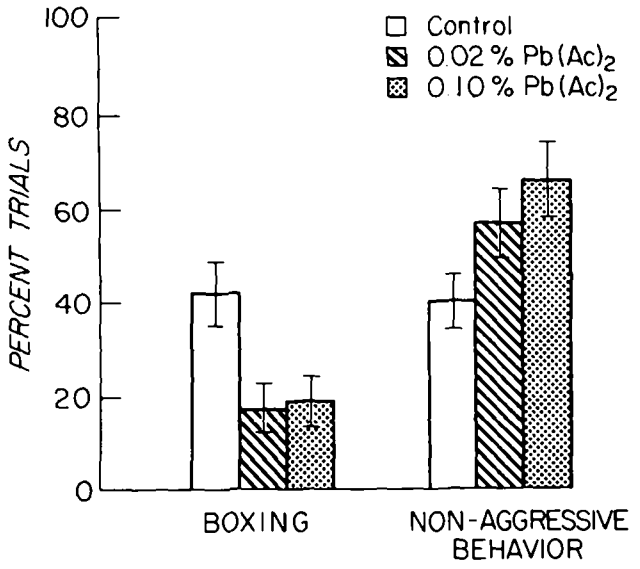

FIG. 2. Frequency of shock-elicited aggression in adult 9 week rats following neonatal lead exposure.

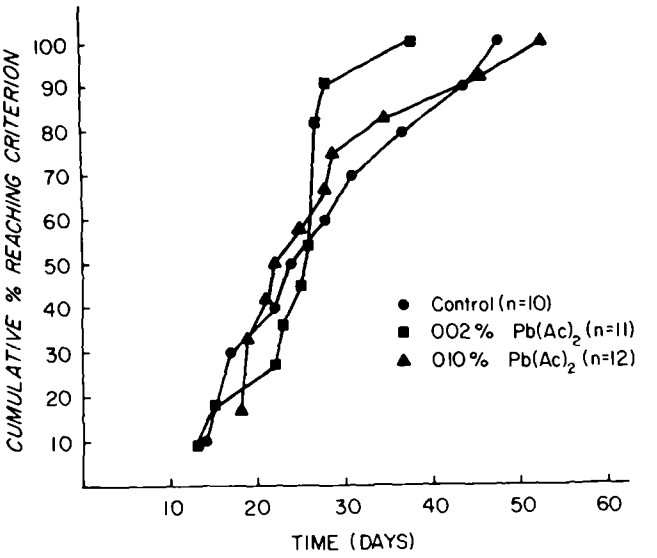

FIG. 3. Rate of acquisition of a successive visual discrimination task by lead-exposed rats.

Aggression Testing

From the reports in the clinical literature, and other sources [10,12] it was hypothesized that Pb-exposed rats would be more aggressive than controls. Results of the shock-elicited aggression test fail to support this. The number of trials on which an animal assumed the boxing position was taken as the independent measure since this behavior was unambiguous and easily scored. Analysis of this data showed that both lead-exposed groups displayed significantly less aggressive behavior than the control group, but did not differ from each other, $F(2,21) = 4.53$, $p < 0.05$; see Fig. 2. The same relationship existed when the trials in which nonaggressive behavior was displayed, were analyzed, $F(2,21) = 3.54$, $p < 0.05$; but the only difference between the high lead-exposed group and controls reached significance.

Flinch-Jump Testing

There were no significant differences among the groups with respect to either flinch threshold, $F(2,45) = 0.157$, $p > 0.05$, or the jump threshold, $F(2,45) = 0.201$, $p > 0.05$. The actual flinch threshold may have been slightly lower than the values obtained ($\bar{x}$ control = 0.059 mA; $\bar{x}$ low Pb = 0.056 mA; $\bar{x}$ high Pb = 0.056 mA) since a large number of animals responded even at the lowest intensity used. However, this seems to be a realistic value, since 0.041 mA has been cited [17] as the aversion threshold when a constant current AC shock source is used. Although it cannot be stated unequivocally that the stimulus used in the shock-elicited aggression test was equally aversive for all groups, the fact that the groups were equal at both flinch and jump threshold support this conclusion.

Discrimination Testing

Acquisition of the successive visual discrimination task by three groups is shown in Fig. 3. Figure 3 represents acquisition data for the original problem plotted as the

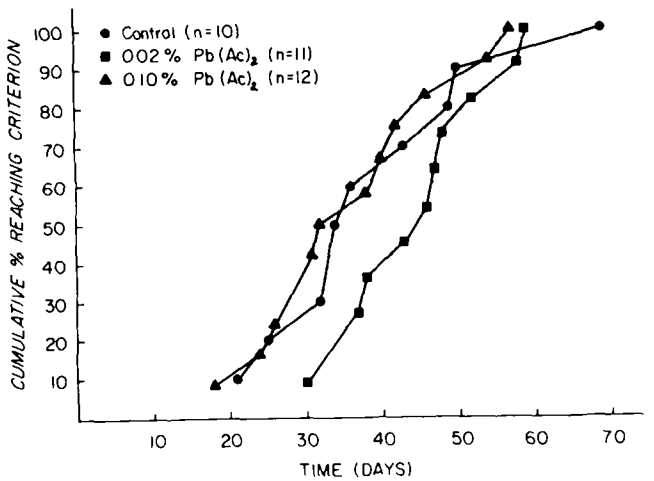

FIG. 4. Rate of reversal of a successive discrimination task by lead-exposed rats.

cumulative frequency over time of the percentage of animals acquiring the task. Figure 4 shows the results of the reversal task plotted in the same manner. Since the number of days to criterion was used as the index of learning speed, and this at most represents only an ordinal measurement, the data was analyzed using a Kruskall Wallis analysis of variance.

Results of the analysis indicate no significant differences among the three groups on acquisition of either the original problem, $H(2) = 0.25$, $p > 0.05$, or the reversal problem, $H(2) = 3.47$, $p > 0.05$. Nor does there seem to be any indication of a dose response relationship. That the task was sufficiently difficult to allow evaluation of the associative or learning capacity of the rats is supported by several factors: (1) mean latency for responding had stabilized at approximately 3–4 sec by trial 200 and (2) the average number of trials required for acquisition of the original

problem was approximately 1400 and for the reversal 2000. Since performance had stabilized rather early in the testing, the acquisition phase should thus reflect how well the rats were learning the contingencies of the discrimination task. It is realized, however, that due to the lengthy test period, variations in other factors, such as motivation, may have exerted some influence.

DISCUSSION AND CONCLUSIONS

In contrast with most other studies, an animal model was used in this study which produced none of the usual overt effects of high dose lead poisoning, such as body weight loss, or stunted growth. In addition, since the exposure was via the dam's milk, the rat pups were not subjected to any postnatal traumatic experiences, such as intubation or injection procedures, which might in themselves induce behavioral changes later in life. When confounding factors such as restricted nutritional status or other early stresses are inherent in the experimental design, the conclusion derived from studies of this nature are severely compromised.

We have previously reported a technique for estimating the daily lead exposure level for rat pups receiving lead via dam's milk [5]. Using this procedure, we estimated that prior to weaning our control, low dose and high dose pups are being exposed to external doses of approximately 0.004 mg/kg, 0.1 mg/kg and 0.5 mg/kg, respectively. Control pups compare favorably with the recommended daily permissible intake for young children which is 0.006 mg/kg [3]. These external exposure levels are considerably lower than the 5 to 50 mg/kg doses being administered by other investigators reporting behavioral changes [7, 8, 23, 24].

It should be emphasized that neither blood nor brain levels of rats used in these studies ever exceeded 47 μg/100 ml during exposure and were comparable to non-exposed animals at time of testing. At the exposure levels used there is no evidence that lead produces hyperactivity under conditions where the rats are maintained continuously in activity measuring devices such as activity wheels. Due to differences in instrumentation, age at testing and duration of the measurement period, there are no other studies with which this report can be compared directly. The present findings, however, are more in agreement with those studies reporting an absence of increased activity [19,20] than those reporting hyperactivity [21,22]. Consequently, the results of this study do not support the earlier findings of lead-induced hyperactivity and indicate instead that if early lead exposure produces hyperactivity, the effect may be minimal or evanescent in nature. A closer examination of both the animal models and techniques used in various studies might provide some information as to why conflicting results have been obtained. First, early nutritional status has been shown to be an important factor in determining the activity levels of rats later in life [2]. The level and duration of exposure reported in previous studies [14,24] are sufficiently large to cause significant changes in growth, especially in earlier developmental periods. A recent study conducted in this laboratory provides strong support for the hypothesis that the observed hyperactivity may be due to malnutrition usually accompanying high lead exposure [16].

A second important factor, the type of activity measured, must also be taken into consideration. Most reports purporting to have examined hyperactivity have looked only at very short intervals of activity. Consequently, the measurements probably reflect the animal's responsiveness or reactivity to a novel environment more than activity per se and might be responsible for the depressed level of activity of lead-treated rats during the first hour of testing in this experiment. In a previous study involving activity measurements in an open field, a similar depression in activity was reported for lead-exposed rats [14]. A valid estimate of the general activity level of an animal should include long term periods of measurement to control these factors.

While early lead exposure does not appear to alter general activity levels, the finding that the lead-exposed rats were less aggressive than controls suggests the possibility that early lead exposure can produce a permanent alteration in behavior which would not be indicated by examination of blood lead levels later in life when blood levels might be essentially normal, as they were in this study. Presumably, the initial high levels of lead shortly after birth produce some degree of central nervous system dysfunction which persists in the adult animals. Consequently, another measure of total lead exposure, such as urinary lead following a chelation challenge, might be a more valid index of possible risk.

The failure to find any significant differences among the groups on the visual discrimination task with reversal was quite unexpected. The difficulty of the present task when compared to tasks used by others [7, 14, 24] should have provided the sensitivity to detect any subtle differences that might have existed. One major difference is that most of the other studies were run in mazes, while this one was conducted in operant chambers. While there are undoubtedly some differences between the two test procedures, the basic paradigms are generally the same, with the operant chamber allowing greater uniformity in test conditions and minimizing the experimenter-subject interaction.

An alternate possibility is that the present task measured an aspect of behavior (successive discrimination learning) that is not affected by early lead exposure. However, lead-exposed rats have previously been shown to be impaired in the acquisition of a successive discrimination task [7]. Consequently, while it does appear that early exposure to lead does result in alterations in behavior later in life, the exact nature of the behavioral impairment and corresponding locus of effect still remains to be defined.

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