

CLINICAL SIGNIFICANCE OF HEMATOLOGIC CHANGES IN LEAD ABSORPTION AND LEAD POISONING

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ANY discussion of the clinical significance of changes in the blood in relation to absorption of lead and lead intoxication can be kept brief for two reasons: First, the facts as to clinical significance have been established and confirmed,¹ and second, the status of knowledge as to pathogenesis of the changes is so equivocal and ill defined as to be of limited general interest. Any merit which added discussion may have, therefore, will be that of emphasis by restatement, in an endeavor to direct the clinical effort to the patient himself and to the more definitive analytic data.

Recent studies of Kench, Gillam and Lane² and the observations of Falconer³ are in support of the thesis that the basic hematologic disturbance in lead poisoning is an interference in the formation of protoporphyrin brought about by depression in cellular activity rather than by blocking of the formation of the iron-prophyrin complex. This interference results in nonutilization of protoporphyrin and consequent porphyrinuria, disturbed synthesis of hemoglobin with hypochromic anemia and an increased hemoglobin metabolism.⁴

At one time or another almost all elements of the blood picture have been studied for their possible significance as criteria of lead intoxication. All deviations were found to be nonspecific. Two changes, however, occur with sufficient frequency and of such an order of magnitude as to be useful, though not definitive, diagnostic aids. These are punctate basophilia (or stippling) and reduction in hemoglobin.

STIPPLING

Stippling, the hematologic change most commonly thought of in connection with plumbism, is, like polychromasia, essentially an abnormality

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1. Kehoe, R. A., and others: Report of the Committee on Lead Poisoning, New York, American Public Health Association, 1943.
2. Kench, J. E.; Gillam, A. E., and Lane, R. E.: *Biochem. J.* **36**:384, 1942.
3. Falconer, E. H.: *Am. J. M. Sc.* **203**:857, 1942.
4. (a) Pfeil, E.: *Ang. Chem.* **53**:374, 1940. (b) Mangeri, S.: *Med. d. lavoro* **31**:97, 1940. (c) Robschey-Robbins, F. S., and Whipple, G. H.: *J. Exper. Med.* **63**:767, 1936.

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mality in the behavior of the erythrocytes to stains. That both polychromasia and stippling are manifestations of reticulation has been fairly well established by the fact that the proportions of polychromatophilic cells and stippled cells are largely determined by the method of staining,⁵ while the sum of the two elements parallels the reticulocyte count. It appears probable,⁶ though not certain, that persistence of the same reticular substance is responsible for all three types of cells, since the form of the reticular material in supravital specimens does not indicate whether the fixed, stained cell will be stippled or polychromatophilic. Toxic agents, such as lead and phenylhydrazine, influence the basic reticulum in some unknown fashion, this alteration being evidenced in the abnormal staining reactions.^{5c}

Significance of Stippling.—Since stippling is not a specific change in the blood unique in lead absorption and is commonly present in the normal, nonexposed population⁷ and since no characteristic morphologic differences in stippling occur, it is evident that any clinical significance that obtains will be determined by quantitative relationships. The first requisite for this is a method of measurement that will give reproducible results characteristic for the method. No standardized method is yet established. It is known that the stain, the time, the pH , etc., will affect the counts,⁸ and there is, moreover, good evidence⁹ that the manner of preparation of specimens, the temperature, the humidity and the time of drying will influence the results profoundly. This status of affairs is responsible in large part for the divergence in values that have been reported for nonexposed groups and greatly limits the practical value of what can be a useful tool. For example, in table 1 are given a number of values reported for nonexposed normal and diseased persons and exposed groups. It may be seen that the ranges in values are extremely wide. Similar, smaller, differences in magnitude are evident in the proposals for threshold values for lead intoxication. A few such are given in table 2. The authors' comments reflect the uncertainty which exists when one attempts the establishment of any threshold value.

It follows that the clinical significance of a single stippled cell count must be interpreted in the light of method, associated disease, etc. With

5. (a) Schmidt, P., and Weyrauch, F.: Ueber die Diagnostik der Bleivergiftung, Jena, Gustav Fischer, 1933. (b) Pappenheim, A.: Folia haemat. **24**:1, 1919. (c) Whitby, L. E. H., and Britten, C. J. C.: Lancet **1**:1173, 1933.

6. Rosegger, H.: Klin. Wchnschr. **15**:158, 1936.

7. (a) Kehoe and others.¹ (b) Footnote 5. (c) Rosegger.⁶ (d) Falconer, E. H.: Ann. Int. Med. **12**:1429, 1939. (e) Teleky, L.: München. med. Wchnschr. **71**:266, 1924. (f) Kehoe, R. A.; Thamann, F., and Cholak, J.: J. Indust. Hyg. **15**:257, 1933. (g) Sanders, L. W.: ibid. **25**:38, 1943.

8. Kehoe.¹ Pappenheim.^{5b} Whitby and Britten.^{5c}

9. Bruckner, H.: Arch. Hyg. **98**:95, 1927.

the same method, however, repeated counts on persons and groups are useful indexes of magnitude of lead absorption, especially when sudden and progressive increases in counts occur. The erratic character of the

TABLE 1.—Means and Ranges in Values of Stippled Cells per Million Erythrocytes

Author	Stain	Number	Mean	Ranges	Sample
Brown, E. W.: J. Indust. Hyg. 113, 1926	Wright	55	0		Normal subjects
Wokan and Smirnowa ¹⁰²	M-B*	...	0		Nonexposed workmen: stippling only with anemia
Mayers ¹⁰³	M-B	250	0	0-1	Normal subjects; only 1 stippled cell found
Falconer ⁷⁴	J-G†	205	92	0-400	Normal subjects; 25% had no stippling
Falconer ⁷⁴	J-G	254	363		Nonexposed patients
Sanders ⁷⁵	M-B	2,231	374	0-5,000	Nonexposed oil refinery workers; 5% had no stippling
Sanders ⁷⁵	M-B	82	416	0-2,500	Medical students; 45% had no stippling
Nelson, Lockwood and McKay ¹⁰¹	M-B	255	937	0-7,000	Nonexposed workers
Lane ¹⁰⁴	M-B	223	...	0-2,000	Normal subjects; 50% had no stippling
Nelson, W. T.: M. J. Australia 1: 310, 1931	M-B	...	...	0-4,000	Healthy men; 15% had no stippling
Nelson, W. T.: M. J. Australia 1: 310, 1931	M-B	...	...	0-7,200	Nonexposed clerks; 24% had no stippling
Kehoe, Thamann and Cholak ⁷⁷	M-B	60	960	0-6,000	Native Indians, men, women and children
Falconer ⁷⁴	J-G	5	2,000+		Patient without lead exposure
Falconer ⁷⁴	J-G	1	27,000	—52,000	Patient without lead exposure
Sanders ⁷⁵	M-B	20	480	0-1,400	Hazardous exposure; 45% had no stippling
Falconer ⁷⁴	J-G	8	2,100		Paint manufacture
Sanders ⁷⁵	M-B	20	2,912	6-7,200	Hazardous exposure; 100% had stippling
Nelson, Lockwood and McKay ¹⁰¹	M-B	59	4,335	0-20,000	Slight exposure to lead
Nelson, Lockwood and McKay ¹⁰¹	M-B	41	14,220	0-20,000	Storage battery workers
Nelson, Lockwood and McKay ¹⁰¹	M-B	12	36,382		Persons with lead poisoning

* Methylene blue.

† Jenner-Giemsa counterstain.

TABLE 2.—Proposed Threshold Values for Stippled Cells per Million Erythrocytes

Author	Value	Note
Schmidt, cited by Falconer ⁷⁴	100	"Indicative of intoxication"
Schmidt and Weyrauch ⁸⁸	500	"Pathognomonic for intoxication"
Schmitter, cited by Falconer ⁷⁴	800-1,000	"Suggests increased absorption"
Kehoe and others ⁷⁷	1,000	"Suggests increased absorption by groups"
Sanders ⁷⁵	5,000	"Requires additional evidence to attain diagnostic significance"
Sanders ⁷⁵	9,000	"Defines lead intoxication"
Falconer ⁷⁴	16,000-23,000	"High probability of being due to lead intoxication"

stippled cell response and the dangers of relying on results of a single sampling, even in groups, have been well demonstrated by Sanders,⁷⁵ who found a normal mean value (480 per million) and ranges, for one

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month, in a group of 20 men with hazardous exposure (as evidenced by a mean urinary concentration of lead for the group of 0.128 mg. per liter). These results may be compared with mean stippled cell counts of 2,912 per million (ranges 6 to 7,200) obtained eight months before, when the urinary excretion of lead for the group was 0.191 mg. per liter.

Critical evaluation of the best information at hand¹⁰ makes it possible to elaborate certain statements as to the validity and clinical significance of stippling.

(a) Stippling and polychromasia are the result of the reactions of reticular substance to stains, and are indications of activity of the marrow.

(b) Alterations of the reticular substance, especially the alteration caused by lead, will lead to increases in stippling.

(c) Stippled cells are present in nonexposed, normal persons at times in numbers up to 7,000 per million. In diseases other than lead poisoning (hepatic cirrhosis, pulmonary disease) and especially in the blood dyscrasias, stippled cell counts as high as 50,000 per million may occur without associated lead exposure. Single counts therefore may have value only when critically applied.

(d) Hazardous lead absorption usually but not always causes elevations in stippled cell counts; when it does, the relationship is general and direct but erratic and with wide ranges of variation for single observations.

(e) The greatest value of stippled cell counts derives from recurring observations on groups of exposed workmen and comparison of these results with previous values for the group and with values for nonexposed controls. Repeated observations in individuals are of more limited usefulness when used as an index of hazardous absorption or as a diagnostic or prognostic criterion in lead intoxication.

(f) No critical stippled cell level for hazardous lead exposure can be set. Considerable experience with a uniform method in a given situation may enable prediction of likelihood of occurrence of cases of intoxication in groups. Any threshold value, however, cannot be applied elsewhere owing to the pronounced influence of technic on the counts.

(g) High stippled cell counts occur with great frequency in active lead poisoning. Absence of stippling in cases of suspected poisoning is good evidence that some agent other than lead is responsible.

10. (a) Kehoe.¹ (b) Schmidt and Weyrauch.^{5a} (c) Whitby and Britten.^{5c} (d) Falconer.^{7d} (e) Sanders.^{7g} (f) Mayers, M. R.: *J. Indust Hyg.* 8:222, 1926. (g) Kogan, B., and Smirnowa, L.: *ibid.* 9:435, 1927. (h) Lane, R. E.: *ibid.* 13:276, 1931. (i) Nelson, W. T.; Lockwood, L., and Mackay, K.: *M. J. Australia* 2:317, 1932.

(h) There is urgent need for a standardized method for quantitation of the altered reticular substance.

HYPOCHROMIC ANEMIA

Hypochromic anemia, with reduction in mean corpuscular hemoglobin and porphyrinuria, is believed by some ^{11, 12} to be the most sensitive index of hazardous lead exposure, and where it is possible to repeat examinations at frequent intervals it is undoubtedly an excellent index of the general health of the worker. Despite this, the consensus leads one to the conclusion that hypochromic anemia is even less specific than stippling, since it so frequently results from environmental factors, under-nutrition and disease. Moreover, the degree of reduction in hemoglobin is never great, and the mean levels for groups do not always relate well to the magnitudes of exposure.¹¹ Even in cases of lead intoxication during the acute episode, individual hemoglobin and erythrocyte values fall within ranges like those of nonexposed workmen.¹² I may state, then, that though reduction in the hemoglobin content of erythrocytes may be an early index of hazardous lead absorption, the reductions which occur are usually slight, not closely related to magnitude of exposure and not differentiated from hypochromic anemia arising from other common causes. Hemoglobin concentration, like weight, is best employed as an index of the general state of health and nutrition.

OTHER CHANGES

Significant changes in leukocytes and platelets do not occur except in severe acute intoxication and when large therapeutic doses of lead are given¹³ and are neither noteworthy nor specific. In clinically active poisoning, leukocyte counts are usually within normal limits.¹²

Erythropoietic activity of the marrow is evidenced by the appearance of reticulocytes in the peripheral blood (normally from 0 to 2 per cent of erythrocytes). It is to be expected that any agent, such as lead, which affects hemoglobin metabolism will cause changes in reticulocytes. The qualitative changes (stippling and polychromasia) have been mentioned in a preceding section. In addition, increases in the absolute numbers of reticulocytes are commonly seen with lead absorption. Some reports suggest a rather close correlation between reticulocyte counts and order and duration of exposure when large groups are studied.¹¹ In individuals and small groups, however, reticulocyte counts appear to be a no more sensitive and significant index than does stippling. This is in keeping with the common observation of the erratic character of reticulocyte responses both after therapy and as a result of action of harmful agents.¹⁴ Since

11. Dreesen, W. C.: *J. Indust. Hyg. & Toxicol.* **25**:60, 1943.

12. Ashe, W. F.: *J. Indust. Hyg. & Toxicol.* **25**:55, 1943.

13. Falconer,³ Brookfield, R. W.: *J. Path. & Bact.* **31**:277, 1928.

14. Minot, G. R., and Castle, W. B.: *Lancet* **2**:319, 1935.

stippling is a manifestation of altered reticular material the vagaries of the two will be associated. Correspondingly, the technic for basophilic aggregation of McCord,¹⁵ which enumerates reticulocytes as well as other basophilic material in the erythrocytes, would be expected to give related values, possibly more sensitive, but not more specific.

Corpuscular fragility, in lead absorption at one time received considerable attention, and both increased¹⁶ and decreased fragility has been reported in cases of lead intoxication. No recent, well controlled studies have been reported. In view of the problems of interpretation of corpuscular fragility tests, and the varying criteria used for lead intoxication on which statements have been based, it is my opinion that determinations of corpuscular fragility are of less diagnostic value than are simpler technics such as the technic for stippled cell counts.

CONCLUSIONS

1. Lead interferes with synthesis of protoporphyrin and alters the reticular substance, but there are no specific hematologic changes in lead absorption.

2. Basophilic stippling becomes significant with respect to lead absorption when subject to the following conditions: (a) with employment of a uniform method for which normal ranges of values have been defined, (b) when repeated frequently on groups and used as an index of trends in exposure, (c) as supportive evidence in the diagnosis of lead intoxication and (d) in the exclusion of lead intoxication.

3. Other hematologic changes are more variable and less characteristic than is the stippling.

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15. McCord, C. P.; Holden, F. R., and Johnston, J.: *Am. J. Pub. Health* 25:1089, 1935.