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HEMATOLOGIC STUDY OF LEPROSY PATIENTS TREATED WITH DIASONE¹

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CHARACTERISTICS OF THE ANEMIA PRODUCED BY DIASONE

The use of the sulfones is increasing daily. Diasone is a particularly valuable therapeutic agent for the practising physician, because of the ease with which it can be prescribed by mouth. However, this drug often produces an anemia which

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may interfere with continuous treatment. We have, therefore, thought it useful to study the salient features of this anemia, in order to help the physician confronted with such an occurrence.

Clinical symptoms. In a previous paper two of us (Fernandez and Carboni) drew attention to the fact, also noted by other workers, that treatment with diasone frequently produces an anemia which is characterized by the following symptoms: Asthenia and depression, observed in 89 per cent of cases, especially when more than 1 gram per day of the drug is given; cyanotic color of the skin and mucous membranes, due to the formation of methemoglobin; headache, sometimes associated with dizziness, observed in 74 per cent of cases; fatigue and shortness of breath on exertion, observed in 49 per cent of patients undergoing treatment.

These clinical symptoms often appear early, in the first weeks of treatment, and the greater the degree of anemia the more evident they are. They abate immediately on withdrawal of the drug, or under treatment with antianemia remedies.

Alterations of the blood count. Diasone produces a decrease in the number of red blood cells and the hemoglobin content, but no change in the white cell count. In a study of 140 patients undergoing treatment we found almost all to be suffering from anemia of varying intensity. The number of red blood cells decreased in the following proportions:

| Decrease | less than 1 million | 37 | cases | (26%) |
|----------|----------------------------|----|-------|-------|
| Decrease | between 1 and 1.5 millions | 38 | cases | (27%) |
| Decrease | between 1.5 and 2 millions | 41 | cases | (29%) |
| Decrease | more than 2 millions | 24 | cases | (17%) |

As regards the hemoglobin we observed:

| Hemoglobin 1 | more than 80 per cent | 24 | cases | (17%) |
|--------------|-----------------------|----|-------|-------|
| Hemoglobin ' | 79—70 per cent | 36 | cases | (27%) |
| Hemoglobin | 69—60 per cent | 49 | cases | (35%) |
| Hemoglobin | 59—50 per cent | 24 | cases | (17%) |
| Hemoglobin 1 | less than 50 per cent | 7 | cases | (5%) |

In our first paper we described two cases in which the anemia was of unusual severity. In one of these cases the red blood cells decreased to 2,190,000 and the hemoglobin to 39 per cent; in the other case the red cell count was 2,510,000, with 40 per cent hemoglobin. Since then we have observed a third case where the severity of the anemia was even more alarming, the red cell count being only 1,780,000 and the hemoglobin 32 per cent. In all three cases there was hyperleucocytosis. Happily, all of the cases of severe anemia produced by diasone have responded favorably on withdrawal of the drug and administration of antianemia treatment. Blood transfusion was used in the first two cases mentioned but not in the third in spite of its greater severity.

Relationship between the anemia and the dosage and the length of treatment. We have found that as a general rule the severity of the anemia is in direct relation to the dosage of the drug, though there are individual variations due either to hypersensitivity to the drug or to greater resistance to its toxicity. The occurrence and severity of the anemia were much greater when we started treatment with doses between 1.5 and 2.5 grams daily, than now when the usual daily dose is 1 gram.



TEXT—FIG. 1. Curves showing the red-cell counts, the hemoglobin content, and the reticulocyte counts in three cases, random selection. Solid line: erythrocytes; broken line: reticulocytes; dotted line: hemoglobin. Treatment suspended for Domingo R. at end of 3rd week.

We have also observed that the reduction of the daily dose of diasone decreases the frequency of leprous reaction, which seems significant as we have noted a definite relationship between that condition and the anemia.

The decrease in the number of red blood cells and hemoglobin content is an early symptom, which is already noticeable at the beginning of the second week of treatment and which increases in severity as the treatment continues. The figures tend to return to normal during a resting period of four weeks following interruption of treatment, usually reaching the normal level at the end of that time.

Text—figure 1 indicates the values in three cases taken at random, showing the progress of the anemia in relation to length of treatment.

White blood cells. We have not seen any case of severe leucopenia among our 200 patients under treatment. There was however, a decrease in leucocytes varying between 1,000 and 2,000 in 19 per cent of them, and between 2,000 and 4,000 in another 18 per cent. Several times we started treatment with diasone in patients already showing moderate leucopenia, but it caused no further change.

MECHANISM OF THE PRODUCTION OF ANEMIA BY DIASONE

In order to throw light on the pathogenic mechanism involved in the action of diasone leading to anemia, it seemed desirable to study a group of patients using exact hematologic techniques. We started on the basis of two possible hypotheses: (a) that diasone acted as a toxin on the bone marrow (myelotoxic anemia); or, (b) that it was a red blood cell toxin (hemolytic anemia).

In a group of 22 patients, blood counts, hemoglobin content, and reticulocyte counts were made at the beginning of treatment and repeated weekly for a month. The urobilin and biliary pigments in the urine were followed, and also the direct and indirect bilirubin in the blood. In 12 cases the red blood cell resistance was determined, similar determinations being made in patients undergoing treatment with chaulmoogra oil as controls. Finally, the bone marrow was biopsied by sternal puncture in 5 patients of the diasone group and in 5 of those treated with chaulmoogra.

Reticulocyte count. This count was performed using vital staining by the cresyl blue method. In all cases there was found an increase in reticulocytes proportional to the severity of the

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TEXT—FIG. 2. Illustrating the relative globular resistance to varying concentrations of sodium chloride, in 12 patients under treatment with diasone and 6 patients receiving chaulmoogra. (From a photographic copy of the original chart used to illustrate the paper as read in Havana.)

anemia. Figures which varied between 3.9 per cent and 7.7 per cent were found in the majority, reaching 10.3 per cent in one case and 13.8 per cent in another. These figures decreased, tending to reach normal, on withdrawal of the diasone, there being a strict relationship to the number of red blood cells and the hemoglobin content. These findings indicate that the anemia is of a regenerative type.

Relative red blood cell resistance. The diagram shown in Text—figure 2 demonstrates the fact that patients undergoing treatment with diasone have a moderate tendency to decreased red blood cell resistance. The figures are the more significant when compared with those obtained in patients treated with chaulmoogra.

Urobilin in the urine. The urobilin content was measured weekly in the urine of all the patients in the group. It was found present in all cases, increasing progressively to considerable amounts by the third week of treatment. In two patients whose treatment was discontinued during the study, the urobilin disappeared in reverse proportion to the recovery of the red blood cells and hemoglobin content.

Bilirubin in the blood. Both direct and indirect bilirubin were investigated simultaneously with the urobilin in the urine. There was no appreciable increase in the indirect reaction, and the direct reaction was negative. A positive reaction was obtained in one patient who had previously been treated over a long period with chaulmoogra; thus the finding could not be attributed to the diasone.

Myelogram. Analysis of the data presented justifies the hypothesis that the anemia is due to hemolytic action of the drug while the bone marrow maintains its activity. It was therefore decided to make direct examinations of the bone marrow. In order to have an approximate idea of its cellular content, we adopted the technique of spreading the aspirated material without dilution and examining it dry with the low-power objective after staining by the May-Grimvald-Giemsa technique. Using a quadriculated eye piece, we counted the myeloid cells in 10 consecutive microscopic fields. To have attempted to obtain actual counts per volume would have entailed a much more complicated technique, unnecessary for our purpose.

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| Case | | (Myelogram percentages) | | | | | | |
|-------|---------------------------------|--|----------------------------|---------------------------|-------------------------|------------------|---------------------|---------------------------------|
| | No. of cells in 10 fields | Reticular and undiffer- entiated cells | Erythro- blast group | Granulo- cyte group | Mono- blast group | Lympho- cytes | Other elements * | Leuco-ery throblast ratio |
| | | | DIASONI | E-TREATE | D CASE | 8 | | |
| I. R. | 78 | 1.0 | 53.3 | 21.0 | 0.3 | 23.7 | 0.7 | 2.54:1 |
| J. L. | 135 | 0.7 | 61.7 | 12.0 | 1.0 | 24.7 | 0.0 | 5.14:1 |
| C. L. | 288 | 1.3 | 58.0 | 31.7 | 0.0 | 8.7 | 0.3 | 1.83:1 |
| F. A. | 49 | 0.3 | 75.7 | 8.7 | 1.3 | 14.0 | 0.0 | 8.72:1 |
| R. V. | 279 | 0.3 | 64.0 | 25.0 | 0.0 | 9.7 | 1.0 | 2.56:1 |
| | | СН | AULMOO | GRA-TRE | ATED CA | ASES | | |
| L. S. | 22 | 0.3 | 87.7 | 3.0 | 2.3 | 6.3 | 0.3 | 29.22:1 |
| R. S. | 40 | 1.3 | 48.7 | 20.3 | 0.7 | 28.7 | 0.3 | 2.39:1 |
| C. A. | 73 | 1.3 | 83.3 | 7.7 | 0.3 | 7.0 | 0.3 | 10.80:1 |
| A. P. | 67 | 0.3 | 69.0 | 10.3 | 0.3 | 18.7 | 1.0 | 6.67:1 |
| J. P. | 441 | 1.3 | 67.3 | 18.3 | 0.3 | 11.3 | 1.3 | 3.67:1 |

TABLE 1.—Bone marrow cell counts.

* Plasma cells, Rieder cells, etc.

The first outstanding observation is that the bone marrow of patients treated with diasone, where there was a marked anemia, shows no tendency to hypoplasia. The figures obtained show, in almost all cases, an increase well above the normal; in other words, the marrow showed hyperactivity. This fact is proof of the excellent powers to react possessed by myelopoietec tissue.

Equally noteworthy is the fact that the figures found in the lepromatous patients treated with diasone are three times higher than those of similar patients treated with chaulmoogra. The former gave an average of 166 nucleated cells, against 49 in the latter group. This fact alone is enough to warrant the assertion that diasone has no toxic effect on the bone marrow.

Study of the myelogram shows an orthoplastic reaction without pathologic features. The relation between the granulocytic and the erythroblastic cells (leuco-erythroblast ratio) in three out of five pictures was slightly higher than the normal 3:1.

TREATMENT OF THE ANEMIA PRODUCED BY DIASONE

If we are guided by the facts shown in this study—that is, if we admit that diasone acts as a hemolytic agent—the logical treatment of the anemia will consist in withdrawal of the drug. Experience shows that this simple measure is sufficient to arrest the condition and bring the blood picture back to normal in the vast majority of cases. Administration of the usual antianemic remedies, iron, liver and the vitamin B complex, is therefore not absolutely necessary. Experience has shown, however that the use of such remedies increases the tolerance of the organism to the treatment. We are unable to give precise details, merely reporting our clinical observations.

In a previous paper we described a comparative study of the tolerance in two groups of patients, one of which received antianemic treatment which the other did not. The results were not conclusive, as in our opinion the individual sensitivity to the anemia-producing action of diasone is widely variable.

Our practice in treatment with diasone varies according to whether the patients can be strictly controlled or not. If they can be controlled, we try to reach a maximum tolerated dose without giving antianemic remedies or interrupting the treatment until absolutely necessary. If, however, they can be seen only occasionally, we advise a daily dose of not more than 1 gram of diasone, prescribing also iron and liver, preferably by mouth, and ordering a blood count every three or four weeks. Withdrawal of the drug is advised whenever the blood cells fall below three millions and the hemoglobin content is less than 60 per cent.

SUMMARY

The clinical symptoms, frequency and relation to intensity of treatment, and the course of the anemia produced by diasone are described. It is shown that the changes in the blood picture are limited to the red blood count, without disturbance of other components. The anemia begins early in the first weeks of treatment and as a general rule abates with complete recovery during the periods of rest from the drug.

Investigations made in the treated patients have included the reticulocytosis, urobilinuria, bilirubinemia, and red blood cell resistance; the results of biopsy of the bone marrow in certain cases are also given. The findings show that the anemia is not due to a toxic action of the drug on the bone marrow, since there is good reticulocyte response in all cases and no leucopenia; furthermore, bone marrow biopsy shows a normal or increased erythroblastic activity, and granulopoiesis is also normal or increased. It is, therefore, deduced that the drug acts as a hemolytic toxin, as shown by the decrease in the red-blood-cell resistance, the presence of urobilin in the urine of almost all the cases, the absence of bile pigments in

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the urine, of direct bilirubin in the blood, and the absence of indirect bilirubinemia in the great majority of cases.

Taking these facts into account adequate therapeutic measures, based on clinical experience, are suggested.

CONCLUSIONS

As a result of this study we have come to the following conclusions.

1. Diasone produces an early anemia, which begins in the second week of treatment.

2. The anemia is probably due to a toxic hemolytic effect on the drug, because: (a) there is a definite decrease in the red-cell resistance; (b) urobilin is consistently found in the urine; (c) bile pigments are not found in the urine; and (d) the indirect bilirubin determination has proved negative in almost all cases.

3. The anemia is not due to a toxic effect on the bone marrow, because: (a) there is a satisfactory reticulocyte response in all cases; (b) bone-marrow biopsy shows normal or increased erythroblastic activity; and (c) granulopoiesis also is normal or increased.

4. The toxic effect is transitory, as shown by the fact that the blood changes disappear when the drug is withdrawn.

5. Clinical experience has shown that the anemia is usually benign and seldom requires interruption of the treatment.

6. Use of the common antianemic remedies—iron, liver and vitamin B complex—produces a favorable reaction, increasing the tolerance of the organism for the drug.

We wish to express our gratitude to the Patronato de Leprosos de Rosario for its generous cooperation in the performance of this study, and also to Dr. Juan P. Picena, formerly Professor of Pathological Anatomy of the Faculty of Medicine in Rosario, for his technical advice and valuable suggestions.