CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

THE ANEMIA OF SULFONE TREATMENT

TO THE EDITOR:

An article by Fernandez *et al.* in THE JOURNAL [**16** (1948) 319] deals with the hematological picture of patients under treatment with diasone. The authors state that they had studied the anemia produced by diasone from two angles, (*a*) a possible toxic action on the bone marrow, and (*b*) a possible direct hemolytic action on red blood corpuscles. They concluded that the drug acts as a hemolytic agent, and that consequently the logical treatment of the anemia would be to withdraw it, and that "administration of the usual antianemic remedies is therefore not absolutely necessary."

The evidence on which these conclusions are based is as follows: (*a*) the anemia is of a regenerative type, indicated by the reticulocyte response, (*b*) there is increased fragility of the red blood corpuscles, and (*c*) "considerable amounts" of urobilin are present in the urine of the patients undergoing sulfone treatment.

One must comment that the fact that there is a reticulocyte response does not necessarily signify that the anemia is hemolytic in character. Iron deficiency anemias also produce a reticulocyte response.

The evidence presented for increased fragility is not convincing. Only three of the twelve cases showed increased fragility, and in any event that condition of the red cells is not proof that hemolysis is the only or even the major cause of the anemia.

The finding of increased amounts of urobilin in the urine is not, *per se*, indicative of hemolysis. Such a finding might well be encountered in a state of dysfunction due to the action of the drug upon the liver parenchyma. Before a conclusion can be drawn regarding hemolysis, evidence must be forthcoming of increased *fecal* urobilin/ogen.

The statement that bone-marrow biopsy showed normal or increased erythroblastic activity, and that granulopoiesis was also normal or increased, is surely open to question. The average

number of marrow cells counted in the five diasone patients was 166, whereas hematologists advise 500 for a reasonably accurate count. In those patients the stated percentages of the granulocyte group give an average of 20; therefore a marked depression of myeloid tissue would appear to have been present. Whilst the "erythroblast" group shows a marked increase in percentage over normal, the increase shown is more typical of an iron-deficiency anemia than of a hemolytic process. The constant finding in hemolytic anemia is a marked increase in the reticulocytes, whereas in the case detailed by the authors no increased reticulocyte response in the bone marrow count is apparent.

I suggest that the authors have not presented any evidence to show that the anemia produced by diasone is definitely hemolytic in nature. Therefore their statement that iron and yeast, etc., are not absolutely necessary should not be accepted as a correct assumption.

That the anemia produced by the sulfones is a complex one is evident from the work of Brownlee [*Lancet.* **2** (1948) July 24] and Higgins [*Proc. Mayo Clinic* **19** (1944) 202]. Their work shows that the anemia is a combination of three processes, namely, iron deficiency, dyshemopoiesis and hemolysis. It is my experience here that the hemolytic process is the least important from the point of view of treatment.

BELRA Research Unit MICHAEL SMITH, B. SC.
Leprosy Colony *Biochemist*
Uzuakoli, Nigeria

TO THE EDITOR:

296 We wish to thank Mr. Michael Smith for his critical analysis of our Havana Congress article on anemia in sulfone treatment as published in THE JOURNAL **16** (1948) 317, because it shows his interest in the subject and because it gives us an opportunity to correct certain errors which crept into the translation and printing of that article.

We agree with Mr. Smith that, *taken separately,* no single one of the three symptoms on which our conclusions were based —reticulocyte response, increased fragility of the red cells, and increase of urobilin in the urine—characterizes any particular type of anemia. When they appear together, however, as in the cases we studied, they can be interpreted as the result of the action of a hemolytic agent.

The reticulocyte response in various other anemias appears

secondarily, while in the hemolytic type it appears simultaneously with the anemia. In our Fig. 1 of the article referred to (p. 321) it is quite evident that the increase of reticulocytes begins long before the anemia becomes frankly evident. The numbers of them seen in the peripheral blood, 3.9 to 7.7 per cent in the majority of cases, and 10.3 and 13.8 per cent in extreme cases (p. 324), are obviously high.

The iron deficiency in our patients is not as apparent as, perhaps, it is in patients observed in other places, since our Fig. 1 demonstrates the simultaneous and not dissociated decrease of red cells and hemoglobin.

Although the increase of the fragility of the red cells is less manifest, the graph (Fig. 2, p. 323) shows on the whole an evident tendency to increase under diasone treatment, especially if the findings are compared with those of the chaulmoogra-treated group of patients. We recognize that this single condition is inconclusive, since clinical observations show that the most typical examples of hemolytic anemia (hemolytic icterus) are frequently not accompanied by an increase of red-cell fragility. Be that as it may, we are at present studying the red cell fragility in a larger number of cases, to gather further data.

Up to this point the disagreement of Mr. Smith with our conclusions depends upon the different criteria by which the facts can be interpreted. On the other hand, his objections to the part of our article referring to the study of the bone marrow are more serious, and his criticisms would be irrefutable if they were not due to regretable errors of translation and printing, which we wish to correct.

The average figures of 166 *versus* 49 cells (p. 325) do not refer to the numbers counted to arrive at the percentages, but simply to the result of comparative examinations of ten low-magnification microscopic fields of each of the cases of the two groups, made for the purpose of giving a panoramic view of the greater richness in cells of the bone marrow of the diasone-treated patients. This fact was not made clear in the translation supplied to THE JOURNAL. Nor was it stated, what is the fact, that the myelograms themselves were actually based on differential counts of 1,000 cells in each case. That fact we intended to show by the figures (53.33, 61.66, 75.66, etc.) given in the original table, which were reduced to one-place decimals by the editor.

Another error, this one of printing, refers to the headings "erythroblast group" and granulocyte group" of the second and

third columns of percentages in Table 1. Those headings were transposed, as can be verified in the last column in which the "ratio" obtained shows clearly the proportions of granulocytes and erythroblasts. This table was correctly reproduced (a photographic copy of the handwritten original) in the original Spanish version of the article published in the *Memoria* of the Havana Congress (p. 185).

Furthermore, the heading of the first column of percentages, which reads "reticular and undifferentiated cells," is a literal translation of the original "Células reticular. e indifer." and should have read "histiocytes and hemocytoblasts." Evidently Mr. Smith thought that this column referred to "reticulocytes," and thus he stated that "no increased reticulocyte response in the bone marrow is apparent." We have not counted reticulocytes in the bone marrow.

JOSÉ M. M. FERNANDEZ
EDUARDO A. CARBONI
PEDRO TOMMASINO
MANUEL M. GIMENEZ