HYPOPLASTIC ANEMIA DUE TO ATABRINE

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IT IS the purpose of this paper to present the clinical picture which may follow the prolonged ingestion of atabrine. This picture is characterized by a severe anemia which may or may not be associated with a characteristic dermatitis. The dermatitis has been previously described[1-6]; the anemia warrants further consideration. Custer,[7] basing his conclusions on an analysis of biopsy and autopsy material forwarded from the southwest Pacific to the Army Institute of Pathology, indicated atabrine as the agent responsible for the production of the hypoplastic anemia in the cases he reviewed. His report, based on pathologic data, by its very nature stresses the gravity and the poor prognosis of the illness. However, our experience indicates that a more optimistic approach is warranted. We are reporting the pertinent data regarding 7 patients who developed anemia following the prolonged ingestion of atabrine for malarial suppression while serving in the southwest Pacific area. Four suffered a concomitant dermatitis (fig. 1). The majority recovered. This group of patients illustrates the course and prognosis of hypoplastic anemia due to atabrine.

Hypoplastic anemia indicates a disorder of the bone marrow characterized by diminished hematopoiesis. The anemia fails to respond to the usual methods of therapy other than whole blood transfusion. The degree of anemia is variable; leukopenia and granulocytopenia are invariably present. Thrombocytopenia is usually marked and is responsible for hemorrhagic phenomena. The bone marrow varies histologically in architecture, degree of cellularity and maturity.

Clinical Material

Seven patients with hypoplastic ("refractory") anemia were admitted to Moore General Hospital, a tropical disease center. In each instance the anemia was so severe as to require frequent transfusions of whole blood. Each patient exhibited hemorrhagic phenomena. All had spent several months in the southwest Pacific area, but their military itineraries within the area showed little duplication. Only 2 had served in the jungles. One was a nurse, one a Medical Officer, and the others were enlisted men in combat units. Six were white and one was a Negro. All had taken atabrine for many months. Final hospitalization was occasioned by the development of symptoms of anemia in two instances, the appearance of a skin erruption in four, and diarrhea and acute otitis media in one. Details are presented in table 1.

Etiology

It is indicated in table 1, that 4 of the 7 patients were hospitalized primarily for dermatitis. This was either of a lichenoid (fig. 1) or an eczematoid type. It has been established that these lesions, as seen in patients from the Pacific area, are caused

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by prolonged atabrine therapy.[1-6] This form of dermatitis was not observed in natives or white residents who had never taken atabrine. Moreover, the dermatitis ceased to progress or disappeared entirely after atabrine was discontinued. In case 1 of this series (fig. 2), both dermatitis and a mild anemia appeared while the patient was in the southwest Pacific area. Upon his return to the United States he

TABLE 1.—*History of Antecedent Drug Ingestion, and Primary Reason for Hospitalization in 7 Cases of Refractory Anemia*

Case	Atabrine history	Reason for final hospitalizaion	Other drugs prior to onset of anemia
1—M. W. 33 infantryman	0.1 Gm. daily for 7 mos., none for 11½ mos. except for 2 courses of 5 and 7 days each, then 0.1 Gm. daily for 3 mos. when anemia appeared.	Anemia	Sulfadiazine, 18 mos. and penicillin 12 mos. previously
2—M. W. 26 infantryman	0 1 Gm. daily for 14 mos. when dermatitis appeared; 6 weeks later anemia first discovered.	Dermatitis (lichen planus)	None
3—M. W. 26 infantryman	0.1 Gm. daily for 4 mos., none for 2 mos., 0.1 Gm. daily for 6 mos., none for 8 mos., 0.1 Gm. daily for 2½ mos.; 6 weeks later anemia first discovered	Anemia	None
4—M. W. 37 mechanic	0.1 Gm. daily for 11 mos. Discontinued because of dermatitis, 3 mos. before detection of anemia	Dermatitis (lichen planus)	None
5—F. W. 28 nurse	0.1 Gm. daily for 18 mos. Discontinued because of dermatitis, 1 mo. before detection of anemia	Dermatitis	Penicillin
6—M. W. 47 medical officer	0.1 Gm. daily for 11 mos. Discontinued upon evacuation to U. S., 7 days before detection of anemia	Recurrent diarrhea, cause undetermined, and acute Otitis Media	Sulfadiazine 6 Gm. daily for 9 days (4 mos. before admission). Carbarsone, 1.5 Gm. for 1 day (4 mos. before admission)
7—M. C. 32 infantryman	0.1 Gm. daily for 8 mos. Discontinued because of dermatitis, 1 mo. before detection of anemia	Dermatitis	None

discontinued taking atabrine and both the anemia and the dermatitis disappeared. Later, while still in the United States, he resumed atabrine medication for the suppression and treatment of recurrent malarial attacks; a severe anemia and dermatitis resulted. The anemia was ameliorated and the dermatitis improved by discontinuing atabrine.

It should be emphasized that the duration of atabrine therapy appeared to be the determining factor. Experience with the atabrine dermatitides demonstrates that the drug must be ingested for comparatively long periods of time to produce

the eruption. In experiments which were done to reproduce the skin lesions it was found that they recurred only after the drug had been taken for several weeks.[6] In all 7 cases reported here, the patients had taken the drug for many months. The effect of the drug has been ascribed to idiosyncrasy; in an experimental study

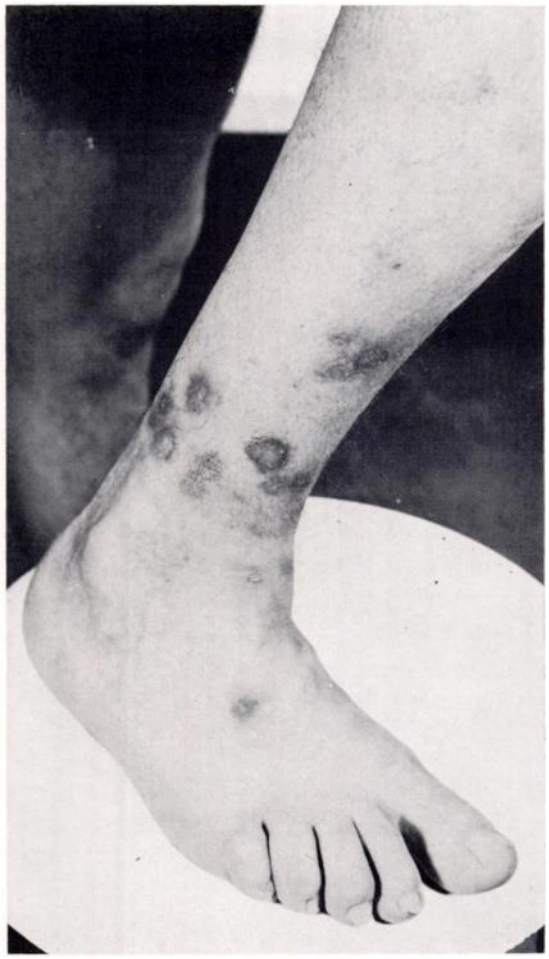

FIG. 1.—CONCOMITANT (LICHENOID) DERMATITIS

by Parmer[9] no correlation could be established between the concentration of atabrine in the various blood cells and the cells predominantly affected by the hypoplastic anemia.

CLINICAL AND HEMATOLOGIC DATA

In table 2, the clinical and hematologic data are tabulated. It will be noted that in each instance anemia was present at the time of original examination; it was usually severe, although in one case (case 5) it was mild. The color index was

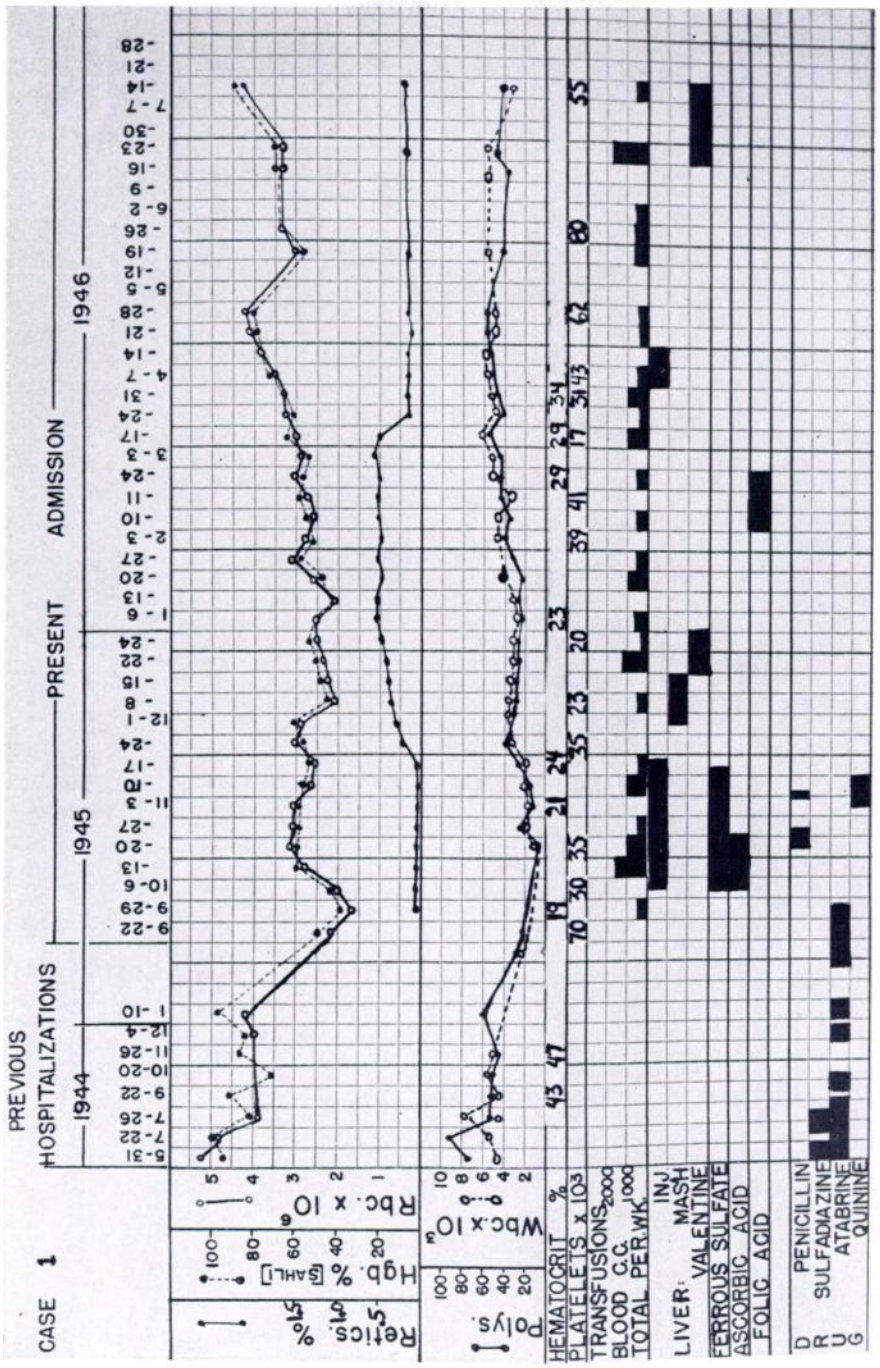

FIG. 2.—THE COURSE IN CASE 2

usually above one. Macrocytosis was the rule. The volume of packed cells (hematocrit) was uniformly low. Leukopenia was invariably present with the polymorphonuclear percentage usually low. The thrombocytes were always below

TABLE 2.—*Clinical and Hematologic Status*

Case	Symptoms of bone marrow alteration	Initial Hemogram							Bone marrow early in disease
		RBC	Hgb. (Sahli)	Cell vol.	WBC	P	Platelets	Retics.	
		mill.	%			%		%	
1	Weakness, dizziness, headaches. Hemorrhages from gums, throat, nose	2.94	56	24	3,500	58	35,000	0.2	Absence of megakaryocytes
2	Dyspnea on exertion tachycardia, weakness. Hemorrhages in retina	1.15	25	13	3,450	32	25,900	1.3	Normal
3	Dizziness, weakness, blurring of vision. Hemorrhages from gums and throat and into skin and retina, hematuria	2.25	60	26	3,500	45	18,500	0.2	Hypocellular; occasional megakaryocyte
4	Fatigability, paresthesias of hands and feet, tachycardia, palpitation. Hemorrhages from nose and into retina	1.83	42	17	1,750	38	17,000	0.9	Absence of megakaryocytes
5	Weakness, dyspnea on exertion, tachycardia. Hemorrhages into skin and retina.	4.1	80	—	4,750	22	29,000	0.7	Marked depression of all elements
6	Hemorrhages into skin and mucous membranes	2.47	46	21	3,200	54	20,000	0.2	Normal
7	Syncope, stomatitis. Hemorrhages from gums	1.91	42	19	2,050	12	13,000	—	Not done

40,000 per cu.mm. With one exception, the reticulocyte count was less than 1 per cent; this patient recovered rapidly. Bone marrow studies were done on 6 patients: in 2 the examination was found to be normal, in 2 normal except for the absence of megakaryocytes, and in 2 there was marked hypoplasia of all elements.

In addition to the data incorporated in table 2, certain additional information is available. Fever was invariably present but was usually not marked. The spleen was barely palpable in only one instance; the lymph nodes were enlarged in two patients and at autopsy were described as hemolymph nodes. In only one patient was the coagulation time prolonged but the bleeding time was always prolonged. The tourniquet test was positive in all cases at the height of the illness. In every instance there was defective clot retraction. There was no evidence of increased

TABLE 3.—*Therapy and Clinical Course*

Case	Therapy*	Clinical Course	Outcome
1	Transfusions, diet, liver mash, liver extract orally and hypodermically, folic acid, iron	Frequent hemorrhages from gums, throat and nose, gradually decreasing. Slow but steady improvement	Recovered
2	Transfusions, diet, liver extract orally and hypodermically, iron	Moderate, steady reticulocytosis persisting when medication was discontinued	Recovered
3	Transfusions, diet, liver extract orally and hypodermically, iron, sternal marrow transplant	Frequent hemorrhages from gums and throat, which became uncontrollable, hematuria, purpura	Died
4	Transfusions, diet, liver extract orally and hypodermically, iron, ascorbic acid hypodermically	No response for a long time. Later reticulocytosis to 10% following liver intramuscularly and maintained by liver mash by mouth. Then gradual improvement temporarily interrupted by homologous serum jaundice	Recovered
5	Transfusions, diet, liver extract orally and hypodermically, iron, penicillin	Gradual improvement. Slow reticulocyte response not related to therapy	Recovered
6	Transfusions, diet, liver extract hypodermically	Persistently downhill in spite of transfusions. Death following mastoiditis and acute endocarditis (Paracolon bacillus)	Died
7	Transfusions, diet, liver extract hypodermically, penicillin, pyridoxine	Hemorrhages stopped after first transfusion but no change in leukocyte or platelet deficiency. Death from staph. albus (hemolytic) septicemia	Died

* Diet: High liver, high carbohydrate, high protein, high vitamin. Iron: Ferrous sulfate orally

hemolysis. In 6 patients, gastric analysis was done and in no case was achlorhydria demonstrated.

In 4 patients, a skin eruption was present when the anemia was first detected. One patient was originally hospitalized because of severe diarrhea and acute otitis media but hemorrhagic phenomena quickly supervened and became the predominant symptom.

THERAPY AND CLINICAL COURSE

The broad outlines of the therapeutic program and the clinical course are summarized in table 3. Four of the 7 cases eventually recovered and 3 died; 2 of the deaths were attributed to intercurrent infection and one to uncontrollable bleeding.

Repeated transfusions of whole blood were necessary to tide the patient over the acute phase of the disease. No other therapeutic measure afforded relief from the manifestations of bone marrow depression. Figure 2 is a reproduction of the course of Case 1. The various measures and their hematologic effects are graphically portrayed. None of the therapeutic agents seemed to influence the course of the illness. Whole blood administration, when effective, was only transiently palliative.

Comment

The mechanism of bone marrow depression by atabrine is complicated by the demonstration that atabrine may remain in body tissues after the drug has been discontinued.[8] Consequently, two factors may cause development of the hypoplastic marrow due to atabrine: (1) the initial cumulative depression due to ingestion of the drug and (2) the perpetuation of the depression by residual stores of drug within the body. Recovery is spontaneous and gradual, apparently uninfluenced by medication.

Summary

Seven patients with severe hypoplastic anemia were studied at an army Tropical Disease Center. Four of the 7 patients had concomitant dermatitis. The relationship of the prolonged administration of atabrine to the anemia and dermatitis is presented. A hematologic remission could not be induced by specific therapeutic measures. Four of the 7 cases recovered spontaneously.

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REFERENCES

[1] Noogin, R. D., and Callaway, J. L.: Generalized exfoliative erythroderma following atabrine. North Carolina M. J. *3:* 239, 1942.

[2] Schmitt, C. L., Alpins O., and Champers, G.: A clinical investigation of a new skin entity. Arch. Derm. & Syph. *55:* 226, 1945.

[3] Nisbet, I. W.: A new cutaneous syndrome occurring in New Guinea and subjacent islands. Arch. Derm. & Syph. *52:* 221, 1945.

[4] Livingood, C. S., and Dieuaide, F. R.: Atypical lichen planus. J. A. M. A. *129:* 1091, 1945.

[5] Goldberg, L. C.: An unusual lichenoid dermatosis. J. A. M. A. *130:* 775, 1946.

[6] Bazemore, J., Johnson, H., Swanson, E., and Hayman, J.: Relation of quinacrine hydrochloride to lichenoid dermatitis (atypical lichen planus). Arch. Derm. & Syph. *54:* 308, 1946.

[7] Custer, R. P.: Aplastic anemia in soldiers treated with atabrine (quinacrine). Am. J. M. Sc. *212:* 211, 1946.

[8] Malaria Research Unit, 3rd. Medical Laboratory, Report No. 13: Clinical and laboratory studies on atypical lichen planus with particular reference to the role of atabrine. Dec. 3, 1944.

[9] Parmer, L. G.: Blood and bone marrow concentration of atabrine and its role in aplastic anemia. J. Lab. & Clin. Med. *33:* 827, 1948.