CHAPTER IV

DISCUSSION

Drug may induce immune hemolytic anemia by several recognized mechanisms, each of which has specific serologic abnormalities, and distinct clinical syndrome. With sensitive techniques (17, 69), it can now be shown that many drugs lead to the development of antidrug antibodies, which can be of two types : first, those apparently directed against the drugs or its metabolites, and second, those apparently directed against body constituents. Many of these antidrug antibodies give rise to no symptom even thouth the drug is continued, but occasionally either type can developed serologic abnormalities, a positive direct antiglobulin test and may be associated with immune hemolytic anemia.

Thus, immune drug-induced hemolysis can be classified into (1) immune hemolytic anemia in which the antibody appears to react with the drug and cannot be detected in the serum with normal red blood cells unless additional drug is also present, penicillin is usually the drug involved in this type of reaction, and (2) autoimmune hemolytic anemia, in which the antibody directly reacts against the normal constituents of the red blood cell membrane and cen be detected with normal red blood cells and is not affected by the addition of the drug, this type of reaction are best examplified by methyldopa.

In the present study, these two types of drug-induced immunohematologic abnormalities involving red blood cells will be discussed separately.

Penicillin type, the ability of patients receiving penicillin therapy to produce antipenicillin antibody has been long known (5). Several cases of hemolytic anemia in which the patients had a positive direct antiglobulin test following by penicillin administration have been reported (7-12). Although penicillin is the most common cause of drug induced a positive direct antiglobulin test and immune hemolytic anemia in which a drug-specific antibody has been identified (7-12). The incidence of a positive direct antiglobulin test in patients having circulating antipenicillin antibody has not previously been studied.

In the present study, five of 99 patients 5.1% with circulating antipenicillin antibody developed a positive direct antiglobulin test. The serologic studies in all patients indicated that a positive direct antiglobulin test was due to IgG antipenicillin antibody. This interpretation is supported by demonstrable antibodies from the eluates of patient's red blood cells reacting only with penicillin treated red cells by antiglobulin technique and resistant to 2-Mercaptoethanol inhibition.

The occurrence of hemolysis by antipenicillin antibody cannot be documented in 4 of 5 cases with positive direct antiglobulin test since there may be some degree of hemolysis due to the underlying

diseases (Table 9) in those who had low hemoglobin level. There was no evidence of hemolysis or anemia in one of 5 patients with positive direct antiglobulin test which was similar to the findings of Abraham et al (78) who found no evidence of hemolysis in all of 3 cases of positive direct antiglobulin test in 125 patients receiving intravascular penicillin. This phenomenon was also observed in occasional case reports (6). It is indicated that not all of positive direct antiglobulin test CAPA patients developed hemolysis but all of hemolysis CAPA patients had positive direct antiglobulin test.

It has been shown in the reported cases that hemolytic anemia may develope only in those capable of sensitizing a high titer IgG antipenicillin antibodies (9, 20, 24). It was interesting that, all of four cases in this study who were anemic, had also high titer IgG antipenicillin antibodies (1:128 to 1:512). In contrast, the case with normal hemoglobin level had a low titer of IgG in addition to IgM antipenicillin antibodies (1:64/1:4, before and after 2 ME treatment).

However, the duration of penicillin administration before the blood specimens were obtained for testing must be considered. All of five patients had reveiving penicillin parenterally 1.2 to 12 million units per day for 3 to 7 days. A positive direct antiglobulin test was detected in 3 to 24 days after cessation of penicillin therapy. It is probably that patients who would be treated with intravascular penicillin for a matter of weeks or who have had frequent penicillin

administration of the recent past would have a significantly higher evidence of immunological abnormality.

In the previous reports (7-12), penicillin induced hemolytic anemia had occurred during prolong penicillin therapy and the hemolytic anemia was diagnosed by rapid-falling hemoglobin level, despite an increasing reticulocyte count and without any evidence of bleeding. In all of their patients mentioned above, the evidence of hemolysis disappeared quickly when the drug was discontunued, and the direct antiglobulin test gradually became weakly positive, until it was found to be negative about 60 to 80 days later. The IgG antipenicillin antibody may remain in the serum for a period of times (81). If penicillin was given again in high doses to those patients, a similar episode of hemolysis would be expected to occur (9).

There were no positive antipenicillin antibody detected in 230 random blood donors, assuming that some of these donors may previously use penicillin and may develop penicillin antibody in some cases. However, the antipenicillin may present in low titer that can not be detected by the technique used in this study.

Methyldopa type, Worlledge (81) has shown that 15% of hypertensive patients treated with methyldopa developed a positive direct antiglobulin test, although under 1% developed hemolytic anemia. In the present study, 3 of 32 patients (9.4%) receiving methyldopa for treatment of hypertension developed a positive direct antiglobulin test of IgG type. This result approximately the percentage found by

Cotton et al (55) of about 9%, and higher than 4% reported by Feizi et al from London (75).

There have been reports of negative results with the red cells of 58 Chinese from Malaya and Singapore (78, 79) and of 75 African and Indian in Durban (76) who were treated with this drug. These last authors suggested that the incidence of a positive test with methyldopa may differ in different racial groups. Certainly the remaining reports have been tested on mainly Caucasian population. In this study, there is evidence that the incidence of a positive direct antiglobulin test of Thai population was similar in some reports of Caucasian population. These findings agree with the first reported by Worlledge et al (62) who reported positive direct antiglobulin test in African and Indian patients taking methyldopa. The incidence of a positive direct antiglobulin test was similar in the European and Afro-Asian groups, i,e., 21% and 17% respectively.

Sera and eluates from patient's red blood cells failed to react with pooled panel O cells, they show no evidence of any irregular antibody to blood group system. Worlledge et al (62) were able to obtain positive eluates of most of their patients, and the eluates often had Rh specificity. Inability to demonstrate positive eluates in this present study may be due to too weak sensitization of red cells to be detected.

All of the three patients developed a positive direct antiglobulin test were mildly anemic, one patient was anemic due to

SLE, two patients had a reticulocyte count in a normal range and no evidence of jaundice. These patients had elevated blood urea nitrogen (BUN) level and evidence of renal insufficiency. However, Carstairs et al (61) found no significant increase of BUN in those who had negative or positive direct antiglobulin test due to methyldopa which were approximately 30% in both groups.

Immune hemolytic anemia as the result of the specific immunohematologic interaction of a drug and antidrug antibody of any type once thought to be uncommon. Whenver patient presents with active hemolysis and is known to be taking a drug, a direct antiglobulin test might be carried out as part of the screening test. The hemolysis was suspected when it was found that the red blood cells of such a patient gave a positive direct antiglobulin test and no antibodies are demonstrable in the sera directed against normal red blood cells. However, there are many causes of a positive direct antiglobulin test without hemolysis (27. 29). Thus, the serologic methods of diagnosis and clinical manifestation are not only necessary to distinguish immunohemologic abnormalities caused by drugs from other causes, but may be important for safety of drug administration.